

POLICY AND REGULATORY INTERVENTIONS TO REDUCE ANTIMICROBIAL  
RESISTANCE: EVIDENCE AND ANALYTIC STRATEGIES

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## **Dissertation abstract**

**Background:** Antimicrobial resistance (AMR) is a widely recognized threat to global health that has been accelerated by the overuse of antimicrobials. Policy and regulatory interventions offer a useful approach to bring about widespread change in antimicrobial use.

**Objectives:** This dissertation aims to investigate and characterize the role of policy interventions on antimicrobial use, to understand which policy levers have been used, which interventions have proven to be effective, and to identify analytic strategies that assist researchers and policymakers in developing evidence-informed approaches to address human AMR.

**Methods:** To investigate effectiveness of policy interventions, I developed a systematic review and evidence map and appraised the quality of research on government policies to reduce antimicrobial use. To evaluate the extent of policy action on AMR in the Canadian context, I conducted an environmental scan of AMR action between 2008-2018. Finally, to facilitate advances in the scientific evidence base on antimicrobial resistance policy, I developed a framework for planning, conducting, and disseminating AMR intervention research.

**Findings:** Governments have a variety of policy options at their disposal to respond to the growing threat of AMR, however, most of these policy options have not been rigorously evaluated and their effectiveness is unknown. Some regulatory, communication, guidelines, and fiscal interventions have been effective in particular settings, however, the interventions were too disparate to generalize about the effectiveness of any particular policy approach and reporting gaps in pose challenges for interpreting and replicating study results. In Canada, policy interventions have been too few, too small and too uncoordinated to achieve our AMR goals. Building on these findings, I developed a framework for planning, conducting, and disseminating AMR intervention research that identifies challenges, areas for increased coordination with policymakers, and best-practices for overcoming common limitations in AMR research.

**Discussion:** Governments around the world have committed to respond to AMR, however, rigorous evidence to inform their policy and regulatory strategies is lacking. As the threat posed by AMR grows, it is increasingly important to strengthen the scientific evidence base on AMR policy interventions, to learn from existing policies and programs, and integrate scientific evidence into the global AMR response.

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Chapters 4 through 7 have been presented in manuscript format but have not yet been submitted for publication.

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SRVK and SJH conceived the idea for the systematic review. SRVK led the design of the methodology, devised the search strategy, led the data collection and analysis, and wrote the first draft of the manuscript. SJH and JG supervised the design of the study and methodology and critically revised the manuscript. MN and RN assisted with the collection and analysis of data. MT and MM provided valuable subject-matter and methodological expertise. All authors contributed to the revision of the manuscript.

**Chapter 6:**

SRVK, SJH, and JG conceived of the project. SJH and JG supervised the project. SRVK designed the methods and collected the data. SJH and TT circulated the questionnaire. SRVK conducted the analysis and all authors contributed to the interpretation of results. SRVK took the lead on drafting the manuscript. All authors critically revised the manuscript and approved the submitted manuscript.

**Chapter 7:**

SRVK, SJH and JMG conceived of the project. SRVK collected the data and developed the framework, and all authors provided critical feedback and helped shaped the research and analysis. SJH and JMG supervised the project. MM and MT provided subject matter expertise. SRVK developed the figures in collaboration with MT. SRVK took the lead in writing the manuscript. All authors have critically revised the manuscript and provided final approval of the submitted manuscript.

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## List of acronyms and abbreviations

|         |                                                                   |
|---------|-------------------------------------------------------------------|
| AMR     | Antimicrobial Resistance                                          |
| ARIMA   | Autoregressive Integrated Moving Average                          |
| CADTH   | Canadian Agency for Drugs and Technologies in Health              |
| CDA     | Canadian Diabetes Association                                     |
| CENTRAL | Cochrane Central Register of Controlled Trials                    |
| CIHR    | Canadian Institutes of Health Research                            |
| COA     | Canadian Orthopaedic Association                                  |
| COMET   | Core Outcome Measures in Effectiveness Trials                     |
| CONSORT | CONsolidated Standards of Reporting Trials                        |
| CSC     | Correctional Services Canada                                      |
| cRCT    | Cluster Randomized Controlled Trial                               |
| DBND    | Do Bugs Need Drugs?                                               |
| EPOC    | Effective Practice and Organization of Care                       |
| GRADE   | Grading of Recommendations Assessment, Development and Evaluation |
| HIC     | High Income Countries                                             |
| ITS     | Interrupted Time Series                                           |
| JPIAMR  | Joint Programming Initiative on Antimicrobial Resistance          |
| LHIN    | Local Health Integration Network                                  |
| LMIC    | Low- and Middle-Income Countries                                  |
| MRC     | Medical Research Council                                          |
| MRSA    | Methicillin-resistant <i>S. aureus</i>                            |
| NCCID   | National Collaborating Centre for Infectious Disease              |

|            |                                                                                    |
|------------|------------------------------------------------------------------------------------|
| OECD       | Organisation for Economic Co-operation and Development                             |
| OMERACT    | Outcome Measures in Rheumatology                                                   |
| PHAC       | Public Health Agency of Canada                                                     |
| PRISMA     | Preferred Reporting Items for Systematic Reviews and Meta-Analyses                 |
| PRISMA-P   | Preferred Reporting Items for Systematic Reviews and Meta-Analyses - Protocols     |
| PROSPERO   | International Prospective Register of Systematic Review                            |
| RCT        | Randomized Controlled Trial                                                        |
| SHS-UHN    | Sinai Health System – University Health Network                                    |
| SQUIRE     | Standards for Quality Improvement Reporting Excellence                             |
| TIDieR     | Template for Intervention Description and Replication                              |
| TIDieR-PHP | Template for Intervention Description and Replication Population Health and policy |
| UK         | United Kingdom                                                                     |
| USA        | United States of America                                                           |
| URTI       | Upper Respiratory Tract Infection                                                  |
| UTI        | Urinary Tract Infection                                                            |
| WHO        | World Health Organization                                                          |

# 1 Introduction

## 1.1 Background

Antimicrobial resistance (AMR) is a widely recognized and increasingly serious threat to global public health. One early estimate suggested that resistance would be responsible for 700,000 deaths per year in 2016 and projected the death toll would reach 10 million per year by 2050 [1]. Antimicrobial drugs — antibiotics, antivirals, antifungals, and antiparasitics — are mainstays of modern medicine. However, the overuse of antimicrobials exerts a selection pressure on microbes and accelerates the evolution of resistant strains of disease-causing organisms [2]. Each use of an antimicrobial offers the potential for resistance to develop, and it is unclear what level — if any — might be a safe or sustainable level of antimicrobial use. Despite this knowledge, global antimicrobial use is still increasing. Between 2000-2010 there was a 36% global increase in antibiotic use [3].

The potential for AMR has been recognized since the earliest days of antibiotics [4], and indeed, penicillin resistance emerged in the early 1940s [5] to become widespread in the wake of World War II [6]. Historically, resistant organisms have been discovered shortly after the introduction of each newly developed antimicrobial agent [7]. For many years, the development of novel antimicrobial agents allowed medicine to stay one step ahead of resistance, however, this strategy has failed recently. No novel antimicrobial agents have been developed in over 20 years and few new potential antimicrobial agents are currently in development [8-10]. Without new drugs, or an alternative strategy for overcoming resistance, medicine stands to lose one of its key tools. This grim outlook has led both the World Health Organization (WHO) and the U.S. Centres for Disease Control and Prevention (CDC) to conclude the world is on the cusp of the post-antibiotic era [11, 12], a situation in which, “common infections and minor injuries can kill [12].”

The diversity of antimicrobial resistance mechanisms, pathogens and outcomes is a challenge for tracking and addressing AMR. The World Health Organization has highlighted the importance of developing new antimicrobial drugs for tuberculosis, malaria, and HIV, and new antibiotics for 12 priority pathogens, the most critical of which are carbapenem-resistant *Acinetobacter*

*baumanii*, carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem and 3<sup>rd</sup> generation cephalosporin-resistant *Enterobacteriaceae* [13]. Other high-priority pathogens include vancomycin resistant enterococci, methicillin and vancomycin resistant *Staphylococcus aureus*, and fluoroquinolone and 3<sup>rd</sup> generation cephalosporin resistant *Neisseria gonorrhoeae*. In Canada, infection rates with carbapenemase-producing organisms in hospital have been stable for the past five years, however, rates of colonization with these organisms has increased almost five-fold [14]. The rates of vancomycin resistant bloodstream infections have more than doubled since 2011 [15], community-associated methicillin resistant *Staphylococcus aureus* infections have increased by nearly 60% since 2012 [14], and 7% of all *Neisseria gonorrhoeae* infections were resistant to azithromycin in 2017 [14]. Overall antimicrobial use in Canada has stayed stable in recent years, and although antimicrobial prescriptions in children have been decreasing, antimicrobial prescriptions in Canadians over the age of 60, which are nearly 60% higher than in the rest of the population, have continued to increase [14]. In animals, the volume of antimicrobials used in 2017 was nearly four times the volume used in humans; however, this represents to lowest volume of antimicrobial use in animals since data collection began in 2006 and reflects decreases in antimicrobial use in pig and chicken farming [14].

Antimicrobials are widely used in both human health care and agriculture, and preventing the spread of resistance between humans, animals and the environment requires a One Health approach that promotes the prudent use of antimicrobials across sectors. Effectively addressing AMR will also require efforts to simultaneously address AMR on three fronts: improving access to antimicrobials for the millions of people who do not currently have access to these drugs, conserving antimicrobial effectiveness through reductions in antimicrobial use and infection prevention, and innovation to develop new drugs and alternative technologies. Tensions exist between these three AMR goals. Increasing access to antimicrobials without corresponding efforts on conservation and innovation will increase use and accelerate the development of resistance. Efforts to conserve antimicrobials may limit access, while also restricting the market for antimicrobial innovation. Finally, innovation without access would be unjust, while innovation without conservation would be wasteful [16]. Balancing these competing requirements requires a suite of policy approaches, some of which are AMR-specific, for example, developing novel funding mechanisms to support innovation on new antimicrobials or

diagnostic tools, others approaches are AMR-sensitive, for example, promoting vaccination and handwashing to reduce infections, or strengthening health systems towards the goal of universal health coverage [17].

Reducing inappropriate antimicrobial use is a key part of the global strategy to conserve antimicrobial effectiveness and reduce AMR, although intervening to reduce resistance is fraught with challenges. Misconceptions among physicians and the public contribute to the overuse of antimicrobials. Systematic review evidence shows that while physicians and the public are aware of antimicrobial resistance as a problem [18, 19], patients often believe that resistance is the result of changes to the human body rather than changes in bacteria [18], and physicians widely believed that AMR was a problem at the global level but not a concern at their local practice level [19]. Research also suggests that even when patients understand the importance of reducing antimicrobial use, they believe this is the responsibility of prescribers and outside their control as patients [18]. By contrast, many clinicians feel obliged to prescribe antimicrobials even when they are not needed because of a perceived demand from patients [18, 19]. Antimicrobials are widely prescribed for conditions — such as viral illnesses — that cannot be treated using antibiotics. Evidence from Canada, the UK, and the USA suggests that as many as half of antibiotic prescriptions for respiratory tract infections are unnecessary and could be eliminated [20-23].

Overcoming the combined challenges of increasing antimicrobial use and misconceptions about AMR will require widespread changes in knowledge of the causes and consequences of AMR, and in the use of antimicrobials on the part of patients and providers. Government policy is one of the most important mechanisms for bringing about collective action [24] and government policy interventions are often well-worth considering when public health challenges require widespread and uniform compliance with a defined set of minimum standards [25]; research to date suggests that government-level intervention may play a key role in reducing AMR [26]. Governments have the ability to set laws, establish standards, limit antimicrobial distribution and marketing, and to act across sectors to address human, animal, and environmental components of AMR. Well known examples of successful government action on AMR have included the “Antibiotics are not automatic” campaign in France which substantially reduced prescribing in

one of the highest prescribing European countries [27, 28], and the work of Professor Dame Sally Davies as Chief Medical Officer of the England to draw attention to AMR [29]. In Canada, the Public Health Agency of Canada is the federal lead on antimicrobial resistance, and, supported by other federal agencies including Health Canada, the Canadian Food Inspection Agency, Agriculture and Agri-Food Canada, the Canadian Institutes for Health Research and others, is responsible for conducting AMR surveillance, establishing policies and standards for animal health, supporting AMR research, and regulating the safety and effectiveness of antimicrobials. The governments of the provinces and territories are responsible for healthcare delivery, establishing policies and standards for healthcare settings, approving antimicrobials for medical formularies, and regulating the distribution and use of antimicrobials in agriculture and veterinary medicine [30].

National and international action on antimicrobial resistance is also politically necessary. Drug resistant organisms can easily spread across political borders, posing a threat to health care systems globally. There have recently been several high-profile political efforts to address antimicrobial resistance; these have included the WHO's global strategy on AMR and calls for the development of national action plans [31, 32], the promise by G20 leaders to tackle AMR [33], major funding calls [34], civil society partnerships [35], and the high-level meeting on AMR at the UN [36]. These high-profile political statements have also generated increased interest in global governance strategies to address AMR and there have been several recent calls from the academic community for an international legal agreement on AMR [16, 26, 37-40].

Despite the political importance of AMR — and the substantial global economic threat posed by resistance [41] — engaging governments in public health action can prove difficult.

Governments often fail to act on evidence-informed policy recommendations for reasons of ideology, political feasibility and competing local priorities [42]. However, many governments around the world are actively considering policy interventions that could reduce antimicrobial use, including mechanisms such as legislation, taxation, economic incentives and public awareness campaigns [25]. Some governments have successfully achieved reductions in antimicrobial use using the policy levers at their disposal [43-46]. These policy levers can work at many levels, by creating structural reforms that reduce externalities or regulate prescriber

behaviours, or by educating and providing information such that consumers are aware and have the capacity to make better choices [25]. It is insufficient, however, to implement AMR policy based on what theoretically will work, or worse, based simply on the premise that the intervention seemed like a good idea at the time. A key barrier to tackling AMR is the lack of evidence on effective policy strategies, and the lack of data to adequately characterize the scope of the AMR threat. Evaluations are needed that can test the effectiveness of programs and policies in different settings and clarify the pathways and mechanisms through which these interventions are effective. Lack of surveillance data on AMR and antimicrobial use has made it difficult even to determine the magnitude of the AMR threat in many countries [12, 47, 48]; yet, reliable data on antibiotic consumption and intervention effectiveness is essential to generate political will for action on AMR [49, 50]. Researchers, therefore, need to emphasize the importance of collecting high-quality data and conducting rigorous evaluations of AMR interventions in order to inform the actions of both policy makers and clinical decision makers.

## **1.2 Research objectives**

The overall goal of this dissertation was to explore and appraise the evidence base for large-scale, human-health focused interventions to address antimicrobial use and the looming threat of antimicrobial resistance. Directly addressing objective 4 of the Global Action Plan on AMR — to optimize the use of antimicrobial medicines — we aimed to provide a rigorously evaluated evidence base on AMR-specific government policy interventions to inform policymaking and regulation of antimicrobials as a public good [32]. Specifically, we aimed to:

- I. Investigate and characterize the role of government policy interventions on AMR and antimicrobial use, to understand which policy levers have been used, appraise the state of the evidence, and identify which interventions have proven to be effective;
- II. Describe and evaluate policy action on antimicrobial use and resistance in the Canadian context;
- III. Evaluate and propose analytic strategies for improving research on population health interventions on antimicrobial use and resistance.

### **1.3 Organization of dissertation**

This manuscript-based thesis contains 6 substantive chapters that have each been formatted as manuscripts for publication. Chapter 2 describes the protocol for a systematic review of government interventions to reduce antimicrobial use in humans. The next three chapters report on elements of this systematic review: a systematic review and evidence map of government interventions to reduce antimicrobial use in humans (Chapter 3), a systematic analysis of reporting quality in reports of government interventions to reduce antimicrobial use in humans (Chapter 4), and a systematic review of the effectiveness of government interventions to reduce human antimicrobial use (Chapter 5), all of which address the first specific objective of this dissertation. Chapter 6 consists of an environmental scan of Canadian programs to address antimicrobial resistance between 2008-2018 which addresses the second specific objective of this dissertation. Chapter 7 draws upon the findings of earlier manuscripts and outlines a framework for planning, conducting and disseminating research on population health interventions to address antimicrobial use and resistance. Finally, Chapter 8 presents a discussion of the key findings, limitations and conclusions of the thesis. Each section is introduced by a brief preface to describe the specific objective addressed by the study, the contribution of co-authors, and any related appendices and approvals.

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## **2 Government policy interventions to reduce human antimicrobial use: protocol for a systematic review and meta-analysis**

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## 2.1 Preface

This published manuscript presents the protocol for a systematic review that addresses the first aim of my dissertation: to investigate and characterize the role of government policy interventions on AMR and antimicrobial use, to understand which policy levers have been used, appraise the state of the evidence, and identify which interventions have proven to be effective.

I conceived the idea for this systematic review along with Dr. Hoffman and I led the design of the protocol and methodology. I developed the initial systematic search strategy in collaboration with 2 research librarians (Lindsey Sikora and Catherine McGoveran) at the University of Ottawa and wrote the first draft of this manuscript. Drs. Hoffman and Grimshaw supervised the design of the protocol and methodology and critically revised the manuscript. Drs. Taljaard, Mendelson, and Tam provided valuable methodological and subject-matter expertise to inform this protocol and revised the manuscript. All authors have read and approved the final manuscript, which was published in the journal *Systematic Reviews* in 2017.

**Manuscript status:** Published

**Ethics approval:** Not required

## 2.2 Abstract

**Background:** Antimicrobial resistance (AMR) is a recognized threat to global public health. Increasing AMR and a dry pipeline of novel antimicrobial drugs have put AMR in the international spotlight. One strategy to combat AMR is to reduce antimicrobial drug consumption. Governments around the world have been experimenting with different policy interventions, such as regulating where antimicrobials can be sold, restricting the use of last-resort antimicrobials, funding AMR stewardship programs, and launching public awareness campaigns. To inform future action, governments should have access to synthesized data on the effectiveness of large-scale AMR interventions. This planned systematic review will (1) identify and describe previously evaluated government policy interventions to reduce human antimicrobial use and (2) estimate the effectiveness of these different strategies.

**Methods:** An electronic search strategy has been developed in consultation with two research librarians. Seven databases (MEDLINE, CINAHL, EMBASE, CENTRAL, PAIS Index, Web of Science, and PubMed excluding MEDLINE) will be searched, and additional studies will be identified using several grey literature search strategies. To be included, a study must: 1) clearly describe the government policy; and 2) use a rigorous design to quantitatively measure the impact of the policy on human antibiotic use. The intervention of interest is any policy intervention enacted by a government or government agency in any country to change human antimicrobial use. Two independent reviewers will screen for eligibility using criteria defined a priori. Data will be extracted with Covidence software using a customized extraction form. If sufficient data exists, a meta-analysis by intervention type will be conducted as part of the effectiveness review. However, if there are too few studies or if the interventions are too heterogeneous, data will be tabulated and a narrative synthesis strategy will be used.

**Discussion:** This evidence synthesis is intended for use by policymakers, public health practitioners and researchers to inform future government policies aiming to address antimicrobial resistance. This review will also identify gaps in the evidence about the effectiveness of different policy interventions to inform future research priorities.

**Systematic Review Registration:** PROSPERO: CRD42017067514

## 2.3 Background

Antimicrobial resistance (AMR) is widely recognized as a serious threat to global public health. One estimate suggests that resistance is currently responsible for 700,000 deaths per year, a death toll that is projected to reach 10 million a year by 2050 [1]. The potential for AMR has been recognized since the earliest days of antibiotics [2], yet, the misuse and overuse of antimicrobials has persisted over decades, contributing to the development of resistance.

Overuse of antibiotics exerts a selection pressure on microbes and accelerates the evolution of resistant strains of disease-causing organisms [3]. In the past, the threat of AMR was addressed by developing novel antimicrobial agents; however, there have not been any such novel agents developed in over 20 years and few new potential agents are in development [4, 5, 6]. As a result, there is increasing awareness around the need to minimize the development of AMR through better conserving the effectiveness of existing antimicrobials.

AMR is a complex and multi-faceted problem and intervening to minimize resistance is difficult. A key part of the global strategy on AMR is promoting the appropriate use of antimicrobials; inappropriate-use and over-use of antimicrobials are major drivers of resistance [3]. Evidence suggests that reducing antibiotic use is associated with lower rates of resistance [3]. Two systematic reviews have linked community antimicrobial use to resistance; one found that individuals prescribed an antibiotic in primary care developed resistance to that antibiotic with detectable effects for up to a year [7], while the second found higher resistance rates among pathogens circulating in areas with higher antibiotic use [8]. Mathematical modelling suggests that reductions in antibiotic use would result in lower resistance rates because genetically less 'fit' resistant strains would be outcompeted by susceptible strains [9]. Recent analyses of a Scottish intervention found substantial decreases in methicillin-resistant *S. aureus* (MRSA) and *C difficile* infections associated with decreases in prescribing of key antibiotics [10, 11]. Reducing antimicrobial use among humans is important given the relationship between hospital and community infections; the same Scottish study found that prevalence of MRSA in the community was predicted by hospital MRSA rates. Stewardship activities within the community were associated with a 32% reduction in community MRSA, while hospital-based interventions were responsible for an additional 37% reduction in community MRSA [11].

Reducing antimicrobial use is, therefore, one of the most common strategies that has been pursued to reduce AMR, and antimicrobial use is one of the most commonly measured intervention evaluation indicators. Many hospitals, for example, have implemented AMR stewardship programs to reduce physician prescribing [12]. Governments — which have various policy levers at their disposal — have also had success at reducing antimicrobial use. Mexico [13], Brazil [14] and Chile [15], for example, all saw reductions in antibiotic use after implementing policies to prevent over-the-counter sales of antibiotics. Less direct interventions have also reduced antibiotic use; in Canada, a policy to provide free universal influenza immunization was associated with a 64% reduction in inappropriate antibiotic prescriptions for influenza [16].

Using government policy to promote public health is generally well-worth considering when challenges require widespread and uniform compliance with a defined set of minimum standards [17]; in that vein, research to date suggests that government-level intervention may play a key role in reducing AMR [18]. Currently, however, global antimicrobial use is increasing; between 2000-2010 there was a 36% global increase in antibiotic use, 75% of which came from five of the world's fastest growing economies: Brazil, Russia, India, China and South Africa [19].

While the importance of government-level intervention is clear, to our knowledge there has not yet been a systematic review evaluating the extent to which different government policy interventions successfully reduce antimicrobial use. This gap is worth filling urgently considering that many governments around the world are actively considering numerous types of policy interventions that could reduce antimicrobial use, utilizing policy levers such as legislation, taxation, economic incentives, funding support, public awareness campaigns, and regulation of professionals and businesses whose work might affect AMR [17]. The magnitude of AMR's combined threat to human health and economic development [1] is already incentivizing governments to take a greater role in addressing AMR. Given the World Health Organization's recent call for the development of National Action Plans on AMR [20], a focus on the potential impact of government policy interventions on antimicrobial use is extremely timely. In light of these motivations and challenges, this systematic review intends to support evidence-informed action on AMR at the government level, by identifying, describing, and assessing the impact of government policy interventions on human antimicrobial use. More specifically, this systematic

review aims to produce: 1) a *descriptive review* that identifies and describes the government policy interventions that have been implemented and evaluated with the objective of changing antimicrobial use in humans; and 2) an *effectiveness review* that assesses the impact of these government policy interventions on reducing human antimicrobial use.

## 2.4 Methods

### 2.4.1 Protocol and registration

This systematic review protocol has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) guidelines [21] (see details in Appendix A2-1). Our review will be carried out in accordance with this protocol and details of any changes to this protocol will be reported in the final review manuscript. This study has been registered in PROSPERO, the international prospective register of systematic reviews (Registration number CRD42017067514).

### 2.4.2 Criteria for including studies in this review

#### *Types of study designs*

For the *descriptive review*, we will include any study that quantitatively describes the impact of a government policy intervention to reduce inappropriate antimicrobial use. Inclusion of all quantitative study designs allows us to identify a broad range of policy interventions and facilitates our goal of identifying and describing the government policy interventions to address antimicrobial consumption that have been implemented and evaluated to date (Table 2-1).

For the *effectiveness review*, our goal is to assess the impact of government policy interventions on the quantity of antimicrobials consumed by humans. We will include experimental designs like randomized controlled trials (including stepped wedge designs) and quasi-experimental designs like interrupted time-series analyses and controlled before and after studies. Quasi-experimental designs will need to meet the minimum methodological requirements of the Cochrane Collaboration's Effective Practice and Organization of Care (EPOC) Group. This means that all controlled studies, including controlled before and after studies, randomized controlled trials, and non-randomized controlled trials studies must have at least two

intervention and two control sites, and interrupted time series studies must have at least three measurements pre- and post- intervention to be included. Uncontrolled before/after studies with at least three measurements pre- and post- intervention may also be included if it is possible to re-analyse the data using an interrupted time-series analysis. We anticipate most included studies will evaluate impact using routinely collected data from before and after the intervention's implementation; a recent review of government policy interventions addressing dietary sodium consumption found this to be the most popular study design [22]. Qualitative studies, editorials, commentaries, reviews, and other syntheses will be excluded; however, the reference lists of relevant reviews and syntheses will be hand-searched to identify other potentially relevant studies.

### *Types of participants*

The impact of a government policy may be evaluated at any level, from the population level to the single hospital or clinic level; for example, a study investigating the impact of a national guideline might evaluate the impact on antibiotic sales at a national level, but it could also evaluate the impact on prescribing rates in a single hospital. However, in their statistical analysis, studies may include data from anyone involved in the sale, purchase, prescription or consumption of antimicrobial drugs such as patients, health professionals, hospitals, pharmacies and other healthcare facilities. Studies that evaluate interventions in any country or simultaneously in multiple countries (e.g., European Union) are eligible for inclusion.

### *Types of interventions*

Any policy intervention enacted by a government to reduce human antimicrobial use will be included. Interventions may be population-based, or targeted to specific groups such as health professionals. To be included, a study must clearly describe the government policy by providing a description that includes the intervention's aim, enacting government authority, timing, and form.

Globally, many levels of government have jurisdiction over health issues. As such, we will follow an inclusive approach to defining "government". A study is eligible for inclusion if the evaluated policy intervention is enacted by any level of government, including national, state, provincial,

regional and municipal governments, or by a government-controlled agency, ministry, or department. Studies evaluating interventions developed by individual hospitals, pharmacies and other healthcare facilities will not be included, even if these healthcare facilities are owned, operated, governed or otherwise controlled by governments. As such, a study evaluating the impact of an audit and feedback program developed by a single hospital or even a network of healthcare facilities would not be eligible.

Policy interventions will be defined in accordance with the Behaviour Change Wheel framework; as such, policy interventions are defined as those that create change in antimicrobial use through education, persuasion, incentivization, coercion, training, restriction, changing the physical or social context, modelling appropriate behaviour, or reducing barriers to action [23]. Examples of such policy interventions at the government level would include regulating where antimicrobials can be sold, restricting the use of last-resort antibiotics, or launching public awareness campaigns. Comparators or control groups may include the absence of the government policy or comparison with another policy. Eligible interventions can target all antimicrobials (e.g. all antibiotics), specific antimicrobials, or particular groups of antimicrobials (e.g. 4C antibiotics).

### *Types of outcomes*

Many countries do not collect sufficient regional or national surveillance data on AMR to allow analysis of the impact of policy level interventions on resistance, and surveillance definitions of resistance vary between countries [24]. As such, we chose to focus on antimicrobial use, which is an intermediary between policy interventions and AMR. Better data exists for this outcome, as prescribing and sales of antibiotics are often captured as routine health administrative data. Relevant outcome measures of antimicrobial use include self-reported antimicrobial consumption, measured antimicrobial consumption, antimicrobial prescribing, antimicrobial dosing, and/or antimicrobial sales. Secondary outcomes will include any other reported beneficial or adverse outcomes related to the intervention. These secondary outcomes might include, for example, changes in rates of AMR, or increases and decreases in the rates of hospital re-admission or return clinic visits, resulting from a government policy intervention to reduce human antimicrobial consumption.

Table 2-1. Summary of inclusion/exclusion criteria for Phase 1 and Phase 2 of screening

|                                        | Criteria                                                                                                                                                                     | <i>Include if</i>                                                                                                                                                                                                                        | <i>Exclude if</i>                                                                                                              |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Phase 1 / Title-and-Abstract Screening | 1) The study assesses a primary outcome measure of interest                                                                                                                  | Study reports on <b>human antimicrobial use</b> , including consumption, prescribing, dosing, and sales of an antibiotic, antiviral, antiparasitic, or antifungal drug.                                                                  | Study does not report on antimicrobial use or only reports on antimicrobial use in animals or agriculture.                     |
|                                        | 2) The study quantitatively evaluates the effect of an intervention                                                                                                          | Study is a <b>quantitative impact evaluation</b> .                                                                                                                                                                                       | Study is a qualitative study, editorial, commentary, review, or synthesis, or does not evaluate the impact of an intervention. |
|                                        | 3) A policy intervention is evaluated                                                                                                                                        | A <b>policy intervention</b> using education, persuasion, incentivization, coercion, training, restriction, changing the physical or social context, modelling appropriate behaviour, or reducing barriers to action is being evaluated. | Intervention was not a change to a policy (e.g. clinical study)                                                                |
| Phase 2 / Full-Text Screening          | 1) The study assesses a primary outcome measure of interest                                                                                                                  | Study reports on <b>human antimicrobial use</b> , including consumption, prescribing, dosing, and sales of an antibiotic, antiviral, antiparasitic, or antifungal drug.                                                                  | Study does not report on antimicrobial use or only reports on antimicrobial use in animals or agriculture.                     |
|                                        | 2) The study quantitatively evaluates the effect of an intervention                                                                                                          | Study is a <b>quantitative impact evaluation</b> .                                                                                                                                                                                       | Study is a qualitative study, editorial, commentary, review, or synthesis, or does not evaluate the impact of an intervention. |
|                                        | 3) The study reports on a policy intervention enacted at the government level.                                                                                               | The policy intervention was <b>enacted by a government or government agency</b> at the federal, state, provincial or municipal level.                                                                                                    | Intervention was not enacted by a government (e.g. intervention was enacted in a single hospital or network of hospitals).     |
|                                        | 4) The intervention is clearly described                                                                                                                                     | The study provides a description that includes the intervention's aim, enacting government authority, timing, and form.                                                                                                                  | The study does not describe the aim, governing body, timing of the intervention or form of the intervention.                   |
|                                        | <i>Effectiveness Review Only:</i><br>5) The study design is sufficiently rigorous to meet the minimum methodological requirements of the Cochrane Collaboration's EPOC group | <i>Effectiveness Review Only:</i> Study design is experimental or quasi-experimental, such as randomized controlled trial, interrupted time series, controlled before/after study, or it can be re-analyzed to meet this standard.       | <i>Effectiveness Review Only:</i> Study does not have a control group or use pre-intervention data, and cannot be re-analyzed. |

### 2.4.3 Information sources

Seven electronic databases will be searched: MEDLINE, CINAHL, EMBASE, PAIS Index, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science from inception to March 2017. PubMed will also be searched for relevant articles that are not indexed in MEDLINE, using the search filter developed by the Canadian Agency for Drugs and Technologies in Health [25]. The MEDLINE search strategy is available in Table 2-2; the search strategies for all databases is in Supplemental Information A2-2. The search strategies for the four biomedical databases (MEDLINE, EMBASE, CENTRAL and Pubmed) include search terms for 172 antibiotics names; this list of antibiotics was used the recent Cochrane review of interventions to improve antibiotic prescribing in hospitals [12]. The search strategies for the social science and allied health databases (CINAHL, PAIS Index, Web of Science) included the generic terms “antibiotic” and “antimicrobial” instead of specific antibiotic names. No date or language limits have been applied; we will endeavor to translate studies that are not in languages spoken by members of the study team (i.e., English and French). To identify grey literature, we will use keywords to conduct targeted web searching to identify government and civil society reports, and hand-search reference lists of included studies to identify non-indexed articles. We will also use the ProQuest Dissertations and Theses database to identify dissertations on this topic. After full-text screening, we will also contact six subject-matter experts — one from each WHO region — to identify any additional studies from their region that meet our inclusion criteria. This search strategy was designed in consultation with a health science research librarian and a government information research librarian at the University of Ottawa. The search strategy has been peer-reviewed using PRESS [26].

### 2.4.4 Screening and eligibility

We anticipate that some studies may not clearly state in the title or abstract that the intervention is based on a government policy intervention. To ensure that these articles are not inadvertently excluded, we will conduct screening and eligibility assessment in two stages. First, at the Title/Abstract screening stage, articles will be assessed to determine if they meet a set of basic criteria. Second, at the Full Text review stage, articles will be assessed thoroughly to determine whether the study meets the remaining inclusion/exclusion criteria. The inclusion/exclusion

criteria for both stages are listed in Table 2-1. Conference abstracts and proceedings will be eligible for inclusion in the descriptive review if they provide sufficient detail to describe the intervention. However, given that conference abstracts often differ in major ways from the final published papers [27], they will be excluded from the analysis in the effectiveness review.

#### 2.4.5 Data management and extraction

Search results from all electronic databases will be aggregated using EndNote X7 software. Deduplication will be carried out using the methods described by Bramer et al. [28] which aims to reduce the number of false duplicates excluded while minimizing the need for manual deduplication. Title/abstract screening, full-text Review, data extraction, and risk of bias assessment will be carried out independently by two reviewers. Any disagreements between reviewers will be resolved by consensus or in consultation with a third reviewer (SJH) if needed. A PRISMA diagram will be generated to summarize the flow of studies through the stages of the review [29]. Covidence software [30] will be used for screening. Data extraction will be conducted using a customized data extraction tool that will be pilot tested in advance. Table 2-3 summarizes the data that will be extracted from each included study.

#### 2.4.6 Quality assessment and risk of bias

Studies that meet the inclusion criteria for the effectiveness review will be assessed for bias using the risk of bias criteria developed by Cochrane's EPOC group [31] which is based upon Cochrane's Risk of Bias Tool [32] and provides advice on assessing randomised trials, controlled before-after studies and interrupted time-series studies. Studies will be assessed with regards to selection bias, performance bias, detection bias, attrition bias, reporting bias and other sources of bias. For controlled studies, we will examine baseline imbalances in antibiotic prescribing levels, and population age and sex/gender distributions. Studies will be assessed as 'low risk of bias', 'high risk of bias,' or 'unclear risk of bias' on each criterion, and a summary table will be produced for each study.

Table 2-2. MEDLINE search strategy

| Theme           | Search Terms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibiotic Use  | <p>1. Anti-Bacterial Agents/<br/> 2. Anti-infective Agents/<br/> 3. 1 or 2<br/> 4. ((antibiotic? Or alamethicin? Or amdinocillin? Or amdinocillin pivoxil? Or amikacin? Or amoxicillin? Or amoxicillin-potassium clavulanate combination? Or amphotericin? Or ampicillin? Or anisomycin? Or antimycin? Or aurodox? Or azithromycin? Or azlocillin? Or aztreonam? Or bacitracin? Or bacteriocin? Or bambermycin? Or bongkreic acid? Or brefeldin? Or butirosin sulfate? Or calcimycin? Or candidin? Or capreomycin? Or carbenicillin? Or carfecillin? Or cefaclor? Or cefadroxil? Or cefamandole? Or cefatrizine? Or cefazolin? Or cefixime? Or cefmenoxime? Or cefmetazole? Or cefonicid? Or cefoperazone? Or cefotaxime? Or cefotetan? Or cefotiam? Or cefoxitin? Or cefsulodin? Or ceftazidime? Or ceftizoxime? Or ceftriaxone? Or cefuroxime? Or cephaetrite? Or cephalixin? Or cephaloglycin? Or cephaloridine? Or cephalosporin? Or cephalothin? Or cephamycin? Or cephapirin? Or cephradine? Or chloramphenicol? Or chlortetracycline? Or citrinin? Or clarithromycin? Or clavulanic acid? Or clavulanic acid? Or clindamycin? Or cloxacillin? Or colistin? Or 21verprescri? Or dactinomycin? Or daptomycin? Or demeclocycline? Or dibekacin? Or dicloxacillin? Or dihydrostreptomycin sulfate? Or diketopiperazine? Or distamycin? Or doxycycline? Or echinomycin? Or edeine? Or enviomycin? Or erythromycin? Or erythromycin estolate? Or erythromycin ethylsuccinate? Or filipin? Or floxacillin? Or fluoroquinolone? Or 21verprescr? Or framycetin? Or fusidic acid? Or gentamicin? Or gramicidin? Or hygromycin? Or imipenem? Or josamycin? Or kanamycin? Or kitasamycin? Or lactam? Or lasalocid? Or leucomycin? Or lincomycin? Or lincosamide? Or lucensomycin? Or lymecycline? Or mepartricin? Or methacycline? Or methicillin? Or mezlocillin? Or mikamycin? Or minocycline? Or miocamycin? Or moxalactam? Or mupirocin? Or mycobacillin? Or nafcillin? Or natamycin? Or nebramycin? Or neomycin? Or netilmicin? Or netropsin? Or nigericin? Or nisin? Or norfloxacin? Or novobiocin? Or nystatin? Or ofloxacin? Or oleandomycin? Or oligomycin? Or oxacillin? Or oxytetracycline? Or paromomycin? Or penicillanic acid? Or penicillic acid? Or penicillin?? Or piperacillin? Or pivampicillin? Or polymyxin b? or polymyxin? Or pristinamycin? Or prodigiosin? Or ribostamycin? Or rifabutin? Or rifamycin? Or ristocetin? Or rolitetracycline? Or roxarsone? Or roxithromycin? Or rutamycin? Or 21verpresc? Or sisomicin? Or spectinomycin? Or spiramycin? Or streptogramin?? Or streptomycin? Or streptovaricin? Or sulbactam? Or sulbenicillin? Or sulfamerazine? Or sulfamethoxypyridazine? Or talampicillin? Or teicoplanin? Or tetracycline? Or thiamphenicol? Or thienamycin? Or thioestrepton? Or ticarcillin? Or tobramycin? Or troleandomycin? Or tunicamycin? Or tylosin? Or tyrocidine? Or tyrothricin? Or valinomycin? Or vancomycin? Or vernamycin? Or viomycin? Or virginiamycin? Or beta-lactams adj2 (use* or misuse or consume or consumption or intake or dose or dosage or prescription* or 21verpresc* or 21verprescribe* or sale* or rate*)).ab,ti.<br/> 5. 3 and 4</p> |
| Change / Impact | <p>2. (adjust* or alter* or change or changes or changing or control* or decreas* or limit* or modify or modified or modifying or reduce or reducing or reduction* or restrict* or appropriate or inappropriate or rational* or irrational*).ab,ti.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Policy          | <p>7. exp policy/<br/> 8. exp policy making/<br/> 9. exp legislation as Topic/<br/> 10. exp Government/<br/> 11. Government Regulation/<br/> 12. (program* or campaign* or policy or policies or guideline* or ban or banned or Regulat* or law or laws or prohibit* or restrict* or legislat* or report* or tax* or audit* or formular* or expenditure* or spending or label* or market* or advertis* or consultation*).ab,ti.<br/> 13. (health\$ adj2 (policy or policies or planning or priorit\$)).ab,ti.<br/> 14. 7 or 8 or 9 or 10 or 11 or 12 or 13</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|                 | 15. 5 and 6 and 14                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Humans Only     | <p>16. exp animals/ not humans.sh.<br/> 17. 15 not 16</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

Table 2-3. Data extraction fields

|                                            |                                                                                                                                                                                              |
|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b><i>General Information</i></b>          | Authors<br>Publication year<br>Journal<br>Country of study                                                                                                                                   |
| <b><i>Study Characteristics</i></b>        | Intervention aim<br>Study aim<br>Study design<br>Study duration, including duration of pre-intervention period and duration of follow-up                                                     |
| <b><i>Study Participants</i></b>           | Description of population of interest<br>Method of recruitment<br>Inclusion/exclusion criteria for study participants<br>Sample size calculation/power calculation                           |
| <b><i>Intervention Characteristics</i></b> | Enacting government authority<br>Description of policy intervention<br>Description of intervention groups<br>Number of intervention groups<br>Intervention duration and timing               |
| <b><i>Data Analysis</i></b>                | Type of analyses conducted<br>Statistical tests conducted<br>Confounders                                                                                                                     |
| <b><i>Intervention Effects</i></b>         | Baseline and post-intervention results<br>Estimates of effect, including by time or subgroup as appropriate<br>Secondary outcomes: beneficial outcomes<br>Secondary outcomes: adverse events |

## 2.4.7 Strategy for analysis

### *Descriptive review*

Data collected for the descriptive review of government policy interventions will be tabulated and summarized narratively. Articles will be categorized into seven groups by policy type based on the Behaviour Change Wheel framework [23]: communication/marketing, guidelines, fiscal, regulation, legislation, environmental/social planning, and service provision. We will produce summary figures to report on the characteristics of each intervention type.

### *Effectiveness review*

The government policy interventions that we identify are likely to be implemented across many populations, settings, and healthcare systems and with different goals. Some studies may aim to reduce all antimicrobial use, while others may target inappropriate antimicrobial use, or aim to reduce the use of specific antimicrobial agents. Given this diversity, it would be useful to generate estimates of effect by policy type. Therefore, if appropriate, we will conduct meta-analyses as part of our effectiveness review using the data from those studies that employed a rigorous study design. To be included in the meta-analysis, quasi-experimental studies will need to meet the minimum methodological requirements of the EPOC group. The two preferred analysis methods for interrupted time series studies are segmented regression analysis with time trends before and after the intervention adjusting for autocorrelation and any periodic changes, or ARIMA analysis. Results for outcomes can be presented as changes along two dimensions: change in level, which is the immediate effect of the intervention, and change in slope, which is the change in the trend from pre- to post- intervention. Change in level is measured as the difference between the fitted value for the first post-intervention data point (e.g., one month after the intervention) minus the predicted outcome for the first post-intervention data point based on the pre-intervention slope only. Change in slope is the change in the trend from pre- to post-intervention and can be used to determine the long-term effect of the intervention. Since the interpretation of changes in slope can be difficult, we anticipate presenting the long-term effects of the interventions as proposed for the immediate effects: for example, the difference between the fitted value six months post-intervention (half a year after the intervention) minus the predicted outcome six months post-intervention based on the pre-intervention slope only. As

appropriate, effects after one year, two years etc. will be measured similarly. Where possible, we will re-analyse the results of any interrupted time series studies that have not used these analytic strategies; we will also re-analyse the results of uncontrolled before and after studies using segmented regression analysis if the studies have at least three measurements pre- and post-intervention. Where necessary, time series data will be extracted from tables and figures using a software package that reads values from images.

If feasible and appropriate, meta-analysis will be conducted for each category of policy described in the descriptive review. We do not anticipate that studies will share a common unit of measurement; as such, individual study effect estimates will be generated for continuous outcomes using standardized mean differences, and odds ratios will be converted to standardized mean difference. A random-effects model will be used for meta-analysis. We will present forest plots to explore variation due to the inclusion of non-randomized studies. If more than 10 studies are included in the meta-analysis, we will investigate publication bias using funnel plots. Asymmetry will be assessed visually and using the Egger test [32], and additional exploratory analyses will be conducted if we identify evidence of reporting bias. If individual studies report the necessary data, we will undertake a sex- and gender- based analysis to determine whether government interventions have differential effects across these subgroups. Additionally, if we determine that there are sufficient sex- and gender-based data from studies on a specific policy (e.g. restriction of over-the-counter antimicrobial sales), we will determine whether meta-analysis is feasible in this case. Sensitivity analyses will be conducted to consider the impact of dropping weaker study designs and studies at high risk of bias.

We expect to see substantial variability across studies and will explore this using the  $I^2$  statistic [33]. In line with the Cochrane Handbook's guideline that an  $I^2$  statistic  $>50\%$  may indicate substantial heterogeneity [32], we will pool studies and conduct exploratory subgroup analyses if we find an  $I^2$  greater than this value. Planned subgroup analyses include interventions that have been implemented in low- and middle-income countries, and interventions that targeted particular audiences, for example, health care providers.

Should meta-analysis not be feasible, a narrative review and structured synthesis of the evidence will be conducted using the studies with rigorous study designs. Within and across the categories

of policy intervention described above, we will report on ranges of effects, heterogeneity, and quality of the evidence. If appropriate, we will also report on the intervention effects by target population (e.g., health professionals vs. general public) and, if data are available, by sex and gender.

#### **2.4.8 Missing data**

Where necessary statistical data are missing (e.g., standard deviations), we will contact the study authors directly using the email address of the corresponding author provided in the article or by searching the Internet for another email address for the corresponding author if the published address is invalid. Authors will be contacted twice before data are marked as missing. Any missing data that we are not able to obtain will be documented in the data extraction form.

If we identify cluster randomized trials that have not appropriately accounted for the unit of randomization, we will contact the authors for an estimate of the intra-cluster correlation coefficient or use external databases to impute an appropriate estimate to adjust for clustering.

#### **2.4.9 Interpretation of review findings**

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for rating the quality of evidence will be used in presenting the findings of this systematic review, as recommended by the Cochrane Collaboration [34]. The major outcomes for the effectiveness review will be presented in a summary of findings table.

### **2.5 Discussion**

To our knowledge, this will be the first systematic review to investigate the range of government interventions on antibiotic use, and to consider the impact of government policy or regulatory action on antibiotic use. In identifying and describing government level interventions (aim 1) using a systematic search strategy, we will be creating a valuable tool for policy makers. Since we will be conducting this search systematically, we will be maximizing our likelihood of identifying the full set of government policy interventions that have been implemented and evaluated to date. In transparently synthesizing evidence that assesses the effectiveness of these interventions, we can offer higher-quality evidence from around the world to inform the consideration,

prioritization and adoption of new government policies to reduce human antimicrobial use. The identification of any gaps in the evidence about the effectiveness of different government policy interventions will also help inform future priorities for researchers and research funders.

### *Strengths and limitations*

As the first systematic review to focus on government policy interventions addressing AMR, the review will provide valuable information for policymakers, public health practitioners, and researchers. Our search strategy has been carefully designed in consultation with two research librarians at the University of Ottawa — a health research librarian and a government research librarian — to incorporate databases from multiple academic disciplines, and to employ several grey literature searching techniques to assist in locating relevant non-academic information sources. The protocol has been designed to meet the Cochrane Collaboration's standards for conducting a systematic review.

We recognize the potential for publication bias in this review, particularly since much of the data we seek may not reside in easily searchable databases of peer-reviewed academic literature. We have gone to great lengths in designing this study to minimize the impact of such publication bias. First, we consulted with an additional librarian focused on government research to identify strategies for identifying government documents online. Second, we will be consulting with subject-matter experts to identify other sources. These two mechanisms, along with hand-searching reference lists of articles will assist us in identifying the relevant literature.

A second concern for this study is data quality. Since we are investigating government policy interventions, we do not expect to identify, for example, many randomized controlled studies. Although there is a greater risk of bias associated with quasi-experimental analyses, we have chosen to include these studies in addition to randomized controlled trials in both the descriptive and effectiveness reviews. In so doing, we will identify a broader range of government policy interventions, rather than identifying only those that suit the randomized controlled design. For the effectiveness review, we have chosen to include quasi-experimental studies, but to analyze only those studies with more rigorous study designs. This way we can place greater confidence in the estimates of effectiveness in these studies as they must, at the very least, include control

groups or pre-intervention data. Additionally, all studies will be analysed for risk of bias and in accordance with GRADE quality of evidence criteria.

## 2.6 Declarations

**Acknowledgements:** We would like to thank librarians Catherine McGoveran and Lindsey Sikora at the University of Ottawa who provided advice, support, and peer review for the development of our search strategy. We would also like to thank Miriam Nkangu and Theresa Tam for their advice on this project.

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**Competing interests:** SJH and MM have both advised several governments on interventions they could use to address antimicrobial resistance in their personal capacities. The other authors declare that they have no competing interests.

**Ethics Approval:** Not Applicable

**Consent for Publication:** Not Applicable

**Availability of data and material:** Not Applicable

## 2.7 List of supplemental files

The following can be found in the supplemental information for Chapter 2:

|      |                                                                                                                                                                |
|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A2-1 | PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) checklist: recommended items to address in a systematic review protocol |
| A2-2 | Additional search strategies                                                                                                                                   |

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### **3 Reducing human antimicrobial use: a systematic evidence map of government policy interventions**

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### 3.1 Preface

This published manuscript reports on the *descriptive review* described in Chapter 2, and addresses the first aim of my dissertation: to investigate and characterize the role of government policy interventions on AMR and antimicrobial use, to understand which policy levers have been used, appraise the state of the evidence, and identify which interventions have proven to be effective.

I conceived the idea for this systematic review along with Dr. Hoffman and I led the design of the protocol and methodology. I developed the systematic search strategy in collaboration with 3 research librarians (Lindsey Sikora, Michael Boutet and Catherine McGoveran) at the University of Ottawa. I screened all studies by title and abstract with Global Strategy Lab research assistants Sara Jones, A Srivastava, Ranjana Nagi as second reviewers. I screened all-full text studies with Ranjana Nagi and Miriam Nkangu as second reviewers. I led the data interpretation with input from all co-authors and wrote the first draft of this manuscript. Drs. Hoffman and Grimshaw supervised the design of the protocol and methodology and critically revised the manuscript. Drs Taljaard, Mendelson, and Tam provided valuable methodological and subject-matter expertise to inform this review and revised the manuscript. All authors have read and approved the final manuscript, which was published in the journal *PLOS Medicine* in 2019.

**Manuscript status:** Published

**Ethics approval:** Not required

## 3.2 Abstract

**Background:** Growing political attention to antimicrobial resistance (AMR) offers a rare opportunity for achieving meaningful action. Many governments have developed national AMR action plans, but most have not yet implemented policy interventions to reduce antimicrobial overuse. A systematic evidence map can support governments in making evidence-informed decisions about implementing programs to reduce AMR, by identifying, describing, and assessing the full range of evaluated government policy options to reduce antimicrobial use in humans.

**Methods and findings:** Seven databases were searched from inception to January 28, 2019, (MEDLINE, CINAHL, EMBASE, PAIS Index, Cochrane Central Register of Controlled Trials, Web of Science, and PubMed). We identified studies that (1) clearly described a government policy intervention aimed at reducing human antimicrobial use, and (2) applied a quantitative design to measure the impact. We found 69 unique evaluations of government policy interventions carried out across 4 of the 6 WHO regions. These evaluations included randomized controlled trials ( $n = 4$ ), non-randomized controlled trials ( $n = 3$ ), controlled before-and-after designs ( $n = 7$ ), interrupted time series designs ( $n = 25$ ), uncontrolled before-and-after designs ( $n = 18$ ), descriptive designs ( $n = 10$ ), and cohort designs ( $n = 2$ ). From these we identified 17 unique policy options for governments to reduce the human use of antimicrobials. Many studies evaluated public awareness campaigns ( $n = 17$ ) and antimicrobial guidelines ( $n = 13$ ); however, others offered different policy options such as professional regulation, restricted reimbursement, pay for performance, and prescription requirements. Identifying these policies can inform the development of future policies and evaluations in different contexts and health systems. Limitations of our study include the possible omission of unpublished initiatives, and that policies not evaluated with respect to antimicrobial use have not been captured in this review.

**Conclusions:** To our knowledge this is the first study to provide policy makers with synthesized evidence on specific government policy interventions addressing AMR. In the future, governments should ensure that AMR policy interventions are evaluated using rigorous study designs and that study results are published.

**Protocol registration:** PROSPERO CRD42017067514

### **3.3 Author summary**

#### **Why was this study done?**

- Despite global commitments to reduce antimicrobial resistance and protect the effectiveness of antimicrobials, most countries have not yet started implementing government policies to reduce their overuse and misuse of antimicrobials.
- To the best of our knowledge, no evidence syntheses have attempted to identify the policy options available to government policy makers to tackle antimicrobial resistance by reducing antimicrobial use in humans.

#### **What did the researchers do and find?**

- We searched 7 academic databases to identify impact evaluations of government policy interventions aiming to reduce human antimicrobial use that were published in any language before January 28, 2019.
- We found 69 studies that evaluated government policy interventions to reduce antimicrobial use around the world. From these, we were able to describe 17 different types of policies that governments have used to tackle this major driver of antimicrobial resistance in humans.
- Commonly used policy strategies included public awareness campaigns and antimicrobial guidelines; however, other policy strategies focused on vaccination, stewardship, and changing regulations around prescribing and reimbursement.
- We found 4 randomized controlled trials and 35 studies using rigorous quasi-experimental designs. The remaining 30 studies used uncontrolled and descriptive study designs.

#### **What do these findings mean?**

- Our systematic evidence map suggests that governments have a variety of policy options at their disposal to respond to the growing threat of antimicrobial resistance.
- Unfortunately, most existing policy options have not been rigorously evaluated, which limits their usefulness in planning future policy interventions.
- To avoid wasting public resources, governments should ensure that future antimicrobial resistance policy interventions are evaluated using rigorous study designs, and that study results are published.

### 3.4 Introduction

Antimicrobial resistance (AMR) is currently high on the global political agenda. This attention has opened a rare policy window for achieving meaningful action on AMR [1–7]. Although the potential for AMR has been recognized since the earliest days of antibiotics [8], the misuse and overuse of antimicrobials has persisted over decades, contributing to the development of resistance [9]. AMR is now expected to have severe consequences for human health, social well-being, and economic development. AMR has already rendered some infections untreatable using existing antimicrobials [10,11], and global projections suggest that AMR could derail the Sustainable Development Goals, driving an estimated 24 million people into extreme poverty and exacerbating global economic inequality [12], and potentially resulting in tens of millions of deaths [13].

Successfully overcoming the threat posed by AMR will require multi-sectoral and multi-jurisdictional cooperation to protect the effectiveness of existing and future antimicrobials [2,3,5]. Recent political initiatives addressing AMR, including the 2016 United Nations resolution [14] and the 2017 Berlin Declaration of the G20 Health Ministers [15], are promising signs that governments and international agencies are mobilizing to act on AMR. The 194 member states of the World Health Organization (WHO) agreed to develop national AMR action plans by 2017 [16], and countries have largely responded [17].

Despite these positive steps, most countries have not yet started implementing policies to reduce their overuse and misuse of antimicrobials [17]. Evidence from high-income countries suggests that reducing antimicrobial use is associated with lower rates of resistance [9], yet there is limited evidence on what types of government policy interventions effectively reduce antimicrobial use. Typically, government policy changes are useful tools for improving public health when the health threat requires widespread change and uniform compliance with a set of minimum standards [18]. However, research on AMR has principally focused on changing the prescribing behaviours of individual physicians [19], rather than creating large-scale reductions in antimicrobial use through population-wide interventions.

Given that governments are currently grappling with the challenge of implementing AMR policies under their recently developed national action plans, a focus on the potential impact of

government policy interventions on antimicrobial use is timely. Governments are currently attempting to weigh the merits of numerous types of policy interventions that could safely reduce antimicrobial use, utilizing policy levers such as legislation, taxation, economic incentives, funding support, public awareness campaigns, and regulation of professionals and businesses whose work might affect AMR [18]. Policy makers would benefit from a tool that catalogues and assesses the government policy responses that have been used in various contexts and health system settings. Thus, we undertook a systematic evidence mapping project to support evidence-informed action on AMR at the government level, by identifying, describing, and assessing the full range of government policy interventions aiming to reduce human antimicrobial use that have been implemented and evaluated.

### **3.5 Methods**

A protocol describing the full methods of this project was published in advance [20] and registered in PROSPERO (CRD42017067514). Deviations from the protocol are noted below, and the paper has been reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [21]. In brief, we produced an evidence map that identifies government policy interventions aiming to reduce antimicrobial use in humans. To be included in the evidence map, studies had to (1) clearly describe a government policy intervention aiming to reduce human antimicrobial use and (2) apply a quantitative design to measure the impact.

#### **3.5.1 Search strategy and selection criteria**

We searched 7 electronic databases from medicine and the social sciences (MEDLINE, CINAHL, EMBASE, PAIS Index, Cochrane Central Register of Controlled Trials, Web of Science, and PubMed [articles not indexed in MEDLINE]) from inception to January 28, 2019, without language or date limits. Targeted web searching was used to identify grey literature, and the ProQuest Dissertations & Theses database was used to identify dissertations. We contacted subject-matter experts in each of WHO's 6 regions to identify missing studies.

We screened titles and abstracts against 3 inclusion criteria: (1) the evaluated intervention was a policy intervention defined as an intervention enacted by a government or government agency at

the federal, state, provincial, or municipal level that aimed to change antimicrobial use through education, restriction, incentivization, coercion, training, persuasion, changing the physical or social context, modelling appropriate behaviour, or reducing barriers to action [22]; (2) the study quantitatively evaluated the effect of the intervention; and (3) the study assessed an outcome measure related to human antimicrobial use such as consumption, dosing, prescribing, or sales of an antibiotic, antiviral, antiparasitic, or antifungal drug. Examples of interventions include regulating the sales of antimicrobials, restricting the use of last-resort antibiotics, and launching public awareness campaigns. Titles and abstracts were each independently screened by 2 reviewers (SRVK and S Jones, A Srivastava, or RN), and disagreements were resolved by consensus. The full text of potentially relevant studies was screened by 2 reviewers (SRVK and MN or RN). Non-English articles were translated using Google Translate, or a translation was requested from the corresponding author.

### 3.5.2 Data analysis

Data on study characteristics, study participants, interventions, analyses, and measured effects were extracted in duplicate by 2 reviewers (SRVK and MN or RN) using a customized data extraction tool (see Supplemental Information A3-3). In consultation with SJH and JMG, SRVK grouped studies according to the Behaviour Change Wheel framework's intervention functions and our definition of policy intervention [22]. Where appropriate, studies were coded with multiple Behaviour Change Wheel intervention functions; however, studies were coded with a single Behaviour Change Wheel policy approach. We inductively identified and described policy options based on groupings of similar interventions, and coded studies according to their region, study design, and the intervention functions of the Behaviour Change Wheel. WHO regions were used to group countries; the region of the Americas was subdivided into Canada/US and Latin America.

## 3.6 Results

From 13,635 abstracts, we identified 69 evaluations of government policy interventions to reduce human antimicrobial use. Fig 1 shows the full summary of screening and inclusion. Of the 69 included studies, 67 focused on antibiotics and 2 on antimalarials; no studies aimed to reduce the

use of other antimicrobial agents. The majority of policies targeted healthcare workers ( $n = 44$ ) or healthcare workers and the community ( $n = 13$ ), while the remaining 12 policies exclusively targeted a community audience. We found evaluations in 4 of the 6 WHO regions: the Americas ( $n = 24$ ), Western Pacific ( $n = 22$ ), Europe ( $n = 21$ ), and Africa ( $n = 2$ ), but did not identify any evaluations from the South East Asian region or the Eastern Mediterranean region. Of the 69 included studies, 67 were published in English and 2 were published in Spanish.

Using our definition of policy intervention, we organized studies according to the policy categories of the Behaviour Change Wheel framework. Table 3-1 describes the interventions of the included studies. The largest grouping of policies was regulatory interventions ( $n = 27$ ), followed by guidelines ( $n = 18$ ), communication policies ( $n = 17$ ), legislation ( $n = 3$ ), and fiscal measures ( $n = 3$ ). One evaluation was identified for service provision policies; however, we did not identify any social planning policies. Regulatory policies ( $n = 20/27$ ) and legislation ( $n = 3/3$ ) were largely organized at the national level. Communication policies were organized at different levels of government; 8 were at the national level, 3 were at the state/provincial level, and 6 were at the regional level (municipality, county, or other geographic unit). Similarly, 12 of the guidelines were at the national level, 2 were at the state/provincial level, and 4 were at the regional level. One of the fiscal measures policies was at the national level, and 2 were at the regional level. The sole service provision policy was organized at the national level.

The majority of the 69 included studies were retrospective evaluations using routinely collected data from health insurance databases or electronic health records ( $n = 46$ ), or sales data from IMS Health ( $n = 14$ ). Four of the included studies were randomized controlled trials, 3 were non-randomized controlled trials, 7 used non-randomized controlled before-and-after designs, 25 used time series designs, 18 used uncontrolled before-and-after designs, 10 used descriptive methods, and 2 used cohort study designs (Box 3-1). The included studies predominantly used antibiotic consumption measured as defined daily doses ( $n = 25$ ) or physician prescribing rates ( $n = 26$ ) as an outcome measure.

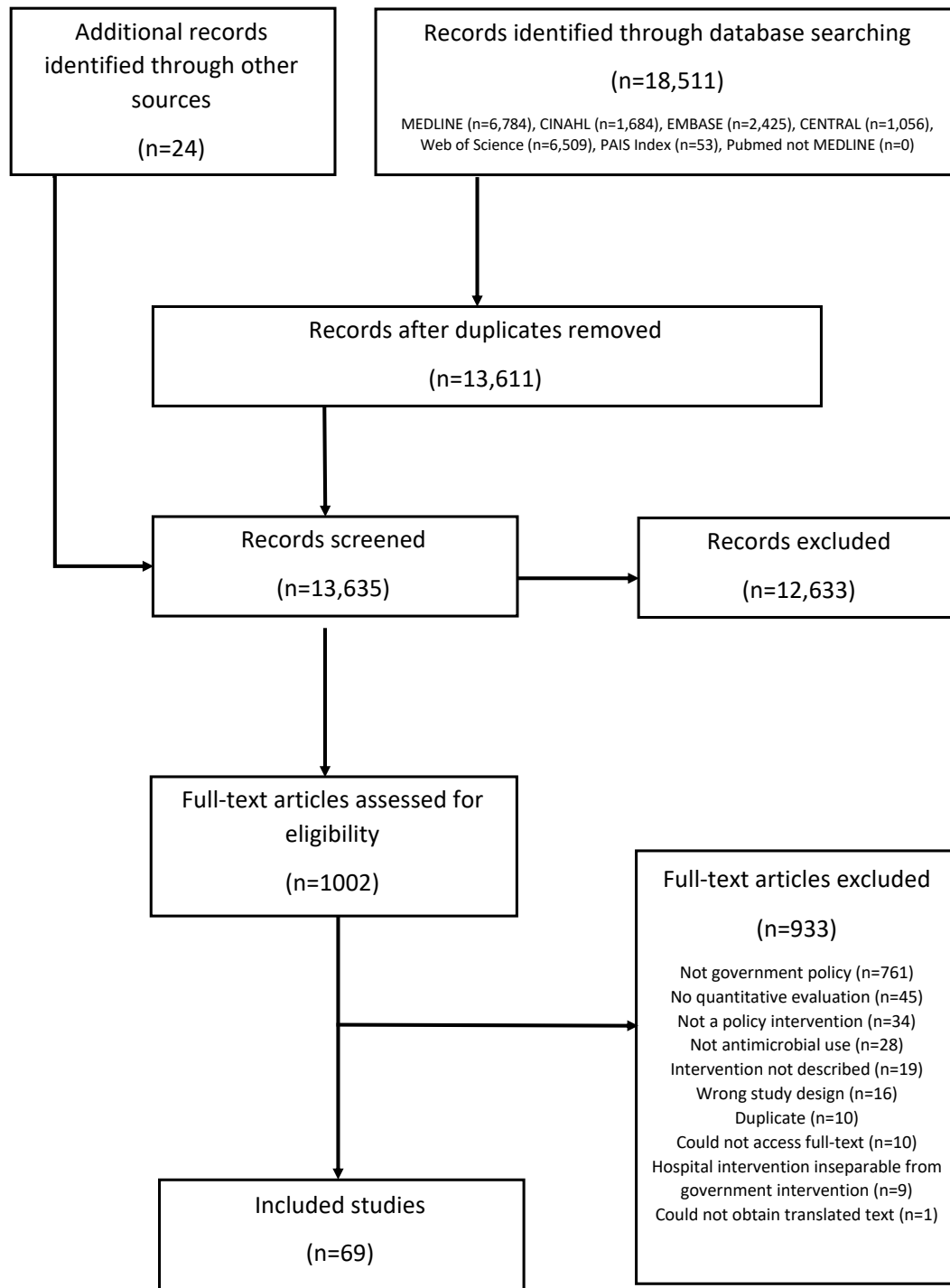


Figure 3-1 – PRISMA summary flow chart.  
CENTRAL, Cochrane Central Register of Controlled Trials

Table 3-1. Included studies by policy approach.

| Policy approach                             | Description*                                                                               | Studies |
|---------------------------------------------|--------------------------------------------------------------------------------------------|---------|
| Regulatory interventions                    | Establishing rules or principles of behaviour or practice                                  | [23–49] |
| Guideline interventions                     | Creating documents that recommend or mandate practice                                      | [50–67] |
| Communication interventions                 | Using print, electronic, telephonic, or broadcast media                                    | [68–84] |
| Legislation interventions                   | Making or changing laws                                                                    | [85–87] |
| Service provision interventions             | Delivering a service                                                                       | [88]    |
| Environmental/social planning interventions | Designing or controlling the physical or social environment                                | None    |
| Fiscal interventions                        | Using the tax system and other financial measures to reduce or increase the financial cost | [89–91] |

\*Policy approach descriptions from the Behaviour Change Wheel framework [22].

Box 3-1. Definitions of included study designs.

**Randomized controlled trial:** An experimental study in which people are allocated to different interventions using methods that are random.

**Non-randomized controlled trial:** An experimental study in which people are allocated to different interventions using methods that are not random.

**Time series design:** A study that uses observations at multiple time points before and after an intervention. The design attempts to detect whether the intervention has had an effect significantly greater than any underlying trend over time.

**Non-randomized controlled before-and-after design:** A study in which observations are made before and after the implementation of an intervention, both in a group that receives the intervention and in a control group that does not.

**Uncontrolled before-and-after design:** A study in which observations are made before and after the implementation of an intervention in a single intervention group.

**Cohort design:** A study in which designated groups of people are followed over time to ascertain the occurrence of an event.

**Descriptive design:** A study that employs observational, cross-sectional, ecological, or other descriptive methods, to infer or hypothesize the impact of an intervention.

All definitions except “descriptive design” and “cohort design” were taken from Cochrane’s Effective Practice and Organisation of Care Group [92].

Among the 69 included evaluations, we identified 17 distinct policy options that have been evaluated for their ability to reduce antimicrobial use. Table 3-2 summarizes these policy options and lists the studies that evaluated specific manifestations of them. By far the most common of these policy options were informational strategies, including public awareness campaigns ( $n = 17$ ), which informed healthcare workers and/or the public about AMR and antimicrobial overuse, and antimicrobial guidelines ( $n = 13$ ), which provided information to healthcare workers on the preferred use of antimicrobial drugs or preferred treatments for resistant infections. These strategies were widely used across most regions, and in particular represented a large proportion of the interventions evaluated in Canada/US [52,53,59,61,62,69,74,76–78,80,81] and Europe [63,65,67,68,70,71,73,75,79,82,90,91].

Other policy options were less commonly reported and tended to group regionally, as can be seen in Fig 2. For example, 7 studies were categorized as “prescription requirement” policies, which were regulatory and legislative policies essentially banning the sale of over-the-counter antibiotics by requiring a prescription from a healthcare professional [24,25,39,40,44,85,86]. These policies were implemented starting in the late 1990s in countries or regions in Latin America where over-the-counter antibiotic sales were not previously prohibited, or where existing regulations were not enforced. Countries in WHO’s Western Pacific region tried a diverse range of strategies, most of which were evaluated only once or twice. These policies were largely implemented in China [27,29,33,42,43,45–49,60,66,89], South Korea [32,49,57,87], and Taiwan [26,30], and included disclosure requirements for hospitals to post their antibiotic use rates online, professional regulation strategies that changed the codes of practice around the prescribing and dispensing of antibiotics by different health professions, and reimbursement penalties for physicians, who were not paid for their services unless their prescriptions met the guidelines for antibiotic prescribing. Along similar lines, 1 European country (Denmark) explored using reimbursement penalties targeting patients, where the national health insurance plan reimbursed patients a smaller proportion of the antibiotic cost than was previously reimbursed [41]. Three studies in Canada/US [34,36,38] and 1 each in Europe [31] and the Western Pacific [30] also tried reimbursement restrictions, where the patient was not reimbursed the cost of an antibiotic by their national health insurance plan unless the physician met particular guidelines such as proving the existence of an infection or consulting with an

infectious disease specialist. In the African region, we found only 2 studies, both targeting the use of antimalarial drugs, and both employing published guidelines to change prescribing [50,51]. Some national-level interventions were evaluated in multiple studies using different methods, populations, and evaluation time frames; these included the ban on over-the-counter sales of antimicrobials in Chile [24,25,44], the Antibiotics Are Not Automatic campaign in France [70,71,73,82], and the national essential medicines policy in China [29,45,46,49].

Table 3-2. Description of policy options that have aimed to reduce human antimicrobial consumption.

| Policy option                                                                                                | Description                                                                                                                                                                       | Studies                |
|--------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| <b>Policies to improve infection prevention and stewardship efforts</b>                                      |                                                                                                                                                                                   |                        |
| Published antimicrobial guidelines                                                                           | Information provided to healthcare workers on the preferred use of antimicrobial drugs, or preferred treatment for resistant infections                                           | [50–53,55,57–64]       |
| Vaccination guidelines                                                                                       | Guidelines and policies recommending vaccinations likely to reduce antimicrobial use                                                                                              | [90]                   |
| Committee development                                                                                        | Guidelines encouraging the formation of expert groups on stewardship and resistance                                                                                               | [56]                   |
| Stewardship                                                                                                  | A requirement that specific stewardship policies be introduced                                                                                                                    | [27,33,65]             |
| Disclosure                                                                                                   | A requirement for public disclosure of antibiotic use level                                                                                                                       | [32]                   |
| Funding                                                                                                      | Provision of funding towards a specific stewardship program or goal                                                                                                               | [88]                   |
| <b>Policies to educate health professionals, policy makers, and the public on sustainable antibiotic use</b> |                                                                                                                                                                                   |                        |
| Public awareness                                                                                             | Public educational campaigns drawing on media and internet to inform healthcare workers and/or the public about antimicrobial resistance                                          | [68–84]                |
| Feedback                                                                                                     | Audit and feedback to providers about their antimicrobial use habits                                                                                                              | [54,66]                |
| <b>Policies to change incentives that encourage antibiotic overuse and misuse</b>                            |                                                                                                                                                                                   |                        |
| Reimbursement penalty for patients                                                                           | A reduction in the amount that a patient is reimbursed for a prescription by a drug plan                                                                                          | [41]                   |
| Reimbursement penalty for prescribers                                                                        | The prescriber is not paid for their services unless the guidelines for prescribing antimicrobials are met                                                                        | [26]                   |
| Restricted reimbursement                                                                                     | Introduces an additional step in the prescribing pathway such as consultation with a specialist or provision of proof of infection in order for the prescription to be reimbursed | [30,31,34,36,38]       |
| Restricted use                                                                                               | Introduces an additional step in the prescribing pathway such as consultation with a specialist or provision of proof of infection in order for the prescription to be dispensed  | [23,28,35,43,47,48]    |
| Pay for performance                                                                                          | Pay-for-performance funding provided to healthcare centres that meet particular antimicrobial-use-related guidelines and targets                                                  | [67,89,91]             |
| <b>Policies to change features of the health system</b>                                                      |                                                                                                                                                                                   |                        |
| Professional regulation                                                                                      | Changes to codes of practice with regards to what can be done by members of different healthcare professions                                                                      | [87]                   |
| Prescription requirement                                                                                     | Requirement of a prescription to purchase antimicrobial drugs                                                                                                                     | [24,25,39,40,44,85,86] |
| Formulary change                                                                                             | Removal of a drug from the formulary or addition of a drug to the formulary                                                                                                       | [37]                   |
| National essential medicines policies                                                                        | Introduction of policies in line with WHO's essential medicines policies                                                                                                          | [29,45,46,49]          |

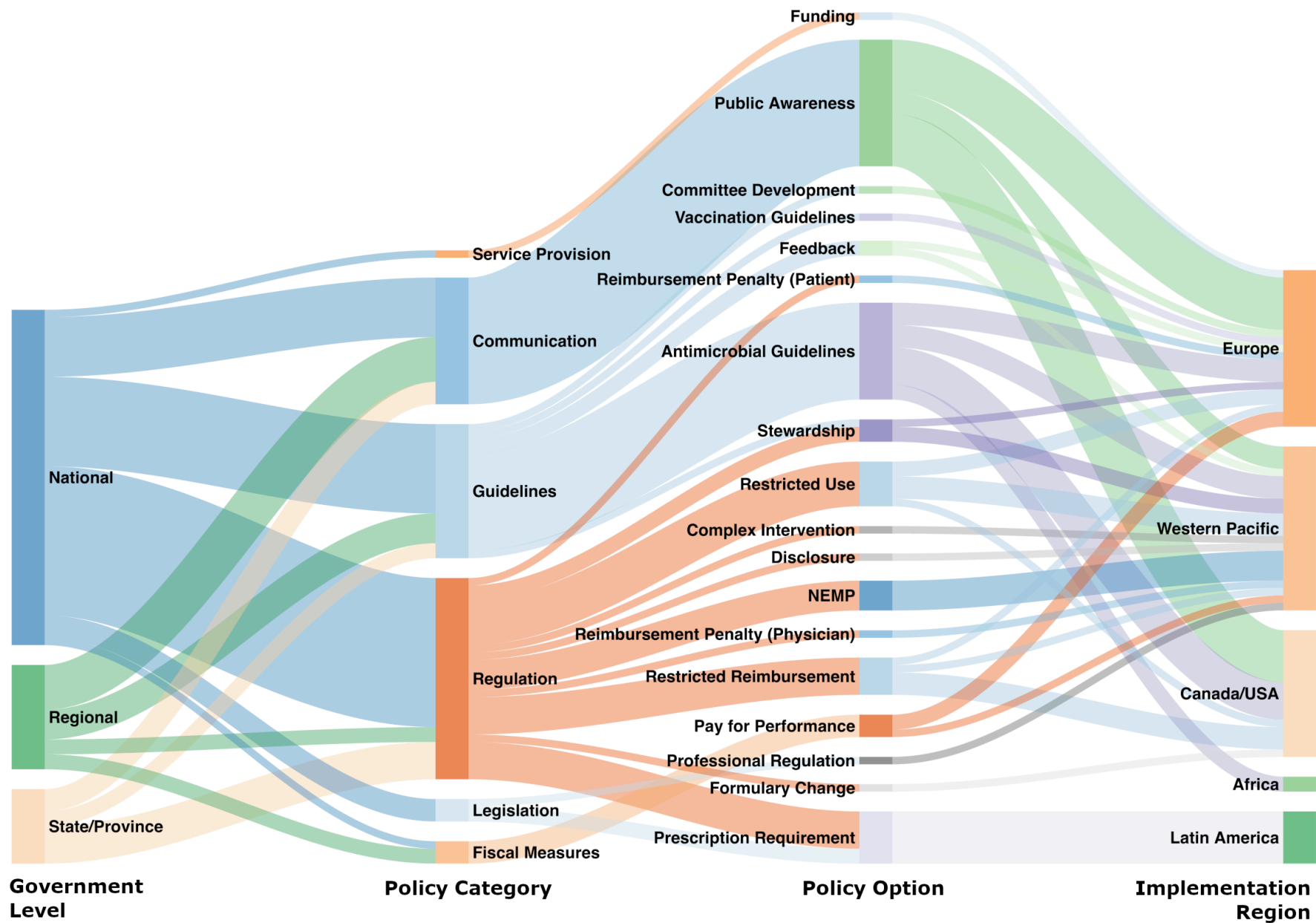


Figure 3-2 - Evidence map of the relationships between government level, policy approach (policy category), policy option, and region of implementation. The thickness of lines represents the proportions of included studies. The colors show the grouping of policies and trace the flow of policies between categories. NEMP, national essential medicines policy.

## 3.7 Discussion

### 3.7.1 Principal findings

Around the world, governments are currently working to develop policy responses to the growing threat of AMR. In our evidence map, we identified 69 evaluation studies looking at the impact of policy interventions on antimicrobial use across 4 of WHO's 6 regions. From this search, we were able to identify 17 different policy options and examples of each that governments can use to inform their future AMR policies.

Many of the policy options identified in this map were evaluated in only a few studies. These evaluations were highly regionalized, which likely results from similarities between contexts and health systems within regions of a country, or in neighbouring countries. Policy makers in other parts of the world who operate with similar contextual problems or health systems may find these policies useful models for policy development in their countries. For example, the prescription requirement policies [24,25,39,40,44,85,86] were implemented in 5 Latin American countries where over-the-counter antibiotic sales were formally or informally permitted. While this type of policy would not be useful in Canada and the US, where prescriptions are already required, the regulations and legislation used in Latin America may be a useful model for many other countries, such as those in Africa, the Eastern Mediterranean, South East Asia, and the Western Pacific that currently allow over-the-counter sales of antibiotics, and where overuse of antimicrobials is likely to decrease in response to this restriction.

Similarly, we identified several policies that used electronic medical records and national health insurance systems to change physician and patient behaviours around antimicrobial use. These policies, including restricted reimbursements and reimbursement penalties for patients and prescribers, were used in high-income jurisdictions such as Canada, Sweden, and Taiwan. These policies take a different approach, targeting overuse through restrictive and coercive financial mechanisms.

### 3.7.2 Policy implications

Given the complexity of AMR, and the need to balance conservation of antimicrobial effectiveness with ensuring access to appropriate antimicrobials for those who need them [2], there is unlikely to be a “silver bullet” intervention that solves the global AMR problem. These 17 government policy interventions offer a starting point for countries to adapt to their local context. Since most of these 17 policies have been evaluated only once or twice and in particular contexts, it would be unwise to draw strong conclusions about their effectiveness. Indeed, many of these interventions were evaluated using low-quality, non-randomized designs; while many systematic reviews would exclude studies on this basis, we retained them in our evidence map to ensure that we captured the widest range of policy options possible. To avoid future waste of public resources, and in line with WHO recommendations for national action on AMR [93], governments should ensure that AMR policy interventions are evaluated using rigorous study designs and that study results are published.

Not surprisingly, our evidence map found that public awareness campaigns and guidelines were commonly used strategies for reducing antimicrobial use across all regions. These educational approaches are traditional public health strategies and have been promoted by both WHO and the UK’s Review on Antimicrobial Resistance [13]. While launched at the government level, many of these programs and policies still focus on changing the practice of individual prescribers, usually physicians, rather than targeting other healthcare professionals or altering healthcare structures to reduce overuse and misuse of antibiotics. Different governments have different policy levers at their disposal, including the ability to implement complex regulatory, legislative, fiscal, and service provision policies, which could potentially bring about more dramatic change than policies focused on individual prescriber behaviour change. Many approaches to reducing antimicrobial consumption can only be implemented by governments, including many of the policies we identified (e.g., professional regulation, restricted reimbursement, and prescription requirements) as well as policies identified by others in academic literature for which we did not find any evaluations (e.g., creating human-only classes of antimicrobials [1], banning direct-to-consumer advertising [3,6], and using tax or fiscal measures [94]). Given that governments can employ a broad range of policy options beyond

public awareness campaigns and guidelines, the full range of possible AMR policies should be further explored.

### **3.7.3 Strengths and limitations**

Our evidence map represents the first systematic effort, to our knowledge, to identify government policy interventions and specific policy mechanisms for reducing human antimicrobial use. We worked with 3 research librarians from 3 disciplines and contacted experts around the world to identify published and grey literature on government and AMR policies. However, we recognize that there are implemented policies (e.g., [95]) that have not been captured in this evidence map. We suspect that these studies have not been evaluated, or have not been evaluated with respect to antimicrobial use, or the results of these studies have not been made public.

As with many studies about AMR, we were unable to directly investigate the human health impact of government action on AMR due to the complex relationships among AMR, the use of antimicrobials in humans, animals, and agriculture, and health outcomes. This complexity will continue to be a challenge for AMR research until such a time as “one health” monitoring systems for both antimicrobial use and AMR improve. However, reductions in antimicrobial use are a more immediate measure of policy impact, and large-scale reductions in antimicrobial use are likely to lead to lower levels of resistance [96]. Reducing antimicrobial use is therefore a valuable target for policy makers tackling AMR at the population level.

## **3.8 Conclusions**

Our identification of 17 different policy strategies for reducing human antimicrobial use suggests that governments have a variety of policy options at their disposal for mitigating AMR. However, we also note that most existing policy options have not been rigorously evaluated, and some commonly discussed policy options have not been evaluated for their impact on antimicrobial use. To avoid wasting public resources, governments should ensure that future AMR policy interventions are evaluated using rigorous study designs and that study results are published.

### 3.9 Declarations

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The corresponding author affirms that this paper is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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**Ethics approval:** Not required

### 3.10 List of supplemental files

The following can be found in the supplemental information for Chapter 3:

|      |                                                                                                                                                    |
|------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| A3-1 | Intervention and study design summary table of all included studies                                                                                |
| A3-2 | PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) checklist: recommended items to address in a systematic review protocol |
| A3-3 | Data Extraction Tool                                                                                                                               |

### 3.11 Citations

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#### **4 Study reporting quality is a barrier to evidence-informed policymaking on antimicrobial resistance**

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## 4.1 Preface

This manuscript describes a systematic evaluation of reporting quality among studies of government interventions to reduce antimicrobial resistance, and addresses one component of the first aim of my dissertation: to appraise the state of the evidence on government policy interventions to change antimicrobial use.

I conceived the idea for a review of study quality and led the design of the methodology. I reviewed all included studies against the SQUIRE 2.0 guidelines with Miriam Nkangu and Sasha Van Katwyk acting as second reviewers. I led the data interpretation with input from all co-authors and wrote the first draft of this manuscript. Drs. Hoffman and Grimshaw supervised the design of the protocol and methodology. Drs. Taljaard and Mendelson provided valuable methodological and subject-matter expertise to inform this review. All authors critically revised the manuscript. The manuscript has been prepared for submission to the *Journal of Antimicrobial Chemotherapy*.

**Manuscript status:** Prepared for submission

**Ethics approval:** Not required

## 4.2 Abstract

**Background:** Countries are currently seeking evidence-informed policy options to address antimicrobial resistance (AMR). While rigorous evaluations of AMR interventions are the ideal, they are far from the current reality. Additionally, poor reporting and documentation of AMR interventions impede efforts to use evidence to inform future evaluations and policy interventions.

**Methods:** To evaluate the reporting quality of studies, we conducted a descriptive synthesis and comparative analysis of studies that were included in a recent systematic review of government policy interventions aiming to reduce human antimicrobial use. Reporting quality was assessed using the SQUIRE 2.0 checklist of 18 items for reporting system-level interventions to improve healthcare. Two reviewers independently applied the checklist to 66 studies identified in the systematic review.

**Results:** None of the studies included complete information on all 18 SQUIRE items (median score = 10). Reporting quality varied across SQUIRE items with between 3% and 100% of studies including the recommended information for each item. Only 20% of studies reported the elements of the intervention in sufficient detail for replication, and only 24% reported the mechanism through which the intervention was expected to work.

**Conclusions:** Gaps in the reporting of impact evaluations pose challenges for interpreting and replicating study results, and can lead decision-makers to design and implement policies without evidence. Failure to improve reporting practice of policy evaluations is likely to impede efforts to tackle the growing health, social and economic threats posed by AMR.

### 4.3 Background

Antimicrobial resistance (AMR) poses an increasingly urgent threat to global health. Over the past 5 years, increasing government attention to the health, social and economic threats posed by AMR have opened a rare policy window for achieving meaningful action on AMR [1-7]. To date, 100 countries have developed national action plans to combat AMR, although many of these plans are vague and most are devoid of specific policy directions. Having made commitments to tackle AMR and reduce inappropriate antimicrobial use, many countries are now actively searching for evidence-informed policy options to fulfil their obligations.

While rigorous evaluations of AMR interventions are the ideal, they are far from the current reality. A Cochrane review of hospital-level interventions to improve antibiotic prescribing found that the quality of the reporting among the 163 non-randomised studies was so poor that it was difficult for health professionals to use the research findings or implement interventions that were shown to be useful [8].

This failure to adequately report intervention studies is not unexpected, though it is both scientifically and economically indefensible. Poor documentation is common in health research [9, 10], and researchers have estimated that at least 50% of published health research is not sufficiently clear, complete or accurate for others to interpret or use [11, 12]. Yet, reliable evidence is essential for decision-makers who must responsibly allocate government resources to tackle AMR.

AMR has already rendered some infections untreatable using existing antimicrobials [13, 14], and World Bank projections suggest that AMR could derail the Sustainable Development Goals by driving an estimated 24 million people into extreme poverty, exacerbating global economic inequality [15], and potentially resulting in tens of millions of deaths [16]. It is therefore of the utmost importance that policy interventions are guided by high-quality evidence rather than the principle of “it seemed like a good idea at the time”. Gaps in the reporting of impact evaluations pose challenges for interpreting and replicating study results and can lead decision-makers to design and implement policies without evidence. It is of the utmost importance therefore, that studies clearly report on the development and elements of their intervention, their choices of

measures and metrics, and their findings and conclusions. In this article, we apply the SQUIRE 2.0 (Standards for Quality Improvement Reporting Excellence) framework [17] to critically evaluate reporting practice gaps of policy intervention evaluations that aim to reduce human antimicrobial use.

## **4.4 Methods**

### **4.4.1 Study Design**

We conducted a descriptive synthesis and comparative analysis to evaluate AMR policy intervention studies' reporting quality. Two reviewers (SRVK/MN) independently applied the SQUIRE 2.0 checklist to 66 studies identified in a systematic review of government policy interventions aimed at reducing the human use of antimicrobial drugs [18, 19]. SQUIRE 2.0 is an 18-item checklist which is intended to guide the reporting of system level interventions to improve healthcare. Full details of the systematic review's methodology were published in advance in a protocol [18, 19].

### **4.4.2 Eligibility**

All studies were included if they clearly described a government policy intervention to reduce human antimicrobial use, and applied a quantitative design to measure the impact [18, 19].

### **4.4.3 Data Selection**

A search strategy encompassing 7 electronic databases from medicine and the social sciences (MEDLINE, CINAHL, EMBASE, PAIS Index, CENTRAL, Web of Science, and PubMed articles not indexed in MEDLINE) was developed in consultation with research librarians, and searched from inception to January 2019 without language or date limits. Targeted web searching was used to identify grey-literature, and ProQuest Dissertations and Theses database was used to identify dissertations. Subject-matter experts in each of the World Health Organization's 6 regions were contacted to identify missing studies.

Titles and abstracts were screened against 3 inclusion criteria: 1) the evaluated intervention was a *policy intervention* defined as an intervention enacted by a government or government agency at the federal, state, provincial or municipal level, that aimed to change antimicrobial use through education, restriction, incentivization, coercion, training, persuasion, changing the physical or social context, modelling appropriate behaviour, or reducing barriers to action [20]; 2) the study *quantitatively* evaluated the effect of the intervention; and 3) the study assessed an outcome measure related to *human* antimicrobial use, including consumption, dosing, prescribing or sales of an antibiotic, antiviral, antiparasitic or antifungal drug. Titles and abstracts were independently screened by 2 reviewers (SRVK and SJ/AS/RN) and disagreements were resolved by consensus. The full texts of potentially relevant studies were screened by 2 reviewers (SRVK and MN/RN).

#### 4.4.4 Data extraction

To identify gaps in reporting practice, we assessed the quality of reporting against the SQUIRE 2.0 [17] tool; the 18 SQUIRE items are detailed in Table 4-1. We evaluated each of the systematic review's English language studies against the SQUIRE 2.0 items; research abstracts and translated studies were excluded from this analysis because they lacked sufficient detail, or the translation was of insufficient quality to grade them fairly on SQUIRE criteria. Two reviewers (SRVK and MN/SVK) independently scored each study against the SQUIRE 2.0 criteria using a decision guide developed *a priori* (Supplementary information A4-1) based on the SQUIRE guidelines [17] and SQUIRE explanation and elaboration documents [21]. Each item was coded as “fully reported” where complete information on all elements of the SQUIRE item was available, “not fully reported” where there was incomplete information in the report on one or many elements of the SQUIRE item, or “Not Applicable” where the SQUIRE item was not relevant to the study in question. The reviewers kept notes on the missing or unclear elements in each study which are available in Supplementary information A4-2. Disagreements were resolved by consensus. We report the distribution of score by element, as well as the distribution of overall scores, which were calculated by assigning 1 point for each element that was fully reported. A simple linear regression model was fit to assess whether reporting improved over time, and we compared the reporting quality of studies by evaluation design.

Table 4-1. SQUIRE 2.0 checklist items

| <b>SQUIRE ITEM</b>               | <b>Explanation in SQUIRE 2.0</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patient- centeredness, timeliness, cost, efficiency, and equity of healthcare).                                                                                                                                                                                                                                                                                                                                                   |
| <b>Abstract</b>                  | a. Provide adequate information to aid in searching and indexing.<br>b. Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions                                                                                                                                                                                                                                                                      |
| <b>Problem Description</b>       | Nature and significance of the local problem                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Available Knowledge</b>       | Summary of what is currently known about the problem, including relevant previous studies.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Rationale</b>                 | Informal or formal frameworks, models, concepts and/or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s), and reasons why the intervention(s) was expected to work.                                                                                                                                                                                                                                                                                                                                            |
| <b>Specific Aims</b>             | Purpose of the project and of this report                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Context</b>                   | Contextual elements considered important at the outset of introducing the intervention.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Intervention</b>              | a. Description of the intervention(s) in sufficient detail that others could reproduce it<br>b. Specifics of the team involved in the work                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Study of the intervention</b> | a. Approach chosen for assessing the impact of the intervention(s).<br>b. Approach used to establish whether the observed outcomes were due to the intervention(s)                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Measures</b>                  | a. Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability<br>b. Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost<br>c. Methods employed for assessing completeness and accuracy of data                                                                                                                                                            |
| <b>Analysis</b>                  | a. Qualitative and quantitative methods used to draw inferences from the data<br>b. Methods for understanding variation within the data, including the effects of time as a variable                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Ethical Considerations</b>    | Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Results</b>                   | a. Initial steps of the intervention(s) and their evolution over time (e.g., time-line diagram, flow chart, or table), including modifications made to the intervention during the project<br>b. Details of the process measures and outcome<br>c. Contextual elements that interacted with the intervention(s)<br>d. Observed associations between outcomes, interventions, and relevant contextual elements<br>e. Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s).<br>f. Details about missing data |
| <b>Summary</b>                   | a. Key findings, including relevance to the rationale and specific aims<br>b. Particular strengths of the project                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Interpretation</b>            | a. Nature of the association between the intervention(s) and the outcomes<br>b. Comparison of results with findings from other publications<br>c. Impact of the project on people and systems<br>d. Reasons for any differences between observed and anticipated outcomes, including the influence of context<br>e. Costs and strategic trade-offs, including opportunity costs                                                                                                                                                                                             |
| <b>Limitations</b>               | a. Limits to the generalizability of the work<br>b. Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis<br>c. Efforts made to minimize and adjust for limitations                                                                                                                                                                                                                                                                                                                  |
| <b>Conclusions</b>               | a. Usefulness of the work<br>b. Sustainability<br>c. Potential for spread to other contexts<br>d. Implications for practice and for further study in the field<br>e. Suggested next steps                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Funding</b>                   | Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting                                                                                                                                                                                                                                                                                                                                                                                                                         |

## 4.5 Results

### 4.5.1 Description of included studies

A PRISMA flow diagram of the systematic review is available in Supplementary Information A4-3. Sixty-six impact evaluations were identified that met the inclusion criteria. Of the 66 included studies, 64 focused on interventions to reduce the use of antibiotics, and 2 focused on interventions to reduce the use of antimalarials. These policy interventions spanned a wide range of topics including policies to improve hospital infection prevention and stewardship; policies to educate health professionals, policymakers and the public on sustainable antimicrobial use; policies to eliminate incentives for antimicrobial overuse and misuse; and policies to change features of the health system to limit antimicrobial overuse [19]. We found evaluations in 4 of the 6 World Health Organization (WHO) regions: Americas (n=22), Western Pacific (n=22), Europe (n=20), and Africa (n=2), but did not identify any evaluations from the South-East Asian or Eastern Mediterranean regions. The majority of studies focused on national-level policies (n=42), with fewer studies focused on state/province (n=10) and regional (n=14) policies. Studies were published between 1997 and 2019.

The reporting quality was found to vary by SQUIRE item, with 3% to 100% of studies including the recommended information for each item. The overall reporting quality of each study is shown in Figure 4-1, and the quality of reporting for each SQUIRE element is shown in Figure 4-2. Figure 4-3 shows the distribution of overall quality scores. We found a very slight trend towards better reporting over time ( $p=0.013$ ) although there remains substantial variation in quality scores in recent years (Figure 4-4). However, when studies published before the year 2000 are excluded, this trend towards better reporting is no longer statistically significant.

|  | Title                   | Abstract | Problem Description | Available Knowledge | Rationale | Specific Aims | Context | Interventions | Study of the Intervention | Measures | Analysis | Ethical Considerations | Results | Summary | Interpretation | Limitations | Conclusions | Funding |
|--|-------------------------|----------|---------------------|---------------------|-----------|---------------|---------|---------------|---------------------------|----------|----------|------------------------|---------|---------|----------------|-------------|-------------|---------|
|  | Altunsoy 2011           |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Bastiaens 2011          |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Belongia 2005           |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Bernier 2014            |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Bou Antoun 2018         |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Chahwakilian 2011       |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Chang 2001              |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Curry 2006              |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | D'Acremont 2011         |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Dommergues 2012         |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Dowell 2012             |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Duval 2007              |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Ellegard 2018           |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Eythorsson 2018         |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Fan 2015                |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Finkelstein 2008        |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Formoso 2013            |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Fuertes 2010            |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Furst 2015              |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Gong 2016               |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Gonzales 2005           |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Hallsworth 2016         |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Hennessy 2002           |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Hernandez-Santiago 2015 |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Ho 2004                 |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Kelly 2017              |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Klieman 2016            |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Kurt 2010               |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Lambert 2007            |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Lambert 2015            |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Lee 2014                |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Long 2017               |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Ma 2016                 |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | MacCara 2011            |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Mamdani 2007            |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Manns 2012              |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Marra 2005              |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Marshall 2006           |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | McKay 2011              |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Molstad 1999            |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Moura 2015              |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Ouldali 2017            |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Park 2005               |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Perz 2002               |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Sabuncu 2009            |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Santa Ana Tellez 2013   |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Santa Ana Tellez 2015   |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Shin 2014               |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Song 2017               |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Steffensen 1997         |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Sun 2015                |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Tang 2018               |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Tao 2013                |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Thornhill 2011          |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Walker 2019             |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Wei 2017                |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Weiss 2011              |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Wirtz 2013              |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Wu 2018                 |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Wutzke 2007             |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Xiao 2016               |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Yang 2013               |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Yip 2014                |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Zhang 2008              |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Zhen 2018               |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |
|  | Zou 2014                |          |                     |                     |           |               |         |               |                           |          |          |                        |         |         |                |             |             |         |

Figure 4-1. Reporting quality by element of the SQUIRE 2.0 checklist for the 66 included studies. Green represents fully reported items, yellow represents items that were not fully reported, and grey indicates that the item was not applicable.

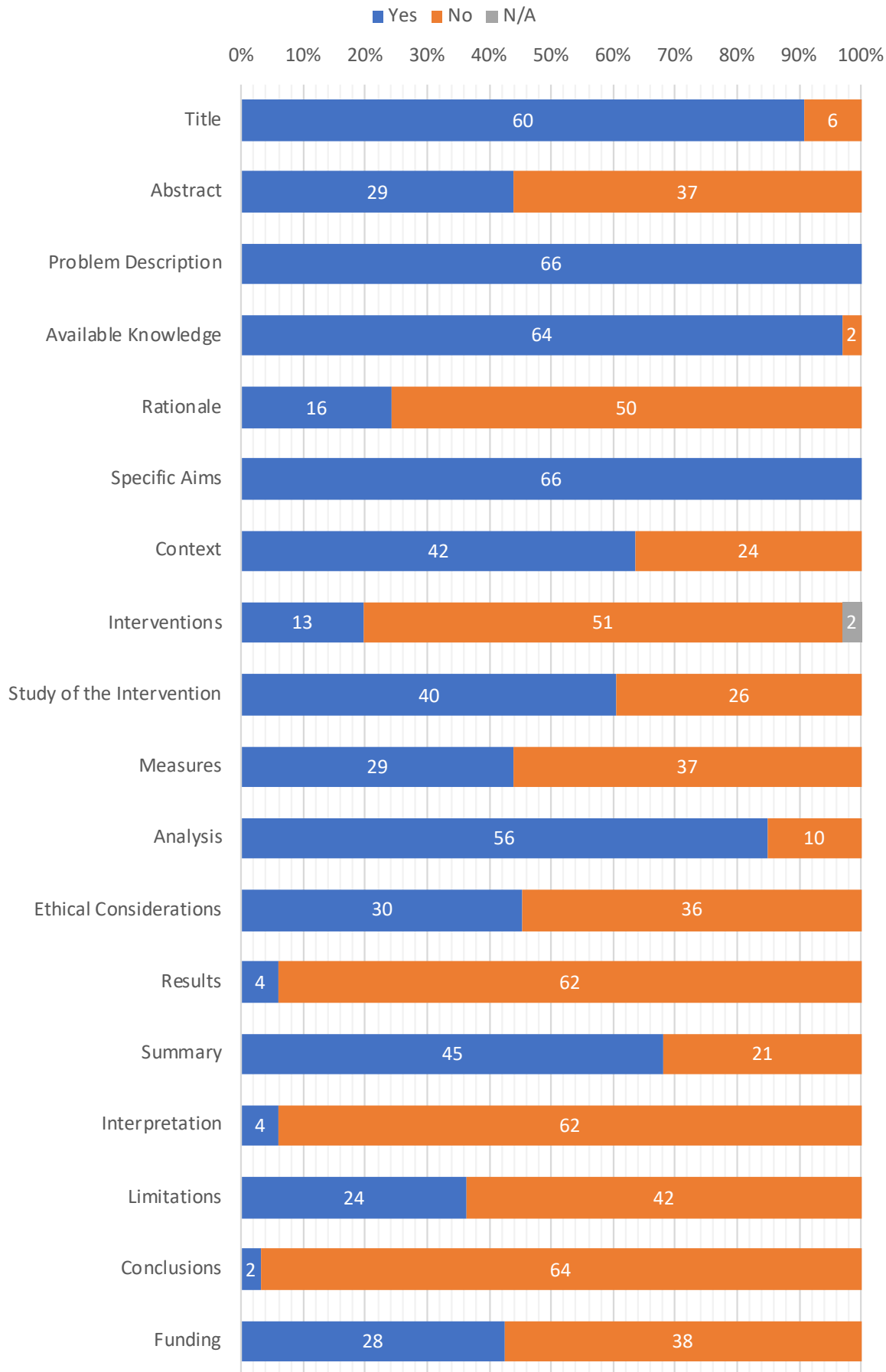


Figure 4-2.  
Percentage of the  
66 included  
studies that fully  
reported each  
SQUIRE 2.0 item

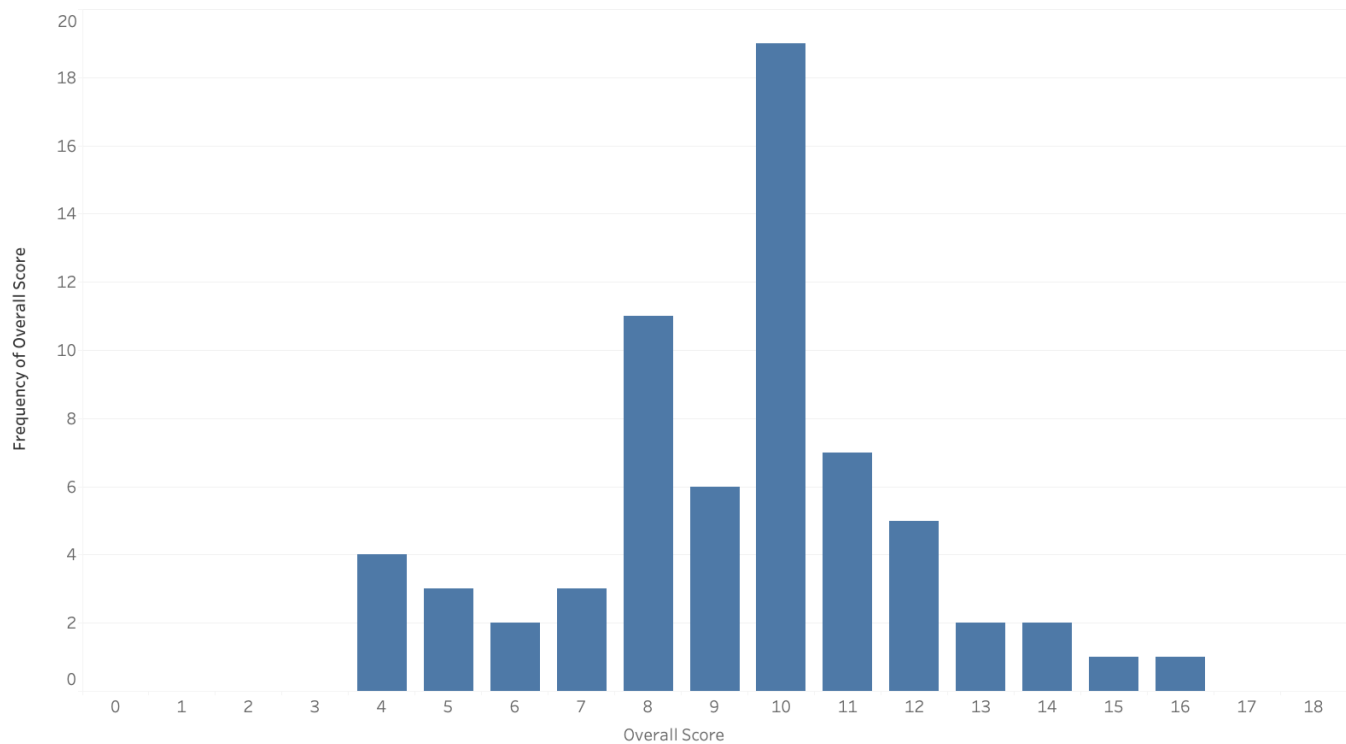


Figure 4-3. Distribution of the overall study quality scores (i.e. the number of fully reported SQUIRE items) among the 66 included studies.

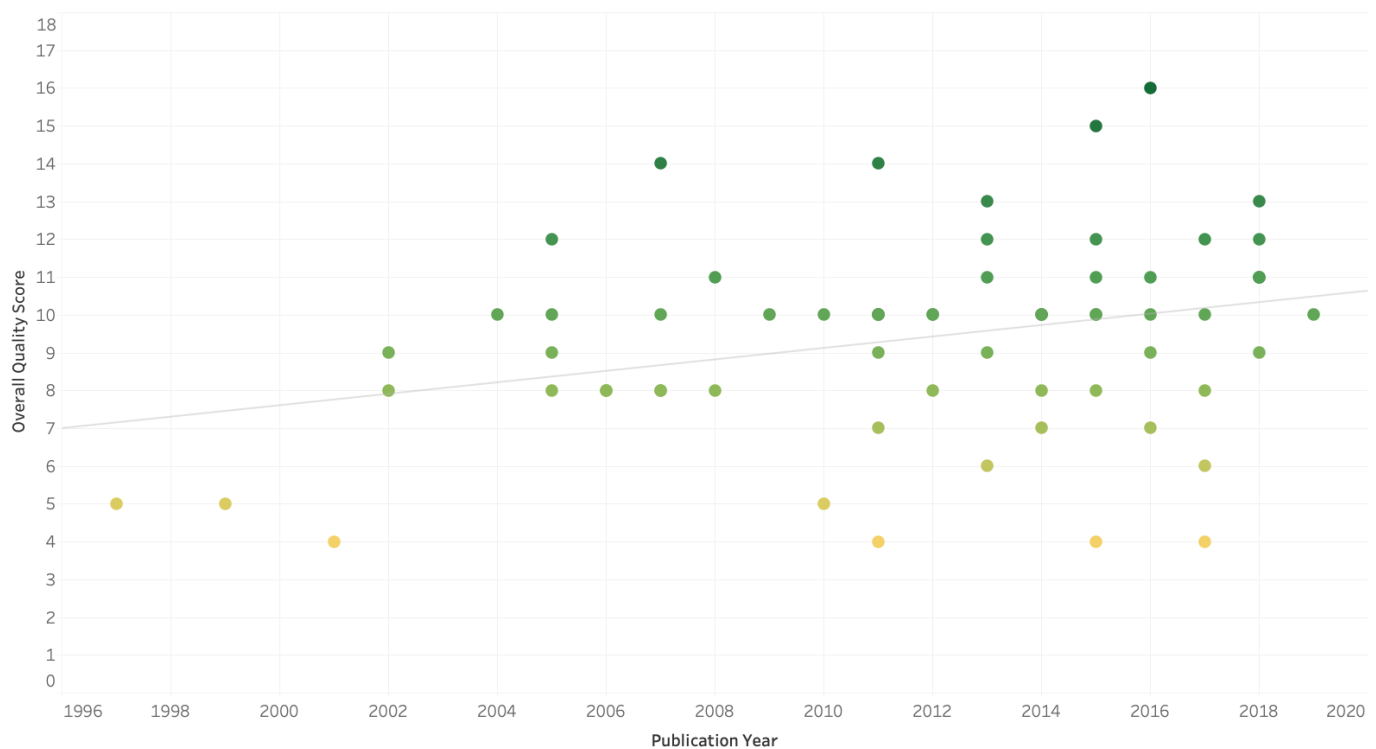


Figure 4-4. Trend in overall quality scores (i.e. the number of fully reported SQUIRE items) by publication date among the 66 included studies.

#### 4.5.2 Findings for key SQUIRE items

Several SQUIRE items were incompletely reported in more than half of eligible studies including the abstracts (Item 2), rationale (Item 5), description of the intervention (Item 8), measures (Item 10), ethical considerations (Item 12), results (Item 13), interpretation (Item 15), limitations (Item 16), conclusions (Item 17) and funding (Item 18). The lowest scoring studies were uncontrolled before-after studies; however, there was no clear indication that studies with more rigorous designs were better reported. As Figure 4-3 shows, most studies fully-reported approximately half of the SQUIRE items.

Only 28 articles were judged to have a complete abstract (Item 2) that provided adequate information for searching and indexing and summarized all key information from various sections of the text. Articles that failed to fully report this item often did not include either keywords or a summary of the background and importance of the problem.

Fewer than half (n=16, 24%) of the included studies adequately reported the study rationale (Item 5); in particular, studies failed to report the reasons why the intervention was intended to work. Studies rarely used a formal theory or framework from the fields of behaviour change or implementation science. The 16 studies that reported a mechanism by which the intervention was intended to work used informal theories, as in Park's 2005 rationale for why an intervention to limit physicians' power to dispense medications would reduce antimicrobial use: "*When physicians have a financial incentive to dispense medications, they are likely to prescribe more drugs. In previous research, dispensing doctors, in comparison with non-dispensing doctors, were found to prescribe greater numbers of drugs.* [22] "

Only one-fifth of the included studies (n=13, 20%) reported the intervention in sufficient detail that it could be replicated (Item 7), with a complete description of the activities and tools used, the inputs, internal activities, outputs, and mechanisms by which the components are expected to bring about change. Among these studies, several failed to report details of the personnel participating in the project, including the type of health professionals engaged and their experience, and the level of training received by personnel leading programs and workshops. Many studies also neglected to report what the intervention contained, such as the subject or

content of workshops, and how often and over what timespan the intervention was implemented. We noted that these details were most often missing when the evaluation was carried out retrospectively by a third party.

Fewer than half of included studies (n=29, 44%) fully reported on the measures employed for studying the intervention process and outcomes (Item 10). Many studies failed to report the rationale for choosing their selected measures, the validity and reliability of their chosen measures, or their approach to assessing the completeness and accuracy of data. However, most studies (n=56, 85%) fully reported the methods employed in the analysis including the methods employed for drawing inferences from the data and assessing variation in the data (Item 11). In evaluating the reporting quality of both items, we only considered whether the methods were clearly reported. It was not within the scope of this project to evaluate whether the methods described were of sufficient rigour to adequately answer the research question. Forty percent of the included studies (n=26) used descriptive methods or an uncontrolled before-after design.

Four studies fully reported the SQUIRE item for the results section (Item 13, 6%). The most common omission in this section was a description of the initial steps of the intervention, along with modifications made to the intervention during the project, and the unintended consequences and costs of the intervention. The small number of studies that adequately reported the steps of the intervention either used tables and timelines to depict intervention activities and dates (e.g., [23-25]), or were single time point interventions, such as enacting a new law, evaluated using interrupted time-series methods where the intervention date could be clearly indicated in a figure (e.g., [26, 27]).

Despite only 4 articles fully reporting the SQUIRE elements for interpretation (Item 15, 6%), the majority of the elements that make up this item were well reported. Nearly all included studies reported the nature of the association between the intervention and outcomes, compared the results with findings from other publications, and commented on the impact of the project on people and health systems. However, nearly all included studies failed to report on the costs of the intervention and any strategic trade-offs associated with the intervention; a puzzling oversight given that all included studies were policy interventions enacted by government authorities. Similarly, the full limitations of the study were only described by 24 of the included

studies (Item 16, 36%). Although many studies reported on factors that might have limited the internal validity of the study (confounding, bias, etc.), they largely failed to report on the efforts made to minimize and adjust for these limitations. Many studies also failed to report on the generalizability of the research.

The conclusions section was the worst reported SQUIRE item. Only 2 studies fully reported all of the elements of the conclusion (Item 17, 3%). While most articles did report on the usefulness of their study, many failed to report on the implications of the research for practice in the field, the potential for spread to other contexts, the sustainability of the intervention, or to suggest next steps.

Ethical considerations of implementing and studying the intervention and how they were addressed, including formal ethics review and potential conflicts of interest, were only reported by 30 of the included studies (Item 12, 45%). Similarly, only 28 studies fully reported the SQUIRE item on funding (Item 18, 42%). Many articles reported the source of their funding but failed to report what role the funder had played in design, implementation, interpretation, and reporting of the research.

## **4.6 Discussion**

### **4.6.1 Principal findings**

Although other systematic reviews have commented on the poor reporting practices in AMR studies [8], to the best of our knowledge this is the first study to *systematically* identify gaps in reporting practice. Our critical appraisal shows that the majority of impact evaluations of government policy to reduce antimicrobial use fully-reported on approximately half of the key items identified in the SQUIRE reporting tool for health systems interventions. Most troubling is our finding that only one fifth of the included studies reported the intervention in sufficient detail that it could be replicated, and one quarter reported a theory or mechanisms by which the intervention was expected to change the use of antimicrobial drugs.

#### 4.6.2 Policy implications

Poor documentation and reporting of the components of AMR interventions poses a challenge for decision-makers. Faced with an urgent need to act on AMR, and in the absence of clear evaluations and reproducible interventions, decision-makers will be forced to design and implement policies without evidence. Poor documentation is common in health research [9, 10] and the methodological and reporting gaps identified in this paper suggest that this type of “research waste” is a common problem in AMR research. The 66 studies included in this report represent a vast (and unknown) amount of both government program spending and research funding, yet more than half of the included studies provide sufficiently weak descriptions of the intervention that they cannot be replicated.

The failure to report — or to use — theories of behaviour change in the design of the interventions included here is troubling. Our findings of weak reporting for the rationale and description of the intervention are supported by research that suggests interventions planned without the use of theory often results in interventions that are unclear about the behaviours and outcomes being targeted, and the means by which the intervention will achieve their intended effects [28].

Other identified gaps represent challenges for knowledge translation and shared learning in AMR. Before implementing interventions, most stakeholders are keen to understand the costs associated with an intervention, the intervention’s sustainability, its effects on different populations, and whether the intervention had unintended consequences, such as increases in prescriptions for alternative antimicrobial drugs following the introduction of stricter regulations. These gaps suggest that, even in evaluations of government policy interventions, there is room for improved communication between evaluators and decision-makers to ensure that evaluations take into account key stakeholder questions.

Several options exist to improve the quality of reporting in AMR studies. The SQUIRE 2.0 checklist is one among many frameworks that can be used to improve the reporting quality of AMR interventions. Both the TIDieR Checklist (Template for Intervention Description and Replication) [29] and the TIDieR-PHP (Population Health and Policy) [30] are useful tools to improve the reporting and description of interventions. More broadly, Chalmers et al have made

several recommendations to improve replication of research and to minimize research waste, including the suggestion that research funders demand research protocols and develop a catalogue that describes research in progress [31]. Research funders should consider requiring protocols and the use of reporting checklists to raise the quality of funded research projects. Detailed reporting of intervention components by governments would improve the quality of evaluations carried out by third parties.

#### **4.6.3 Strengths and limitations**

We systematically reviewed and critically evaluated the research literature on AMR policy interventions to rigorously identify gaps in reporting practice. Three research librarians from 3 different disciplines provided advice on our search strategy, and experts from all WHO regions were contacted to ensure that all relevant literature was captured. For this evaluation we limited our analysis to study reports published in English to ensure that we were not unfairly penalizing authors for errors in translation.

However, we recognize that the 66 evaluations captured here are only those that were published in the peer-reviewed or grey literature, and that these 66 evaluations do not comprise the full set of interventions launched globally. We suspect that these other interventions have not been evaluated, have not been evaluated with respect to antimicrobial use, or the results of these studies have not been made public; as other examples are scarce, the included studies likely represent some of the best examples of reporting quality.

#### **4.7 Conclusions**

Operating at the intersection of science and global policy debates, shortcomings in the AMR evidence base pose problems for global AMR control efforts. The growing health and economic threat posed by AMR requires prompt policy action on the part of governments around the world, and WHO has called for the development of the economic case for sustainable investment in AMR [32]. Yet, without better research evidence, we may falsely conclude that some interventions are both effective and cost-effective, when in reality there are both ineffective and inefficient. More needs to be done to ensure that gaps in reporting practice do not impede efforts

to develop an evidence-informed approach to tackle the growing health, social and economic threats posed by AMR.

#### 4.8 Declarations

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**Ethics approval:** Not required

#### 4.9 List of supplemental files

The following can be found in the supplemental information for Chapter 4:

|      |                                                               |
|------|---------------------------------------------------------------|
| A4-1 | Decision guide for SQUIRE 2.0 checklist                       |
| A4-2 | Individual notes on reporting quality for each included study |
| A4-3 | PRISMA flow diagram                                           |

## 4.10 Citations

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## **5 Effectiveness of government policy interventions to reduce antimicrobial use: a systematic review**

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## 5.1 Preface

This published manuscript reports on the *effectiveness review* described in Chapter 2, and addresses the first aim of my dissertation: to investigate and characterize the role of government policy interventions on AMR and antimicrobial use, to understand which policy levers have been used, appraise the state of the evidence, and identify which interventions have proven to be effective.

I conceived the idea for this systematic review along with Dr. Hoffman and I led the design of the protocol and methodology. I developed the systematic search strategy in collaboration with three research librarians (Lindsey Sikora, Michael Boutet and Catherine McGoveran) at the University of Ottawa. I screened all studies by title and abstract with Global Strategy Lab research assistants Sara Jones, A Srivastava, Ranjana Nagi as second reviewers. I screened all-full text studies with Ranjana Nagi and Miriam Nkangu as second reviewers. I evaluated risk of bias with Miriam Nkangu as second reviewer. I led the data interpretation with input from all co-authors and wrote the first draft of this manuscript. Drs. Hoffman and Grimshaw supervised the design of the protocol and methodology and critically revised the manuscript. Drs Taljaard, Mendelson, and Tam provided valuable methodological and subject-matter expertise to inform this review. The final manuscript has been prepared for submission to *PLOS Medicine*.

**Manuscript status:** Prepared for submission

**Ethics approval:** Not required

## 5.2 Abstract

**Background** Antimicrobial resistance (AMR) presents a serious threat to global health. While at least 117 governments have developed national AMR action plans, most have not yet implemented policies to reduce antimicrobial over-use. This systematic review of the effectiveness of different policy approaches to reducing antimicrobial use among humans aims to support government efforts to undertake evidence-informed action, engage in shared learning, and adapt policies to suit their local context.

**Methods** We searched 7 databases from inception to January 28, 2019, (MEDLINE, CINAHL, EMBASE, PAIS Index, Cochrane Central Register of Controlled Trials, Web of Science, and PubMed) to identify studies that (1) clearly described a government policy intervention aimed at reducing human antimicrobial use, and (2) rigorously measured the impact of the policy. Risk of bias was assessed using the tool created by the Cochrane Effective Practice and Organisation of Care group. As meta-analysis was infeasible, we conducted a narrative review and structured synthesis of the evidence.

**Results** We found 18 unique evaluations of government policy interventions (including 3 randomized controlled trials and 15 interrupted time-series analyses) carried out across 3 regions of the world that rigorously assessed interventions falling within 4 aggregate policy approaches: communications, fiscal measures, guidelines, and regulations. We found no studies that rigorously evaluated interventions using legislative, service provision or social planning policy approaches. While there is evidence for the effectiveness of particular policy approaches in particular settings — such as banning over-the-counter antimicrobial sales, antimicrobial guidelines, and long-term national public awareness campaigns — the evaluations and interventions are too disparate to comment on the latter's likely effectiveness in other contexts.

**Discussion** This systematic review shows that diverse policy approaches have been successful in reducing global antimicrobial use. Although there is limited evidence about the effectiveness of particular policy approaches it is clear that policy approaches should be considered as part of a comprehensive AMR strategy. Policymakers will need to show considerable judgement about which mix of policy interventions will be relevant, feasible, and affordable in their setting. The 18

included studies also show that it is possible to conduct rigorous evaluations of government AMR policies using randomized controlled trials and quasi-experimental approaches.

Limitations of our study include the possible omission of unpublished initiatives, and that policies not evaluated with respect to antimicrobial use have not been captured in this review.

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#### **Registration**

PROSPERO CRD42017067514

### 5.3 Introduction

Antimicrobial resistance (AMR) is quickly becoming an urgent threat to global health and economic development. Without access to reliable antimicrobials, many routine healthcare procedures will become unacceptably risky in the future. The World Health Organization (WHO) and US Centres for Disease Control and Prevention (CDC) have repeatedly warned that we are on the cusp of a post-antibiotic future in which common infections will become increasingly deadly. The Chief Medical Officer of the United Kingdom (UK) recently equated the magnitude of the AMR threat to climate change [1].

Despite many political declarations about the need for bold action on AMR [2-6], most governments have been slow to respond. WHO's goal — that every country should have a National Action Plan on AMR by 2017 — was met by only 79 out of 154 member countries [7]. In the 2 intervening years, only 26 countries have successfully secured funding, defined their monitoring and evaluation processes, and started implementing their National Action Plans [8].

One challenge in responding to AMR is a lack of evidence on the effectiveness of government policy interventions to support effective policymaking. AMR is a complex and multifaceted threat, and although there is evidence to guide interventions in the hospital setting [9], currently there is no systematically synthesized evidence on the effectiveness of government policy interventions to address AMR. Misuse and overuse of antimicrobial drugs — in both human health and agriculture — is a major driver of AMR. Each use of an antimicrobial drug has the potential to select for AMR [10]; yet despite this risk, a large proportion of antimicrobial prescriptions are unnecessary or inappropriate [11-13].

This link between antimicrobial use and AMR creates an urgent need to reduce antimicrobial use through better stewardship and prescribing practices. Having committed to address AMR and protect the effectiveness of antimicrobial drugs, governments around the world are now considering numerous types of policy interventions to reduce antimicrobial use. Many of the actions implemented to date have consisted of public education campaigns which aim to change patient behaviour by improving AMR awareness [14, 15]. However, governments have other potentially more powerful policy levers at their disposal, such as regulating antimicrobials and

antimicrobial prescribers directly, including through legislation, fiscal policies, taxation, and economic incentives. These policy approaches may be particularly useful for collective action problems like AMR — where fast and uniform compliance with a set of standards is needed to address a public health threat [16].

Ensuring that governments have access to the best-available research evidence on the effectiveness of various policy approaches is an important first step in encouraging the implementation of evidence-informed AMR policies. We have previously published an evidence map describing the full suite of government policy interventions for reducing AMR that have been described in the published literature — including studies that did not rigorously evaluate the effects of the policy interventions [15]. This systematic review aims to support government policymaking on AMR by assessing, to the extent possible, the effectiveness of all government policy interventions intending to reduce human antimicrobial use.

## **5.4 Methods**

### **5.4.1 Protocol and registration**

The protocol for this systematic review has been published [17] and was registered in PROSPERO, the International Prospective Register of Systematic Reviews (CRD42017067514). Deviations from the original review protocol are detailed below. Our review has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [18] (see details in Supplementary information A5-2 and A5-3).

### **5.4.2 Eligibility criteria**

This review includes studies that (1) evaluated a policy intervention, defined as an intervention enacted by a government or government agency at the national, state, provincial, or municipal level that aimed to change antimicrobial use through education, restriction, incentivization, coercion, training, persuasion, changing the physical or social context, modelling appropriate behaviour, or reducing barriers to action [19]; (2) quantitatively evaluated the effect of the intervention using a study design that met the standards of the Cochrane Effective Practice and Organisation of Care group [20]; and (3) assessed an outcome measure related to human

antimicrobial use such as consumption, dosing, prescribing, or sales of an antibiotic, antiviral, antiparasitic, or antifungal drug. Although we designed our search to include all antimicrobials, all but 1 of the studies that met our inclusion criteria focused on antibiotic drugs. As the single study that focused on antimalarial drugs [21] differed substantially from the other included studies, we chose to exclude that record and focus exclusively on antibiotics for this review.

#### 5.4.3 Search strategy and selection criteria

We developed a search strategy in consultation with 3 research librarians to search medical, social science, and government literature. The search strategy was peer reviewed using PRESS [22]. We searched 7 electronic databases (MEDLINE, CINAHL, EMBASE, PAIS Index, Cochrane Central Register of Controlled Trials, Web of Science, and PubMed articles not indexed in MEDLINE) from inception to January 28, 2019, without language or date limits. Targeted web searching was used to identify grey literature, and we contacted subject-matter experts in each of WHO's 6 regions to identify missing studies. Pro-Quest Dissertations & Theses database was also searched for relevant graduate student dissertations.

Titles and abstracts were each independently screened by 2 reviewers (SRVK, and either RN, S. Jones, or A. Srivastava), as were the full texts of studies (SRVK, and MN or RN). Disagreements were resolved by consensus. Translations of non-English records were requested from the corresponding authors; if not available, translations were obtained from Google Translate. Data on study characteristics, study participants, interventions, analyses, and measured effects were extracted in duplicate by 2 reviewers (SRVK, and MN or RN) using a customized data extraction tool (see Supplemental Information A3-3 ). Risk of bias analysis was conducted in duplicate at the study level (SRVK, and MN or SVK) using the EPOC risk of bias tool [23]. Disagreements were resolved by consensus.

#### 5.4.4 Data analysis

We grouped studies by policy approach according to the Behaviour Change Wheel framework's intervention functions [19]. We intended to conduct a meta-analysis within these categories of policy approach, however, on review of the included studies, we determined that in all cases the included studies were either too few, or not sufficiently similar, to allow for meta-analysis at the

policy approach level. We have instead conducted a narrative review and structured synthesis of the evidence. We report on the ranges of effects, heterogeneity, and quality of the evidence for each policy approach. We found insufficient information to comment on the intervention effects by either target population or sex and gender.

## **5.5 Results**

### **5.5.1 Study characteristics**

We screened 13,635 records by title and abstract and reviewed the full texts of 1,002 studies (Figure 5-1). Of these, 69 studies evaluated government policy interventions aiming to reduce human antibiotic use and have been described elsewhere [15]. Eighteen studies (including 3 randomized controlled trials and 15 interrupted time-series analyses) met our inclusion criteria, were included in this systematic review. Table 5-1 presents an overview of the characteristics of the 18 included studies and Table 5-2 lists the included studies by policy approach. Full details of the included studies are provided in Supplemental information A5-1. Studies were conducted in Europe (n=7), the Western Pacific (n=5), and the Americas (Canada and the USA, n=4; Latin America, n=2). The 2 studies from Latin America represented independent interventions in 5 different countries [24, 25]; all other studies described interventions in a single country. No studies meeting the inclusion criteria were from Africa, the Eastern Mediterranean, or South-East Asia.

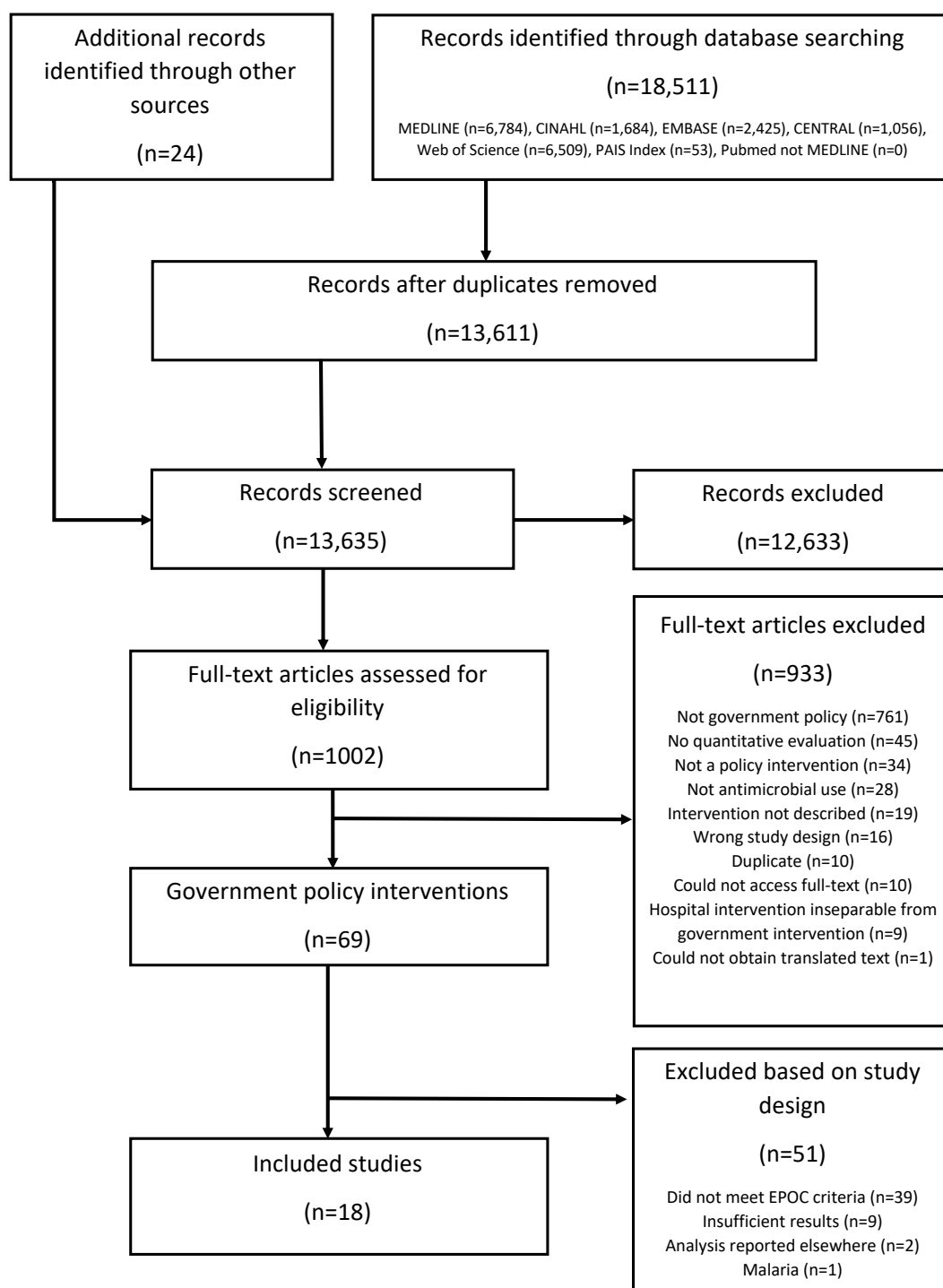


Figure 5-1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Table 5-1. Characteristics of included studies

| Study Characteristics  | Frequencies (Percentages) for the 18 Included Studies                                                                                                                                                                                                             |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Study Methods</b>   | <ul style="list-style-type: none"> <li>• 15 (83%) Interrupted time-series designs</li> <li>• 3 (17%) Randomized controlled designs</li> </ul>                                                                                                                     |
| <b>Study Location</b>  | <ul style="list-style-type: none"> <li>• 7 (39%) Europe</li> <li>• 5 (28%) Western Pacific</li> <li>• 4 (22%) Canada/USA</li> <li>• 2 (11%) Latin America</li> <li>• No Africa</li> <li>• No Eastern Mediterranean</li> <li>• No South-East Asia</li> </ul>       |
| <b>Policy Level</b>    | <ul style="list-style-type: none"> <li>• 11 (61%) National</li> <li>• 2 (11%) State/province</li> <li>• 4 (22%) Regional</li> <li>• 1 (6%) Multiple policy levels</li> </ul>                                                                                      |
| <b>Policy Approach</b> | <ul style="list-style-type: none"> <li>• 6 (33%) guidelines</li> <li>• 6 (33%) regulations</li> <li>• 4 (22%) communication</li> <li>• 2 (11%) fiscal measures</li> <li>• No legislation</li> <li>• No social planning</li> <li>• No service provision</li> </ul> |

Table 5-2. Included studies by policy approach

| <b>Policy approach</b>                      | <b>Description*</b>                                                                        | <b>Studies</b>  |
|---------------------------------------------|--------------------------------------------------------------------------------------------|-----------------|
| Guideline interventions                     | Creating documents that recommend or mandate practice                                      | [26-31]         |
| Regulatory interventions                    | Establishing rules or principles of behaviour or practice                                  | [24, 25, 32-35] |
| Communication interventions                 | Using print, electronic, telephonic, or broadcast media                                    | [36-39]         |
| Fiscal interventions                        | Using the tax system and other financial measures to reduce or increase the financial cost | [40, 41]        |
| Legislation interventions                   | Making or changing laws                                                                    | None            |
| Service provision interventions             | Delivering a service                                                                       | None            |
| Environmental/social planning interventions | Designing or controlling the physical or social environment                                | None            |

\*Policy approach descriptions from the Behaviour Change Wheel framework [19].

### 5.5.2 Quality of included studies

Three of the included studies used randomized controlled designs; all were judged to adequately generate the allocation sequence (3/3), adequately conceal the allocation (3/3), adequately protect against contamination (3/3), and be free from selective outcome reporting (3/3) (Figure 5-2a).

For the other risk of bias criteria, we judged that the baseline outcome measurements were similar in 2 studies, the baseline characteristics were similar in 2 studies, and that incomplete outcome data were adequately addressed in 2 studies. Only 1 study was judged to be free from other risks of bias (1/3). Knowledge of the allocated interventions was not adequately prevented in any of the included studies (0/3).

The majority of the interrupted time-series analyses met the following risk of bias criteria: the intervention was independent of other changes (12/15), the shape of the intervention was pre-specified (13/15), the intervention was unlikely to affect data collection (13/15), knowledge of the allocated intervention was adequately prevented during the study (11/15), and the study was free from selective outcome reporting (14/15) (Figure 5-2b). However, fewer interrupted time-series analyses met the EPOC risk of bias criteria for incomplete outcome data being adequately addressed (6/15) and being free from other risks of bias (8/15).

### A) Randomized Controlled Trials

|                     | Allocation<br>Generated | Allocation<br>Concealed | Baseline<br>Outcome | Baseline<br>Characteristics | Incomplete<br>Outcome | Allocation<br>Knowledge | Contamination | Selective<br>Reporting | Other risks |
|---------------------|-------------------------|-------------------------|---------------------|-----------------------------|-----------------------|-------------------------|---------------|------------------------|-------------|
| Finkelstein<br>2008 | Low                     | Low                     | Low                 | Low                         | Unclear               | High                    | Low           | Low                    | High        |
| Hallsworth<br>2014  | Low                     | Low                     | Low                 | Low                         | Low                   | High                    | Low           | Low                    | Low         |
| Yip 2014            | Low                     | Low                     | Unclear             | High                        | Low                   | High                    | Low           | Low                    | High        |

### B) Interrupted Time Series

|                         | Independent | Shape   | Data<br>Collection | Allocation | Incomplete<br>Data | Selective<br>Reporting | Other Risks |
|-------------------------|-------------|---------|--------------------|------------|--------------------|------------------------|-------------|
| Bauraind 2004           | Low         | Unclear | Low                | Low        | Unclear            | Low                    | Unclear     |
| Bernier 2014            | Low         | Low     | Low                | Low        | Low                | Low                    | Low         |
| Bou-Antoun 2018         | Low         | Low     | Unclear            | Unclear    | Unclear            | Low                    | Low         |
| Dowell 2012             | Low         | Low     | Low                | Low        | Low                | Low                    | High        |
| Hernandez-Santiago 2015 | Low         | Low     | Low                | Low        | Low                | Low                    | Low         |
| Manns 2012              | Low         | Low     | Low                | Low        | Low                | Low                    | High        |
| Marra 2005              | Low         | Low     | Low                | Low        | Unclear            | Low                    | Low         |
| Ouldali 2017            | Low         | Low     | Low                | Low        | Unclear            | Low                    | Low         |
| Santa-Ana-Tellez 2013   | Low         | Low     | Low                | Low        | Low                | Low                    | Low         |
| Sun 2015                | High        | Low     | Low                | Unclear    | Unclear            | Low                    | High        |
| Tang 2018               | Low         | Low     | Low                | High       | High               | Low                    | High        |
| Walker 2019.            | Low         | Low     | Low                | Low        | Low                | Low                    | Low         |
| Wirtz 2013              | High        | Low     | Low                | Low        | Low                | Low                    | High        |
| Wu 2018                 | Low         | Low     | Low                | Low        | Unclear            | Low                    | Low         |
| Zhen 2018               | High        | Low     | Low                | Low        | High               | Low                    | High        |

Figure 5-2. Risk of bias assessment for the 15 included studies. A) Risk of bias in randomized controlled trials, B) Risk of bias in interrupted time series trials

### 5.5.3 Effectiveness of guideline interventions

We identified 6 government-led guideline interventions. Two studies looked at the release of national prescribing guidelines for particular antibiotic use-cases, 1 study looked at the impact of a national strategy for responding to AMR, and 3 studies looked at the impact of providing prescribing advice and guidelines in association with auditing antibiotic prescribing.

Both studies that investigated the release of national prescribing guidelines found that guidelines were an effective strategy for creating long-term reductions in antibiotic use. In the USA [26], new guidelines that removed fluoroquinolones from the list of recommended antibiotics for gonorrhea treatment were released in the scientific journal *Morbidity and Mortality Weekly*. In their study population — 5 health departments participating in a national network conducting enhanced sexually transmitted disease surveillance — the authors found an abrupt and sustained decrease in the prescribing of fluoroquinolones, such that the use of fluoroquinolones had decreased by 21.5% (95% CI: -37.2% to -15.9%) 2 weeks after the guideline release. However, while the overall impact was an abrupt change in prescribing, when stratified by provider type, the study found that prescribing in primary care and emergency departments was more consistent with a gradual change in prescribing. In France [28], national guidelines were released to reduce the number of prescriptions and avoid broad spectrum antibiotics when treating pediatric acute respiratory tract infections. The study found a -15.5% (95% CI: -28.1 to -3.1) change in the level of antibiotic prescribing per 1,000 pediatric emergency department visits, and a -0.4% (95% CI: -0.8 to -0.0) change per 15-day period in the slope; the relative effect 3 years post-intervention was -30.9% (95% CI: -45.2 to -20.1). The study also found no significant changes in the number of acute respiratory tract infection and urinary tract infection diagnoses, or in the percentage of 15-day readmissions.

A study [29] investigating the impact of England's five-year AMR strategy which offered national-level guidance and goals for addressing AMR, found that the effect of this sustained, system-level, commitment to AMR was an overall 14.1% reduction in antibiotic prescribing from 2013 to 2017. The authors found a change in prescribing trend of -46.4 prescriptions per 1,000 Specific Therapeutic group Age-sex Related Prescribing Units (STAR PU) (95% CI: -61.4 to -31.3). The authors estimated that the strategy averted 9.7 million prescriptions, 20% fewer than

had the pre-2013 trend continued. However, this strategy was a multi-pronged complex intervention and the effectiveness of the individual components of the strategy are unknown.

Three studies — 2 in the United Kingdom and 1 in China — looked at the impact of prescribing advice and guidelines in association with auditing antibiotic prescribing. In Scotland [27], a package of policy interventions that included guidelines, education, and audit and feedback aimed to reduce prescribing of 4C antibiotics (fluoroquinolones, clindamycin, co-amoxiclav, and cephalosporins). This intervention was associated with a substantial steepening of the already decreasing trend of quarterly 4C antibiotic prescribing per 1000 patients (change in trend -0.7, 95%CI -0.49 to -0.91) and a shift to prescribing antimicrobials recommended by local and national policy. In China [30], an intervention that introduced guidelines for rural clinics along with audit and feedback also found a significant change in trend (-1.12% fewer prescriptions per month,  $p=0.034$ ), but no significant change in level of prescribing (-6.15%,  $p=0.089$ ). Finally, in England [31], a trial of social norm feedback and patient education was conducted: letters from that country's Chief Medical Officer were distributed to high-prescribing physicians informing them that they were prescribing substantially more than their peers and offering guidelines for improving their prescribing practice, and an educational patient leaflet was distributed. The feedback intervention found a 3.3% decrease (Incidence Rate Ratio=0.967, 95%CI 0.957 to 0.977) in prescribing over a six-month period. The distribution of a patient focused educational leaflet alone did not significantly impact antibiotic prescribing, nor did it significantly improve prescribing when offered in conjunction with prescriber feedback.

### ***Effectiveness of regulation interventions***

#### ***a) Banning over-the-counter sales of antibiotics***

Evidence from 2 studies [24, 25] in 5 Latin American countries suggests that banning over-the-counter sales of antibiotics can be effective in reducing antibiotic use if such regulations are supported by appropriate implementation mechanisms. The first of these interventions was launched in Chile in 1999 and resulted in a significant immediate change in the level of antimicrobial sales (-5.66 DDD per 1000 inhabitants per day,  $p<0.05$ ). Later interventions in Brazil (-1.348 DDD per 1000 inhabitants per day,  $p=0.005$ ), Mexico (-1.172 DDD per 1000 inhabitants per day,  $p=0.001$ ), and the national capital district of Colombia (-1.00 DDD per 1000

inhabitants per day,  $p < 0.001$ ) saw significant but smaller level changes in antimicrobial sales. In Venezuela, the intervention did not have a significant effect on the level of antimicrobial prescribing (+0.0123 DDD per 1000 inhabitants per day,  $p > 0.05$ ). It is of note that none of the intervention regions saw a significant change in slope for antibiotic prescribing. In the case of Brazil, where the underlying trend was increasing antibiotic use, this meant that there was an overall significant increase in antibiotic use despite the effect of the intervention.

Qualitative research conducted by the authors suggested that differences in the implementation of these over-the-counter antibiotic regulations might account for differences in effectiveness. In Chile the intervention covered all therapeutic groups of antibiotics, and included inspections of pharmacies, retention of prescriptions, an information campaign, and involvement of pharmacies in promoting enforcement. Regulations in Mexico, Brazil, and Colombia included a smaller number of mechanisms to support the regulation. By contrast, the authors note that in Venezuela, where the intervention did not have any significant effect, there was minimal implementation of the intervention. The authors report that the intervention in Venezuela lacked both supervision and sanctions and did not involve an information campaign or engagement with pharmacies in enforcing the regulation.

#### *b) Antibiotic restrictions*

The evidence from studies looking at policies to restrict antibiotics was mixed. In China, 1 study [35] investigated the impact of government-issued restrictions on particular groups of antibiotics on the volume of antibiotics dispensed in primary care settings. The study found no significant changes in level (-0.33 million DDD, 95% CI: -2.08 to +1.42) or slope (0.055 million DDD per month, 95%CI: -0.18 to +0.29) for the volume of restricted oral antibiotics dispensed, and only a small decrease in slope for restricted parenteral antibiotics (-0.035 million DDD per month, 95%CI: -0.069 to +0.001,  $p = 0.043$ ) with no significant change in level (-0.18 million DDD, 95% CI: -0.44 to +0.086). The study authors noted that changing primary care prescribing behaviour in China is difficult because reductions in primary care prescribing result in reductions in facility revenues. However, across all antibiotics (including non-restricted antibiotics), the authors did find a small but significant decrease in the slope for the volume of dispensed antibiotics (-0.51 million DDD, 95% CI: -0.97 to -0.05); there was no significant change in the level of antibiotics

dispensed (-0.3 million DDD, 95% CI: -3.92 to +3.27). By contrast, a study in Chinese tertiary care hospitals [34] evaluated the impact of a regulation that placed restrictions on antibiotic prescribing and set hospital prescribing targets. This study found an immediate level change of -4.7% (95% CI: -8.9 to -0.6) in inpatient prescriptions with an oral antibiotic but no change in the prescribing trend (-0.4%, (95%CI: -1.4 to +0.6)), although the authors note that the included hospitals were part of a special national monitoring network and may be atypical.

Two studies in Canada also looked at the impact of different antibiotic restriction strategies. One study [32] evaluated a special authorization program put in place at the provincial level in Alberta, which required physicians to obtain authorization to prescribe quinolone antibiotics unless they had already been pre-authorized to prescribe them through a program of pledging to prescribe the drugs properly. The study found no impact on the overall prescription rate of quinolones (change in level -3.5, 95%CI: -5.5. to 1.4) for all indications, although they did find a substantial decrease in the level of quinolone use for urinary tract infections (-33.6, 95%CI: -23.8 to -43.4) and upper respiratory tract infections (-15.1, 95% CI: -11.6 to -20.6). The second Canadian study investigated the impact of delisting clarithromycin from the provincial drug formulary [33], which resulted in an immediate level change of -0.2929 DDD per 1000 population per day, and a decrease of 0.0037 in the monthly trend in prescribing. However, they also found a simultaneous increase in prescribing for an alternative antibiotic (erythromycin), and the authors do not note whether this represents a shift to more appropriate prescribing.

### ***Effectiveness of communication interventions***

We identified 4 government-led public awareness campaigns that produced media and educational tools focused on reducing antibiotic prescribing. Two of the studies targeted the public [36, 37] and 2 targeted the public and health professionals together [38, 39]. All 4 campaigns were run during cold and flu season over several years. Three of the campaigns were conducted at the national level and 1 was conducted at the regional level. The 3 national campaigns all found reductions in antibiotic prescribing while the campaigns were running. In France, the first year of the “Antibiotics are not Automatic” campaign saw an 11% ( $p<0.0001$ ) reduction in weekly antibiotic prescriptions per 1000 inhabitants relative to the pre-intervention period; the intervention effect peaked at a 30% reduction ( $p<0.001$ ) in prescriptions in the fifth

year of the campaign, before stabilizing during the final 3 years of the evaluation. Substantial decreases in prescribing were also associated with the NPS Medicinewise campaign in Australia, which saw an average monthly reduction of 126,536 antibiotic prescriptions, for an overall reduction of 14% in antibiotic prescribing between 2009 and 2015 [38]. The impact of the identified public awareness campaign in Belgium was only evaluated for 2 years; however, after controlling for influenza-like illness, there was a reduction of 6.5% ( $p<0.05$ ) in the first campaign year and 3.4% (not significant) in the second campaign year relative to the year before the campaign was introduced. The identified regional program launched in Massachusetts [39] specifically focused on reducing antibiotic prescribing for children. Compared to control communities, the five-year program found a 6.7% reduction in prescribing for children 48 to <72 months, and a 4.2% reduction in prescribing for children 24 to <48 months in intervention communities. There was no significant difference between control and intervention communities in antibiotic prescribing for children aged 3 to <24 months (-0.5%,  $p=0.69$ ).

### ***Effectiveness of fiscal policy interventions***

Two studies found reductions in antibiotic use associated with the introduction of pay-for-performance programs introduced in the health system. In England, a financial incentive was provided to health centres to encourage reductions in general practitioners' antibiotic prescribing [40]. The evaluation found an immediate level change of 3% in prescribing for respiratory tract infections (-14.65 items per 1000 respiratory tract infection consultations,  $p=0.0022$ ) which was sustained at 1- and 2-years after implementation. The study found no change in prescribing trend (+0.0018 items per 1000 RTI consultations,  $p=0.9950$ ). In China, a matched pair cluster RCT was conducted to test the impact of a health system change that replaced a fee-for-service model with a capitated budget and pay-for-performance financing system [41]. Twenty-eight clusters, which consisted of a township health centre, the village posts under that centre's supervision, and the population in its catchment area, were paired on baseline characteristics and each pair was randomised to baseline and control by a coin flip. Intervention group health centres and associated village health outposts had 30% of their budget withheld and after assessment, centres that scored better than average received more than the amount of withheld funds in accordance with how much higher than average they scored, while centres that scored

lower than average received less than the withheld amount of funding. The amount of additional funding received or withheld was not reported. Adjusted for age, sex and cluster effects, visits with an antibiotic prescribed decreased by 6.6 ( $p<0.05$ ) percentage points and 6.0 ( $p<0.05$ ) percentage points in township and village health centres, respectively. The decrease was similar for male (-6.3 percentage points) and female (-6.8 percentage points) patients in township hospitals, but the decrease was larger in males (-6.8 percentage points) than females (-5.2 percentage points) in village health centres. Large decreases in prescribing for people diagnosed with a cold were seen in both types of health centres.

### ***Other interventions***

We found no studies that reported on the impact of government-led legislation, service provision, and environmental and social planning interventions to reduce the use of antimicrobials.

## **5.6 Discussion**

### **5.6.1 Principal findings**

This systematic review identified 18 rigorous assessments of policy interventions across 4 different kinds of policy approaches — including regulatory, guideline, communication, and fiscal approaches — to reduce antibiotic use. Although most of the identified policy interventions were only implemented in a single country, most were effective in reducing antibiotic use in their specific contexts suggesting that policy interventions should be considered as part of a comprehensive AMR approach. The limited available evidence makes it difficult to generalize about the effectiveness of these policies, however, the long-term impact of policies such as financial incentives in England [40], large-scale repeating public awareness campaigns [37-39] in the USA, France and Australia, and bans on over-the-counter sales of antibiotics in Latin America [24, 25], is encouraging, as long-term changes in prescribing behaviour are needed to overcome AMR. These programs are likely to be more effective when supported by evidence-based implementation strategies such as audit and feedback, and when they have support from all stakeholders.

The 18 included studies also illustrate that it is possible to conduct rigorous evaluations of AMR policy interventions using RCT and quasi-experimental approaches. It may, therefore, be most useful to see these interventions as rigorous case-studies that illustrate how policy interventions can be incorporated into national strategies for addressing AMR and how they can be rigorously evaluated. We did not find any evidence on the effectiveness of other policy approaches such as legislation, service provision, and environmental and social planning interventions. These other approaches may be appropriate or helpful in some settings, but rigorous evaluations are required. This review should therefore act as a starting point for building and evaluating other similar or new policy approaches to AMR.

### 5.6.2 Policy implications

Despite the diversity of the included studies, many of the included policy interventions successfully brought about small but long-term changes in prescribing and antibiotic use. These small but sustained reductions in monthly antibiotic use can add up to substantial decreases over the long-term, which suggests that policy interventions should be a key part of a comprehensive approach to AMR. Policymakers may also consider whether a comprehensive package of policy interventions is the best strategy for achieving their AMR goals. Multiple policies operating at different levels, targeting different stakeholders, and supported by long-term implementation plans can maximize reductions in antimicrobial use. Given that many of the identified programs were effective, but few programs were evaluated in more than 1 setting, governments should consider the evidence from this systematic review and our previously published evidence map [17], choose a comprehensive suite of interventions that will be relevant, feasible, and affordable in their setting, and evaluate their initiatives to ensure they are having the intended effect.

The effectiveness of any policy approach will certainly be contingent on contextual factors, including health system structures and capacity. For example, governments should not expect that interventions from high-income countries (HICs) are transferable to low- and middle-income countries (LMICs). The lack of available evidence from Africa, Eastern Mediterranean and South East Asia will pose challenges for developing evidence-informed AMR policies in resource-limited settings. Unfortunately, it appears that there have been few evaluations of AMR policy interventions in these regions, even if low-quality studies are included in the evidence base

[15]. This represents a major challenge for global progress on AMR, as there are policy interventions that may be very impactful in LMICs that do not make sense to implement in HICs. The possibility of banning over-the-counter sales of antibiotics, for example, may be worth exploring in those LMICs where antibiotics are currently available without a prescription, whereas, these regulations have already been implemented in many European and North American countries for many years. Even in LMICs, however, the success of such an intervention may be contingent on capacity to implement and maintain the regulation over time.

Despite promising results from many of the included studies, more evaluations of these policy interventions are needed to determine their effectiveness in different settings and contexts. Many of the interventions identified in this review were carried out retrospectively using the limited available administrative and surveillance data. As a result, many of the hospital-based studies were conducted in specialized settings that might be more amenable to intervention on antimicrobial use. For example, although both of the included studies on national prescribing guidelines found that guidelines were an effective tool for changing prescribing, both studies were carried out in specialized settings where prescribers may be primed to respond to new guidelines. Specifically, the US study on gonorrhea guidelines was conducted in regions that were engaged in specialized surveillance of sexually transmitted infections [26], and the French study of pediatric prescribing guidelines was conducted in the emergency departments of pediatric hospitals [28]. Other research has shown that simple production of guidelines without corresponding dissemination and implementation efforts are insufficient to address AMR [42, 43], and, indeed, the US study included in this review found faster uptake in specialized sexually transmitted infection clinics than in primary care. Future efforts to produce guidelines on antibiotic use should draw on this broader body of research literature about developing and disseminating guidelines.

More broadly, our review illustrates the need for more rigorous evaluations of AMR policy interventions and better reporting of both interventions and evaluations. Many of the included evaluations were conducted retrospectively by third-parties who were not involved in the design or implementation of the intervention, using administrative or sales data that was not specifically collected for evaluation purposes. As a result, the included studies used a wide range of measures

to evaluate antibiotic use and lacked important details describing the design and implementation of policy interventions. This lack of standard measures and detailing of the intervention components made it difficult to compare outcomes across studies within this review and to ascertain whether observed reductions in antimicrobial use were clinically relevant. More impactful AMR intervention research and syntheses would be possible through better standardization in data collection, analysis and reporting. Such standards could be developed either by an international network of researchers or mandated by a consortium of research funders (e.g., Joint Programming Initiative on AMR) or journal editors (e.g., the International Committee of Medical Journal Editors). More standardization in reporting on other elements of the interventions that are important to policymakers — for example, the differential impacts of these interventions on particular societal groups, costs, and implementation challenges — would additionally assist policymakers in developing new AMR interventions.

Finally, in the process of conducting this review, we identified many AMR policy interventions that are not represented in this effectiveness review [15] due to their low quality. Further, there are other policy interventions that have not, to the best of our knowledge, ever been evaluated [14, 44-46]. Even within our included studies, we found limited data on the differential impacts of AMR policy interventions by gender and socio-economic status, the challenges associated with implementation, the acceptability of the interventions, and the costs and cost-effectiveness of the interventions. Better data and reporting of data on all of these elements would strengthen the evidence base and provide policymakers with more useful insights to inform their decision-making processes.

### 5.6.3 Strengths and limitations

To our knowledge, this systematic review represents the first effort to synthesize the effectiveness of government policy interventions for reducing human antibiotic use. Our search strategy was developed in consultation with 3 research librarians from 3 different disciplines and included both published and grey literature. We additionally contacted experts from around the world to identify any key literature that was missed in our systematic search. Although many systematic reviews limit their inclusion to randomized controlled trials, we recognize that policy is often evaluated using quasi-experimental methods. We have therefore included quasi-experimental

designs alongside randomized controlled trials in our review provided that they were rigorously conducted, and we have evaluated the risk of bias associated with each study. However, we do recognize that our commitment to synthesizing only rigorous research studies means that there are several implemented policies that have not been analyzed in this review. We also recognize that other government interventions may have been implemented but have not been captured in this review because they were not evaluated with respect to antimicrobial use, or because the results of these studies have not been made public. The diversity of included outcome measures meant that we could not standardize the results to increase their comparability. Similarly, meta-analysis was not feasible given the diversity of the included studies. We attempted to identify studies on all kinds of antimicrobials, including antivirals, antifungals and antiparasitics, although (with one exception) we were ultimately only successful in identifying high-quality studies that examined antibiotic use. More research is needed to specifically explore these other areas of antimicrobial use.

As with many AMR studies, we were unable to directly investigate the human health impact of government policy interventions on AMR, due to the complex relationships among different drivers of antimicrobial use, the emergence of resistant microbes, and the effects of this resistance on health outcomes. However, reductions in antimicrobial use are a more immediate measure of policy impact, as large-scale reductions in antimicrobial use are likely to lead to lower levels of resistance [96]. Reducing antimicrobial use is therefore a valuable target for policymakers aiming to address AMR. It was also beyond the scope of this systematic review to assess the impact of government policy interventions to reduce antimicrobial use in animals, agriculture and the environment, although we recognize that AMR is a One Health challenge that requires collective action across sectors.

#### 5.6.4 Future research directions

To the best of our knowledge, this is the first review to systematically and comprehensively evaluated the effectiveness of government policy interventions to reduce antimicrobial resistance. This review should be regularly updated to incorporate new impact evaluations and to inform global AMR efforts. Ideally, future iterations of this review will include meta-analysis within categories of policy approach and an exploration of the effects of these interventions by gender.

## 5.7 Conclusions

This systematic review shows that a variety of government policy interventions have been successfully used to reduce antibiotic use. There is substantial diversity in these policy approaches, and most approaches have only been evaluated once which limits our ability to generalize about the likely effectiveness in other settings and contexts. However, the success of these identified policy interventions suggests that governments should incorporate policy approaches into their national AMR strategies. Finally, our review clearly shows that it is possible to conduct rigorous evaluations of AMR policy interventions. The dominance of low-quality studies within this evidence base is therefore not justified. Many more rigorous evaluations are needed in order to support governments around the world in developing evidence-informed policies that meet global health needs and their own AMR goals.

## 5.8 Declarations

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**Ethics approval:** Not required

## 5.9 List of supplemental files

The following can be found in the supplemental information for Chapter 5:

|      |                                                                                |
|------|--------------------------------------------------------------------------------|
| A5-1 | Detailed results and study characteristics for each of the 18 included studies |
| A5-2 | PRISMA Checklist for Abstracts                                                 |
| A5-2 | PRISMA Checklist                                                               |

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## **6 Ten years of inaction on antimicrobial resistance: an environmental scan of policies and programs in Canada from 2008-2018**

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## 6.1 Preface

This manuscript describes an environmental scan to describe and evaluate policy action on antimicrobial use and resistance in the Canadian context, which addresses the second aim of my dissertation. We consulted with the University of Ottawa Office of Research Ethics and Integrity and determined that no ethics approval was necessary for the circulation of this questionnaire on the basis that the respondents were not the focus of the research (TCPS-2 Article 2.1); no ethics review is required to obtain information from authorized personnel in the ordinary course of their employment about organizations, policies, procedures, professional practices or statistical reports.

I conceived of this environmental scan with Drs. Hoffman and Grimshaw who supervised the project. I designed the methods and collected the data. Drs. Hoffman and Tam circulated the questionnaire. I conducted the analysis and all authors contributed to the interpretation of results. I took the lead on drafting the manuscript. All authors critically revised the manuscript which has been prepared for submission to the *Canadian Journal of Public Health*.

**Manuscript status:** Prepared for submission

**Ethics approval:** Not required

## 6.2 Abstract

**Objectives** To take stock of existing policies and programs to address antimicrobial resistance (AMR) in Canada between 2008-2018.

**Methods** A survey was conducted among a judgement sample of Canadian healthcare experts, including representatives from healthcare associations, regulatory colleges, hospitals, academia, and federal, provincial, territorial and municipal governments. Respondents were asked to identify all AMR policy interventions they knew were implemented in Canada during the previous ten-year period. Additional policies and programs were identified by following up with respondents, systematically searching for published studies in 7 electronic databases (i.e., MEDLINE, CINAHL, EMBASE, PAIS Index, Cochrane Central Register of Controlled Trials, Web of Science, and PubMed), and reviewing relevant Canadian government documents.

**Results** Fifty-one unique policies and programs were identified, and at least 1 policy or program was identified in every province and territory except Nova Scotia, New Brunswick, and Newfoundland & Labrador. Most common were communications interventions (n=28), followed by guidelines (n=9), regulations (n=7), service provision (n=5), and fiscal measures (n=2). Programs and policies varied considerably in size and scope.

**Conclusion** Efforts to address AMR in Canada have been woefully inadequate for the scale and seriousness of this public health threat. This environmental scan suggests that Canadian AMR efforts are mostly a disjointed series of small projects and policies that are inadequate to meet the Government of Canada's own AMR goals. There has been an overwhelming focus on education campaigns and programs that are not supported by scientific evidence. Governments have mostly refrained from employing the more powerful tools at their disposal, including regulation, legislation, and fiscal measures. Substantially greater efforts are needed to effectively address AMR in Canada.

### 6.3 Introduction

Addressing rising rates of antimicrobial resistance (AMR) will be one of the top challenges for the Canadian health system over the coming decades. The development of resistance is a naturally occurring phenomenon, whereby microbes evolve to become resistant to the antimicrobial drugs that we currently depend upon to treat infections. Human actions — particularly the overuse, misuse and abuse of antimicrobials in humans, animals and agriculture — have accelerated this naturally occurring process [1].

AMR will have severe health and economic consequences as the spread of resistance renders some illnesses untreatable and deadly. The Organisation for Economic Co-operation and Development (OECD) estimates that 2.4 million people may die from resistance between 2015 and 2050 in Europe, North America and Australia [2]. Furthermore, rising antimicrobial resistance jeopardizes future health system capabilities in Canada. Effective antimicrobials are needed for a wide range of routine medical procedures, including surgeries and cancer chemotherapy treatments. As resistance becomes more widespread, our ability to carry out these procedures will be threatened. AMR is also expected to increase health system costs as treating patients with resistant infections is more expensive than treating patients with non-resistant forms of the same illness. The OECD estimates that collectively AMR will cost developed countries \$3.5 billion USD per year [2].

Although antimicrobials are life-saving drugs that facilitate much of modern health care, a large proportion of global antimicrobial use is inappropriate. Antibiotics, which treat bacterial infections, are commonly used in Canada and the USA to treat conditions caused by other microbes for which they are totally ineffective [3]. For example, close to half of Ontario seniors are given antibiotics for respiratory tract infections that are not caused by bacteria [4]. Many Canadians mistakenly believe that AMR does not affect them [5], and research from other developed countries suggests that physicians often fail to see that their own prescribing contributes to the development of resistance [6]. In light of these misconceptions, the leading strategy for tackling AMR around the world has been education to change provider and patient attitudes, with the goal of reducing the inappropriate use of antimicrobials [7, 8]. However, drug resistance in Canada is part of a larger global problem and investments, coordination, and

political support for policy interventions are needed to collectively address AMR at all levels of the health system, from community practice through to health professional regulation.

To date, it has been difficult to take stock of organized efforts to address AMR in Canada, or to identify policies and programs perceived to be successful in the Canadian context. The first Canadian action plan on antimicrobial resistance was released in 1997 with the goal of reducing overall antimicrobial prescriptions by 25% within 3 years [9]. The plan also aimed to change physician prescribing behaviour through guidelines, education, and feedback, and to change patient behaviour and perceptions of antimicrobials through public education and health promotion interventions [9, 10]. Unfortunately, the lack of antimicrobial use data from 1995-1999 impeded efforts to estimate reductions in antimicrobial use resulting from this plan [11] and it is unclear to what extent this call to action was implemented or sustained. A study of national programs undertaken from 1995-2010 described 4 major AMR programs in Canada during that time [12], and other ad hoc programs have been launched since 2010. However, we lack a current description of Canadian policy interventions addressing AMR. Better knowledge of these interventions would be particularly helpful for understanding the context and effects of the Government of Canada's recent national frameworks and action plans on AMR, development of which began in 2014 with the aim of establishing a coordinated federal/provincial/territorial approach to responding to AMR [13-15]. As a result, this environmental scan was undertaken to identify and catalogue recent Canadian policy interventions on AMR, with the aim of better understanding existing AMR efforts across the country and critically evaluating whether Canada has taken sufficient action to mitigate this important threat.

## **6.4 Methods**

### **6.4.1 Policy interventions**

We defined policy intervention as any public- or community-focused intervention that aimed to reduce AMR or inappropriate antimicrobial use in humans through education, restriction, incentivization, coercion, training, persuasion, changing the physical or social context, modelling appropriate behaviour, or reducing barriers to action, in accordance with the Behaviour Change

Wheel [7, 16]. Clinical interventions and interventions focused on individual hospitals, pharmacies and other healthcare facilities were not included as policy interventions.

#### 6.4.2 Data collection

We used 3 approaches to data collection. First, we circulated a brief email survey to key informants in Canada. Second, we conducted a systematic search for published literature on interventions to reduce antimicrobial use in Canada. Third, we conducted a grey literature search for policy and government documents on AMR in Canada. In addition to these 3 data sources, we contacted the Canadian Institutes for Health Research (CIHR) and requested a list of all funding announcements related to AMR between 2008-2018.

##### *A) Survey*

We circulated a short questionnaire by email to identify and gather data on AMR policy interventions undertaken between 2008 and 2018. This email questionnaire asked respondents 1) if they were aware of any policy interventions related to AMR or antimicrobial use in Canada during the specified time period, 2) when and where these interventions were undertaken, 3) what their goals were, and 4) who we could contact to obtain more details about the policies. We used a purposive sampling strategy to ensure a range of responses from federal, provincial, territorial, and municipal levels and across human health sectors; emails were sent to a judgement sample of 253 experts who, in our view, were likely to be aware of AMR programs operating in Canada as a result of their professional roles. We anticipated that experts would potentially identify the same policies and given our multi-stream approach to data collection, our sampling strategy prioritized geographic representation and professional representation above response rate. This sample included the members of Canada's AMR Steering Committee, the Council of Chief Medical Officers, academic researchers, and representatives from health professional associations (medical, dental, pharmacy and nursing), regulatory colleges, hospitals, and federal, provincial, territorial and municipal governments. Experts were additionally encouraged to forward our email to anyone else who they thought might be able to provide relevant insights. Emails in English and French were sent in February 2018, and follow-up emails were sent 2 weeks after the initial emails. Where additional information was needed to

follow-up on a program identified by experts, we followed up with the respondent or with the recommended contact person and conducted web searches using the program name or organization name and key words identified by experts.

#### *B) Systematic literature search*

We conducted a systematic search for published literature on interventions to change antimicrobial use in Canada. In consultation with 3 research librarians from health science, social science, and government, we developed a structured search query to capture published evaluations of interventions that aimed to reduce antimicrobial use. Seven electronic databases from medicine and the social sciences (MEDLINE, CINAHL, EMBASE, PAIS Index, Cochrane Central Register of Controlled Trials, Web of Science, and PubMed articles not indexed in MEDLINE) were searched from inception to January 28, 2019 without language or date limits. The full search strategy has been published elsewhere [17]. We limited the search strategy to records that included the term “Canada” or named a province or territory in the abstract, author affiliations or keywords, and which were published after 2008. One author (SRVK) reviewed the abstracts and full-texts of these studies to identify all studies that described a policy intervention in Canada between 2008-2018.

#### *C) Review of government and policy literature*

Finally, we conducted a grey literature search for policy and government documents on AMR. We conducted targeted web searches of the Government of Canada website and targeted Google searches for “antimicrobial resistance” combined with the names of the provinces and territories. Additional grey literature sources were identified by key informants. We additionally reviewed the reference lists of identified documents to identify other grey literature sources.

### **6.4.3 Analysis**

For each policy intervention identified by survey respondents or in the published and grey-literature review, we attempted to identify the intervention region, setting, timeframe, goals and affiliated organizations. Regions were coded by province/territory, or as a national effort if the policy had a broader reach. We coded interventions as communication, legislation, service provision, regulation, fiscal, guideline, and environmental and social planning interventions in

accordance with the policy categories of the Behaviour Change Wheel [16] and our recent systematic review of policy interventions [7]. The communications category was further broken down into 4 sub-types: educational programs and campaigns, events, action plans, and communication tools.

Survey respondents were not the focus of this research project and as such we did not collect demographic data (gender, age, etc.) in our survey. However, respondents' geographic location and professional affiliation were known from the development of our judgement sample, and we report on the distribution of these characteristics. Respondents who were affiliated with multiple types of bodies (e.g., regional government officials who also held academic appointments or positions in civil society groups) were coded according to their primary affiliation. The University of Ottawa Office of Research Ethics and Integrity determined that ethics approval was not required for this project.

## **6.5 Results**

Thirty-seven experts responded to the survey, including at least one respondent from every province and territory except Newfoundland and Labrador. Experts represented federal (n=3), provincial (n=8) and regional (n=4) governments, as well as academia (n=4), medicine (n=5), nursing (n=4), pharmacy (n=4), dentistry (n=2), veterinary medicine (n=2) and civil society (n=3). CIHR launched 14 funding calls on AMR from 2008-2018. Our structured literature review identified 235 studies that included the term "Canada" or named a province or territory. Ultimately, we identified 7 studies that reported evaluations of Canadian policy interventions between 2008-2018 [18-24]. Our grey literature search identified an additional 63 government and policy documents that were screened to identify policy interventions in Canada between 2008-2018; a full list of these sources is provided in Supplemental Information A6-1. Figure 6-1 summarizes our 3 streams of data collection, and Figure 6-2 shows a timeline of key actions, statements, and policy papers in Canada between 2008 and 2018; the number of major events and policy statements rose starting in 2014 as global attention on AMR increased.

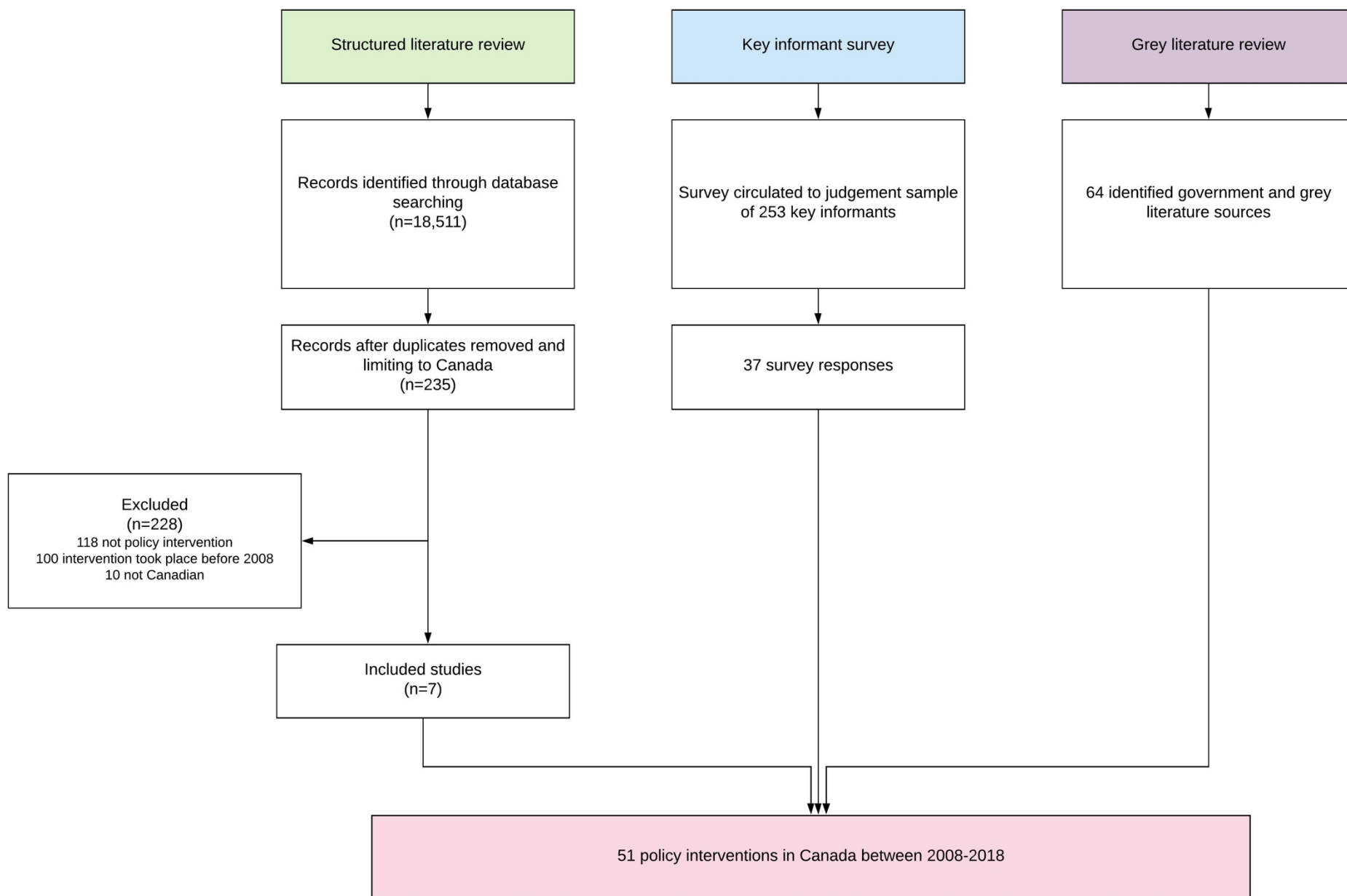


Figure 6-1. Flow chart describing our three-stream approach to for identifying policy interventions in Canada between 2008-2018

| <b>Date</b> | <b>Event</b>                                                                                                                                |
|-------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Jan-2011    | The Public Health Agency of Canada identified antimicrobial resistance as one of the most significant public health risks facing Canadians. |
| Mar-2013    | Ontario Medical Association release policy paper: When Antibiotics Stop Working                                                             |
| May-2014    | Canadian Paediatric Society release position statement: Antimicrobial Stewardship in Daily Practice                                         |
| Jun-2014    | Canadian Public Health Association release a Statement of Concern on Antimicrobial resistance                                               |
| Oct-2014    | Antimicrobial Resistance and Use in Canada: A Federal Framework for Action released                                                         |
| Oct-2014    | EAGAR (Expert Advisory Group on Antimicrobial Resistance) established                                                                       |
| Jan-2015    | Global Health Security Agenda identifies AMR as a priority; Canada is a leading country                                                     |
| Mar-2015    | Federal Action Plan on Resistance and Use in Canada: Building on the Federal Framework for Action                                           |
| Apr-2015    | Auditor General Report on AMR – ‘Significant work remains to be done’                                                                       |
| Apr-2015    | Canadian Federation of Medical Students and SASS release policy paper                                                                       |
| Oct-2015    | Canada and G7 Health Ministers commit to strengthening antibiotic stewardship programs for professionals in medical and vet fields          |
| Oct-2015    | Canada joins TATFAR (Transatlantic Task Force on AMR)                                                                                       |
| Jan-2016    | AMR endorsed as a priority at the Canadian Health Ministers' Meeting                                                                        |
| Apr-2016    | HealthcareCAN report: Building Canada's Antimicrobial Stewardship action plan                                                               |
| Apr-2016    | Pan-Canadian Public Health Network release report: Antimicrobial Stewardship Report                                                         |
| Jul-2016    | COA, CDA, and AMMI release consensus Statement: Patients with Total Joint Replacements having Dental Procedures                             |
| Nov-2016    | Canada announces \$9 million to WHO to support implementation of the GAP                                                                    |
| Nov-2016    | CIHR hosts Multi-Stakeholder Antimicrobial Stewardship Expert Forum                                                                         |
| Jan-2017    | Canadian Paediatric Society re-affirm position statement: Antimicrobial Stewardship in Daily Practice                                       |
| Aug-2017    | Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action                                                |
| Oct-2017    | Canada becomes Chair of the Global Health Security Agenda AMR Action Package                                                                |
| May-2018    | HESA presents: A Study on the Status of Antimicrobial Resistance in Canada and Related Recommendations to the House of Commons              |
| Jul-2018    | Government Response to HESA Study: A Study on the Status of Antimicrobial Resistance in Canada and Related Recommendations                  |
| Jul-2018    | Progress Report on the 2015 Federal Action Plan on Antimicrobial Resistance and Use                                                         |

Figure 6-2. Timeline of Key AMR events and reports, 2008-2018. COA: Canadian Orthopaedic Association; CDA: Canadian Dental Association; AMMI: Association of Medical Microbiology and Infectious Disease; HESA: House of Commons Standing Committee on Health.

Together, the key informants, systematic search and grey literature review identified 51 programs that were active in Canada at some point between 2008 and 2018. The distribution of programs by region is shown in Figure 6-3; at least 1 program was identified in all provinces and territories except Nova Scotia, New Brunswick and Newfoundland & Labrador, however more than half of the identified interventions were organized at the national level (n=33). Programs varied considerably in size and reach, from a one-page leaflet, to a series of tweets, to a fully-integrated regional level stewardship program. As such, a higher number of implemented interventions does not necessarily indicate increased action or focus on AMR.

Between 2008-2018, CIHR announced 14 grant calls related to AMR, and awarded \$32.5M to 77 teams (Box 6-1). These awards were to promote research in strategic areas, ranging from clinical and biological aspects of resistance to social science and global governance efforts. Many of these funding efforts have been in partnership with foreign governments: directly with the United Kingdom in 2008-2010, and, more recently, through the Joint Programming Initiative on AMR (JPIAMR).

The most commonly identified interventions (n=28) were communications interventions, of which 16 were educational programs and campaigns, 3 were events, 4 were action plans, and 5 were communication tools. Other identified interventions were guidelines (n=9), regulations (n=7), service provision (n=5), and fiscal measures (n=2). We did not identify any AMR focused legislation or environmental and social planning programs in Canada from 2008-2018. Among the 51 included interventions, we are aware of 5 that have been quantitatively evaluated in the published or grey literature [19-23].

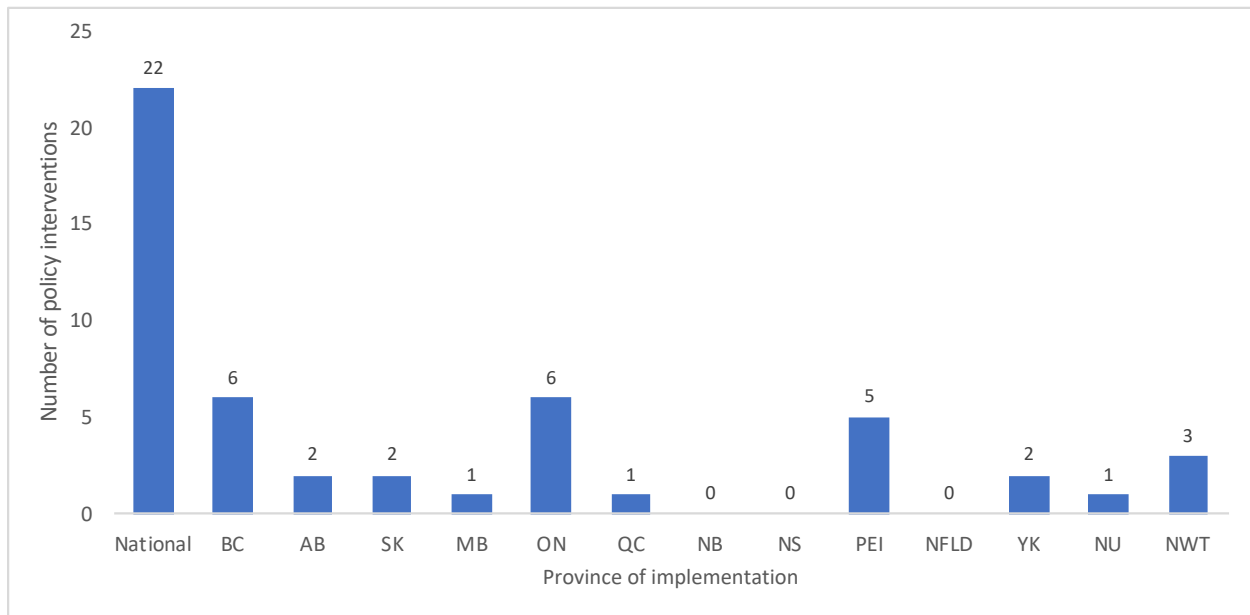


Figure 6-3. Distribution of identified policy interventions and programs across Canada.

Box 6-1. AMR research funding provided by the Canadian Institutes for Health Research, 2008-2018

| Grant Title                                                                                         | Description                                                                                                                                                                                                                                                                                                                         | Timing    | Number of<br>Funded Projects | Amount Disbursed |
|-----------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|------------------------------|------------------|
| Team Grant: Emerging Novel Alternatives Grant                                                       | For applications focused on novel approaches to antibiotic resistance, including research areas such as phage therapy or probiotics in which Canada had little or no research capacity.                                                                                                                                             | 2007-2008 | 17                           | \$14,396,609     |
| Canada-UK Joint Health Research Program on Antibiotic Resistance Catalyst Grant                     | To support the formation of Canadian/UK collaborations in the area of antibiotic resistance, building on the recommendations made at the Canada/UK workshop "Beating the Bugs".                                                                                                                                                     | 2008      | 2                            | \$120,000        |
| CAN-UK Team Grant                                                                                   | To create an environment in which UK and Canadian researchers working in the field of antibiotic resistance can combine their relative strengths in order to advance our understanding of antibiotic resistance and to develop strategies and interventions to mitigate the effects of antibiotic resistance at a population level. | 2010      | 2                            | \$3,977,900      |
| JPIAMR InnovaResistance                                                                             | To combine the resources, infrastructures, and research strengths of multiple countries in order to overcome antibiotic resistance.                                                                                                                                                                                                 | 2014      | 6                            | \$3,795,336      |
| JPIAMR Transmission Dynamics                                                                        | To understand the complex biological and environmental interactions that shape the spread of antibiotic resistance, identify and characterize the determinants that contribute to the spread of resistance in and between different reservoirs.                                                                                     | 2016      | 6                            | \$2,656,994      |
| JPIAMR - Transnational Working Groups                                                               | To assemble motivated groups of leading experts and establish transnational working groups in order to enhance resource alignment and maximize existing and future efforts to combat AMR.                                                                                                                                           | 2016      | 3                            | \$109,799        |
| AMR Point of Care Diagnostics in Human Health Initiative: Expression of Interest                    | To advance innovative point of care diagnostics that distinguish bacterial from viral infections or identify at least one of the AMR priority pathogens by bringing together applicants and industry for a workshop to establish linkages.                                                                                          | 2016      | 16                           | \$136,289        |
| AMR Point of Care Diagnostics in Human Health Initiative PHASE 1                                    | To advance innovative Point of Care Diagnostics in Human Health that distinguish bacterial from viral infections or identify at least one of the AMR priority pathogens to a stage where they are ready for scale-up and, when appropriate, commercialize and implement.                                                            | 2016      | 5                            | \$1,394,976      |
| Global Governance of Antimicrobial Resistance and Related Infectious Disease Threats Catalyst Grant | To support the planning, catalyst, and pilot implementation of social science research projects focused on any topic relevant to improving our understanding of how to design and implement effective global governance arrangements, institutions, and/or structures for addressing AMR.                                           | 2017      | 3                            | \$300,000        |
| JPIAMR Prevention and Intervention Strategies to Control AMR Infections Grant                       | To support the development of optimal intervention strategies across diverse cultural settings and heterogeneous systems of human health and animal health and food production.                                                                                                                                                     | 2017      | 7                            | \$3,226,672      |
| AMR Point of Care Diagnostics in Human Health Initiative PHASE 2                                    | To further accelerate development of technologies or tools that have passed the preliminary design developmental phase.                                                                                                                                                                                                             | 2018      | 3                            | \$1,968,199      |
| JPIAMR - Virtual Research Institute Grant                                                           | To fund a Global Network connecting research performing organisations including institutes, centres, and infrastructures to each other across sectorial and geographic boundaries in a larger global network.                                                                                                                       | 2018      | 1                            | \$75,000         |
| Network for Global Governance Research on Infectious Disease – Letter of Intent                     | To support the development of interdisciplinary research networks for global governance research on infectious diseases. To fund participation in a workshop to foster collaboration and support.                                                                                                                                   | 2018      | 4                            | \$99,368         |
| Project Grant: Priority Announcements                                                               | To support research on antimicrobial resistance.                                                                                                                                                                                                                                                                                    | 2018      | 3                            | \$300,000        |

### 6.5.1 Communication interventions

Among the communications interventions we identified 16 educational programs, largely public awareness campaigns targeting health professionals and the public. Many of the identified programs were provincial or regional variations on well-known programs such as “Do Bugs Need Drugs”, “Bugs and Drugs”, or the annual Antibiotic Awareness Week. Other smaller programs included radio broadcasts from the Northern Antibiotic Resistance Partnership, Twitter campaigns co-led by the Association of Medical Microbiology & Infectious Disease and the National Collaborating Centre for Infectious Disease (NCCID), and events organized by the Students for Antimicrobial Stewardship Society, a program organized by health professional students. The Do Bugs Need Drugs program has been linked to improvement in clinical knowledge of appropriate antibiotic treatment [21], and an ecological study has linked the program to declines in antimicrobial prescribing [20].

We also identified 3 national action plans including the Frameworks and National Action Plans released by the Public Health Agency of Canada: *Antimicrobial Resistance and Use in Canada: A Federal Framework for Action (2014)*, *Federal Action Plan on Resistance and Use in Canada: Building on the Federal Framework for Action (2015)*, and *Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action (2017)*. We also identified a provincial action plan that was in development in Quebec at the time of our survey, but no details were available. Three short educational events (1-2 days) were identified, 2 of which were hosted by CIHR and one by Health PEI. The remaining communication interventions were tools, largely leaflets, posters and other materials for engaging patients and physicians in discussion about antimicrobial use.

### 6.5.2 Fiscal measures

We identified 2 fiscal policies (Table 6-2), but neither policy provided funding for AMR action within Canada. The first policy committed the federal government to provide \$250,000 to support the World Bank in writing a report on AMR ([24]), and the second committed \$9 million to the World Health Organization to support the development of national action plans in low- and middle-income countries.

Table 6-1. Communications interventions on AMR in Canada between 2008-2018

| Intervention Name                     | Description                                                                                                                                                                                                                                                                                                                                                                         | Province | Setting    | Intervention Goals                                                                                            | Timing         | Organization                                                       |
|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|------------|---------------------------------------------------------------------------------------------------------------|----------------|--------------------------------------------------------------------|
| <b>Events</b>                         |                                                                                                                                                                                                                                                                                                                                                                                     |          |            |                                                                                                               |                |                                                                    |
| Beating the Bugs                      | Canada-UK research workshop organized by the CIHR Institute for Infection and Immunity to address topics such as immune modulation, molecular determinants of resistance, clinical aspects, and systems biology approaches.                                                                                                                                                         | National | Academic   | Bring together researchers with different perspectives on the problem of antibiotic resistance                | 2008           | CIHR                                                               |
| Matters Events                        | A series of 3 one-day continuing medical education events: Urine Matters, Cough Matters and Antibiotic Matters with between 100-150 healthcare workers participating in each event. All three events included a discussion of antibiotic safety and over use of antibiotics, with the third event focusing exclusively on wise use of antibiotics and the potential for resistance. | PEI      | Healthcare | Promotion of evidence based local guidelines                                                                  | 2015—2016      | Health PEI, MSPEI and CADTH                                        |
| CIHR Stewardship Workshop             | CIHR hosted a Multi-Stakeholder Antimicrobial Stewardship Expert Forum with Merck Canada to bring together more than 80 participants and develop recommendations on improving antimicrobial stewardship.                                                                                                                                                                            | National | Academic   | To invest in the development of strong and effective antimicrobial stewardship programs in Canada and beyond. | 2016           | CIHR and Merck Canada                                              |
| <b>Educational Programs</b>           |                                                                                                                                                                                                                                                                                                                                                                                     |          |            |                                                                                                               |                |                                                                    |
| Bugs and Drugs                        | A program that provides general recommendations for appropriate antibiotic use and care of patients with infectious diseases.                                                                                                                                                                                                                                                       | National | Healthcare | Limit the development of resistance through the judicious use of antibiotics.                                 | 1998 - ongoing | Alberta Health Services; BC Ministry of Health; Do Bugs Need Drugs |
| Bugs and Drugs North West Territories | Bugs and Drugs was made a standard of practice in the North West Territories                                                                                                                                                                                                                                                                                                        | NWT      | Healthcare | Limit the development of resistance through                                                                   | 2006 – ongoing | NWT Antimicrobial Steering Committee                               |

| Intervention Name                       | Description                                                                                                                                                                                                                                                                                           | Province | Setting         | Intervention Goals                                                                                                           | Timing         | Organization                                              |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-----------------|------------------------------------------------------------------------------------------------------------------------------|----------------|-----------------------------------------------------------|
|                                         |                                                                                                                                                                                                                                                                                                       |          |                 | the judicious use of antibiotics.                                                                                            |                |                                                           |
| <b>Bugs and Drugs Yukon</b>             | The Yukon adopted Bugs and Drugs as their organization and community resource, with access provided in all hospital, physician's offices, and community health centers.                                                                                                                               | YK       | Healthcare      | Limit the development of resistance through the judicious use of antibiotics.                                                | Not reported   | Yukon Hospital Corporation                                |
| <b>MB Southern Health Pilot Project</b> | Pilot project to adapt Do Bugs Need Drugs and Choosing Wisely Canada in the Southern Health-Sante Sud RHA / rural region of Manitoba.                                                                                                                                                                 | MB       | Healthcare      | Not reported                                                                                                                 | Not reported   | NCCID; Southern Health-Sante Sud RHA                      |
| <b>Do Bugs Need Drugs</b>               | Do Bugs Need Drugs? (DBND) is a community education program about handwashing and responsible use of antibiotics. Materials are available for healthcare professionals and the public that explain why antibiotic resistance is an issue, and steps to prevent antibiotic resistance from developing. |          |                 |                                                                                                                              |                |                                                           |
|                                         | <b>Alberta</b><br>DBND was initially developed and piloted in Alberta and provides programs and materials for healthcare professionals, teachers, schools, preschools, workplaces, long term care centres, parents, children and the public.                                                          | AB       | Public / School | To explain to professionals and the public why antibiotic resistance is an issue and steps to prevent antibiotic resistance. | 1998 - ongoing | Alberta Health Services                                   |
|                                         | <b>British Columbia</b><br>DBND in British Columbia provides health care professional education and public education to children and their parents, teachers, older adults in care, their caregivers and the general public.                                                                          | BC       | Public / School |                                                                                                                              | 2005 - ongoing | BC Centres for Disease Control                            |
| <b>AntibioticWise.ca</b>                | The AntibioticWise.ca website supports the Do Bugs Need Drugs media campaign initiatives in BC, directing the public to relevant and specific information about antibiotic stewardship and resistance.                                                                                                | BC       | Public          | Reduce the overuse and misuse of antibiotics at the individual and population level.                                         | 2005 - ongoing | Government of British Columbia; BCCDC; Do Bugs Need Drugs |
| <b>Not All Drugs Need Bugs</b>          | Public awareness campaign                                                                                                                                                                                                                                                                             | NWT      | Public          | Raise Awareness                                                                                                              | 2008           | NWT Antimicrobial Steering Committee                      |
| <b>Not All Bugs Need Drugs</b>          | A campaign featuring "Vinnie the Virus" with three messages: Not all bugs need drugs, wash your hands                                                                                                                                                                                                 | NU       | Public          | Promote the responsible use of                                                                                               | 2008           | Ministry of Health and Social Services                    |

| Intervention Name                     | Description                                                                                                                                                                                                                                                                                                                                                                                      | Province | Setting          | Intervention Goals                                                                                                                                                          | Timing       | Organization                                                                                                                                                                   |
|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                       | – prevent infection, and antibiotics don't work on viruses.                                                                                                                                                                                                                                                                                                                                      |          |                  | antibiotics in Nunavut                                                                                                                                                      |              |                                                                                                                                                                                |
| <b>NARP Radio Broadcasts</b>          | Radio broadcasts aired on Saskatchewan's Aboriginal Radio Network in English, Cree, and Dene, aimed at teaching the general public about skin and soft tissue infections, handwashing, and completing the entire course of antibiotics.                                                                                                                                                          | SK       | Public           | Education and awareness                                                                                                                                                     | Not reported | Northern Antibiotic Resistance Partnership                                                                                                                                     |
| <b>PHAC Public Awareness Campaign</b> | AMR Education Campaign launched by the Public Health Agency of Canada                                                                                                                                                                                                                                                                                                                            | National | Public           | Raise Awareness                                                                                                                                                             | 2014         | PHAC                                                                                                                                                                           |
| <b>Antibiotic Awareness Week</b>      | NCCID has been working with a range of organizations engaged in awareness building on appropriate antimicrobial/antibiotic use as part of the annual Antibiotic Awareness Day.                                                                                                                                                                                                                   | National | Public           | Antibiotic awareness week promotes cautious and correct use of antibiotics to help prevent and control the spread of bacteria that develop resistance to the medications.   | Annual       | NCCID, PHAC, AMMI Canada, Canadian Pharmacists Association, Canadian Patient Safety Institute, Infection Prevention and Control Canada, Choosing Wisely Canada, Alberta Health |
| <b>SASS</b>                           | Students for Antimicrobial Stewardship Society (SASS) is a student-led national organization dedicated to raising awareness of antimicrobial stewardship and resistance across Canada that supports a multidisciplinary approach to stewardship through collaboration with students from health professional programs including dentistry, medicine, nursing, pharmacy, and veterinary medicine. | National | Higher Education | To educate, support, connect, and represent our membership as they foster and champion a culture of stewardship and conscientious, evidence-informed use of antimicrobials. | 2015         | Students for Antimicrobial Stewardship                                                                                                                                         |
| <b>#AntibioticWAKEUP Thunderclap</b>  | AMMI Canada and the NCCID organized a national 'Thunderclap'—an on-line campaign that broadcast one resounding antibiotic awareness message across multiple social media accounts all at the same time. Supported by healthcare organizations and patient                                                                                                                                        | National | Public           | Improve awareness about wise use of antibiotics.                                                                                                                            | 2017         | AMMI Canada, NCCID                                                                                                                                                             |

| Intervention Name                                    | Description                                                                                                                                                                                                                                                          | Province | Setting                 | Intervention Goals                                                                 | Timing  | Organization                                                                         |
|------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-------------------------|------------------------------------------------------------------------------------|---------|--------------------------------------------------------------------------------------|
|                                                      | safety proponents, it called for Canadians to use antibiotics wisely. Resources were shared to help professionals, patients, and members of the public to learn and do more to keep antibiotics working.                                                             |          |                         |                                                                                    |         |                                                                                      |
| #Keepantibioticsworking                              | AMMI CANADA puts out statements about antimicrobial use using a twitter campaign and the hashtag #KeepAntibioticsWorking                                                                                                                                             | National | Public                  | Improve awareness about wise use of antibiotics.                                   | Ongoing | AMMI Canada                                                                          |
| <b>Tools</b>                                         |                                                                                                                                                                                                                                                                      |          |                         |                                                                                    |         |                                                                                      |
| Virus Plan                                           | The Virus Plan is a tool designed to educate patients/parents of pediatric patients who present with a viral illness, and provide additional instructions for managing a viral illness without antibiotics.                                                          | PEI      | Healthcare              | Educate patients/parents about managing a viral illness without antibiotics        | 2015    | Family physicians, pediatricians and the PD&T Antimicrobial Stewardship Subcommittee |
| PEAK                                                 | Article published in Dispatch, in the section called Practice Enhancement and Knowledge (PEAK) entitled "Considerations for responsible antibiotic use in dentistry." The article was distributed to all members of the Royal College of Dental Surgeons of Ontario. | ON       | Dentistry               | Raise awareness                                                                    | 2016    | Royal College of Dental Surgeons of Ontario                                          |
| Correctional Services Canada - Education for Staff   | CSC prepared a two-page sheet to go to staff about antibiotic stewardship, a chart review that CSC conducted, and CSC's proposed actions to improve antibiotic use in institutions.                                                                                  | National | Correctional Facilities | Educate staff about CSC's antimicrobial stewardship plan and planned improvements. | 2017    | Correctional Services Canada                                                         |
| Correctional Services Canada - Education for Inmates | CSC prepared a fact sheet on the proper use of antibiotics that was to all inmates. The factsheet covered key messages about the proper use of antibiotics and the possibility of antibiotic resistance.                                                             | National | Correctional Facilities | Educate inmates about the proper use of antibiotics and antibiotic resistance.     | 2017    | Correctional Services Canada                                                         |
| Regina Area Initiatives                              | Regina Qu'Appelle Health Region has a resource website including viral prescription pads, pamphlets, archived presentations on AMR, resources from                                                                                                                   | SK       | Healthcare              | Develop tools to aid in both patient and health care professional                  | Ongoing | Regina Qu'Appelle Health Region                                                      |

| Intervention Name                 | Description                                                                                                                                                                                                                               | Province | Setting                       | Intervention Goals                                                                                              | Timing  | Organization                                                         |
|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-------------------------------|-----------------------------------------------------------------------------------------------------------------|---------|----------------------------------------------------------------------|
|                                   | other organizations and updates targeting administrators and policymakers.                                                                                                                                                                |          |                               | education around issues of antimicrobial stewardship.                                                           |         |                                                                      |
| Using Antibiotics Wisely          | Campaign and resources developed by Choosing Wisely Canada in partnership with other organizations. Their target audiences bridge primary care practice and the public, which makes them highly relevant for community-based stewardship. | National | Public/<br>Community Practice | To increase knowledge and practice of resource stewardship.                                                     | Ongoing | Choosing Wisely Canada, PHAC, College of Family Physicians of Canada |
| <b>Action Plans</b>               |                                                                                                                                                                                                                                           |          |                               |                                                                                                                 |         |                                                                      |
| Federal Framework for Action      | Antimicrobial Resistance and Use in Canada: A Federal Framework for Action maps out a coordinated, collaborative federal approach to responding to the threat of antimicrobial resistance.                                                | National | Government                    | Respond to the threat of antimicrobial resistance.                                                              | 2014    | PHAC                                                                 |
| Federal Action Plan               | Federal Action Plan on Resistance and Use in Canada: Building on the Federal Framework for Action. The Framework maps out a coordinated, collaborative federal approach to responding to the threat of antimicrobial resistance (AMR).    | National | Government                    | Respond to the threat of antimicrobial resistance.                                                              | 2015    | PHAC                                                                 |
| Pan Canadian Framework for Action | Tackling Antimicrobial Resistance and Antimicrobial Use: Pan Canadian Framework for Action. This document outlines the context and the foundation to guide a pan-Canadian approach.                                                       | National | Government                    | To strengthen Canada's ability to combat the risks of AMR in a coordinated, multisectoral and effective manner. | 2017    | PHAC                                                                 |
| Quebec Action Plan                | Quebec is working to develop a Ministerial action plan on antibiotic resistance.                                                                                                                                                          | QC       | Government                    | N/A                                                                                                             | Ongoing | Ministry for Health and Social Services                              |

Table 6-2. Fiscal interventions on AMR in Canada between 2008-2018

| Intervention Name         | Description                                                                                                                                                                  | Province | Setting    | Intervention Goals                                                                                                               | Timing | Organization         |
|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|------------|----------------------------------------------------------------------------------------------------------------------------------|--------|----------------------|
| <b>World Bank Funding</b> | Minister of Health announces US\$ 250,000 to the World Bank for a study on the economic impacts of AMR entitled "Drug Resistant Infections: A threat to our economic future" | National | Government | Support the 2017 World Bank Report                                                                                               | 2015   | Government of Canada |
| <b>WHO Funding</b>        | Canada announces \$9 million to WHO to support implementation of the Global Action Plan                                                                                      | National | Government | Support low- and middle-income countries to develop and implement their national action plans, and implement key AMR initiatives | 2016   | Government of Canada |

### 6.5.3 Guidelines

We identified 9 guideline interventions, 7 of which were released by the federal or provincial governments, and 2 of which were collaborations among health professional associations. Guidelines were largely in response to the development of resistance in particular pathogens of concern, including methicillin-resistant *Staphylococcus aureus* and extensively drug-resistant *Neisseria gonorrhoeae*. A rigorous quasi-experimental evaluation of the effectiveness of introducing these new gonorrhea guidelines in Ontario found that uptake of the revised treatment guidelines was very slow. Following the release of new guidelines, the proportion of physicians prescribing according to treatment guidelines dropped by over 60% and never returned to pre-intervention levels [19].

### 6.5.4 Regulations

We identified 7 regulation interventions from 2008-2018 in Canada (Table 6-4). The largest among these interventions was a regulation by Accreditation Canada requiring hospitals and long-term care facilities to have an antimicrobial stewardship program in order to receive accreditation. Only two regulations were identified at the level of the federal government: Health Canada implemented a regulation requiring a standard statement about AMR to be included on the drug monographs of all antibiotics, and Correctional Services Canada is in the process of developing a stewardship program for implementation in all of their facilities.

### 6.5.5 Service provision

We identified 5 service provision interventions (6-5), 2 from Ontario and 3 from British Columbia. All 5 interventions provided education and training sessions on antimicrobial stewardship within the health system, often including audit and feedback on antimicrobial use rates. Three programs were delivered by, or in partnership with, provincial governments. Two programs were delivered in partnership with regional health units.

Table 6-3. Guideline interventions on AMR in Canada between 2008-2018

| Intervention Name                                                 | Description                                                                                                                                                                                                                               | Province | Setting        | Intervention Goals                                                                 | Timing       | Organization                                                               |
|-------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|----------------|------------------------------------------------------------------------------------|--------------|----------------------------------------------------------------------------|
| <b>MRSA Guidelines</b>                                            | Standards for Prevention and Management of Methicillin-Resistant Staphylococcus aureus                                                                                                                                                    | AB       | Healthcare     | To minimize the risk of exposure to and prevent transmission of MRSA               | 2008         | Alberta Health & Wellness                                                  |
| <b>PEI Guidelines</b>                                             | PEI Health provides treatment guidelines on the Health PEI Microbiology site for sepsis, CAP, UTI etc.                                                                                                                                    | PEI      | Healthcare     | Disseminate antibiotic use guidelines                                              | Not reported | Health PEI                                                                 |
| <b>MRSA Clinician Desk Reference</b>                              | MRSA Clinician Desk Reference                                                                                                                                                                                                             | NWT      | Healthcare     | Not reported                                                                       | 2010         | Health and Social Services North West Territories                          |
| <b>Medical Directive in LTC</b>                                   | Pilot program: medical directive to decrease ordering of urine cultures in two long term care facilities.                                                                                                                                 | PEI      | Long term care | Decrease ordering of urine cultures                                                | 2014         | Health PEI                                                                 |
| <b>Consensus Statement on Patients w/ Total Joint Replacement</b> | Consensus statement by three associations (Canadian Orthopedic Association, AMMI, Canadian Dental Association) stating no antibiotics for patients with Total Joint Replacement.                                                          | National | Dentistry      | Reduce the unnecessary use of antibiotics in dentistry                             | 2016         | Canadian Dental Association; Canadian Orthopaedic Association; AMMI Canada |
| <b>Ontario Gonorrhea Guidelines</b>                               | Ontario Gonorrhea Testing and Treatment Guide, 2nd Edition to Facilitate diagnosis, and effective treatment and follow-up for cases and contacts, as well as slowing the emergence of extremely drug-resistant N. gonorrhoeae in Ontario. | ON       | Healthcare     | Slow the emergence of extremely drug-resistant N. gonorrhoeae                      | 2013/ 2018   | Public Health Ontario                                                      |
| <b>Canadian Guidelines for Sexually Transmitted Diseases</b>      | Treatment of N. gonorrhoeae in response to the discontinuation of spectinomycin: Alternative treatment guidance statement                                                                                                                 | National | Healthcare     | Not reported                                                                       | 2017         | PHAC                                                                       |
| <b>CWC Dental Guidelines</b>                                      | A Dentistry Choosing Wisely Canada list that contains 8 recommendations, 4 of which address dental cases where antibiotics are not necessary.                                                                                             | National | Dentistry      | Reduce the unnecessary use of antibiotics in dentistry                             | 2018         | Canadian Association of Hospital Dentists; Choosing Wisely Canada          |
| <b>Public Health Ontario Program</b>                              | Resources, tools and presentations to guide development of stewardship programs in acute care, primary care, and long-term care. Includes an interactive tool to compare program elements and strategies between Ontario Hospitals.       | ON       | Healthcare     | Support research and resources to implement and sustain antimicrobial stewardship. | Ongoing      | Public Health Ontario                                                      |

Table 6-4. Regulatory interventions on AMR in Canada between 2008-2018

| Intervention Name                                           | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Province | Setting                   | Intervention Goals                                                                                                                                                                          | Timing       | Organization                                     |
|-------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|--------------------------------------------------|
| SHS-UHN                                                     | The SHS-UHN ASP uses a collaborative and evidence-based approach to improve the quality of antimicrobial use by getting patients the right antibiotics, when they need them. The ASP follows Plan-Do-Study-Act quality improvement methodology to pursue the best possible clinical outcomes for its patients, relying heavily on patient-centred data. The program has been scaled up to a large network of hospitals (including community hospitals). The website also provides guidance on starting an antimicrobial stewardship program. | ON       | Hospital                  | Ensure patients receive the right antibiotics when they need them                                                                                                                           | 2009         | Sinai Health System; University Hospital Network |
| Formulary Changes                                           | Formulary changes affecting fidaxomicin, linezolid, daptomycin                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | PEI      | Healthcare                | Not reported                                                                                                                                                                                | Not reported | Health PEI                                       |
| Antibiotic Labelling                                        | A standard stewardship statement is being required on all currently marketed antibiotics to encourage prudent prescribing.                                                                                                                                                                                                                                                                                                                                                                                                                   | National | Government                | Encourage prudent prescribing                                                                                                                                                               | 2015         | Health Canada                                    |
| Accreditation Canada Required Organizational Practices: AMS | Requires hospitals and Long-Term Care facilities to have an AMS program in order to be accredited. Organizations are encouraged to tailor an approach to antimicrobial stewardship consistent with their size, service environment, and patient population, and to establish processes for ongoing monitoring and improvement of the program over time.                                                                                                                                                                                      | National | Hospital / Long Term Care | To optimize the use of antimicrobials to achieve the best patient outcomes, reduce the risk of infections, reduce or stabilize levels of antibiotic resistance, and promote patient safety. | 2015         | Accreditation Canada                             |
| ASP in Fraser Health Authority                              | Fraser Health Authority has conducted an authority wide stewardship program including audit and feedback of prescribing, development of an ASP handbook and website, pre-printed order revisions, and other quality improvement projects.                                                                                                                                                                                                                                                                                                    | BC       | Healthcare                | Promote appropriate antimicrobial use within Fraser Health, optimize patient care, and slow the emergence of antimicrobial resistance.                                                      | Ongoing      | Fraser Health Authority                          |
| Yukon Hospital Actions                                      | A stewardship policy and working group, stewardship strategies such as pharmacy-initiated surveillance and physician reminders to switch from                                                                                                                                                                                                                                                                                                                                                                                                | YK       | Hospital                  | Not reported                                                                                                                                                                                | Ongoing      | Yukon Hospital Corporation                       |

| Intervention Name                                 | Description                                                                                                                                                                                                      | Province | Setting                 | Intervention Goals | Timing  | Organization                 |
|---------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|-------------------------|--------------------|---------|------------------------------|
|                                                   | IV to PO antibiotics by day 3, a restricted antibiotic formulary, and integration of AMS into the Infection Prevention and Control Committee with multidisciplinary representation from across our organization. |          |                         |                    |         |                              |
| <b>Correctional Services Canada - Stewardship</b> | Correctional Services Canada is developing a stewardship plan for their facilities.                                                                                                                              | National | Correctional Facilities | N/A                | Ongoing | Correctional Services Canada |

Table 6-5. Service Provision interventions for AMR in Canada between 2008-2018

| Intervention Name                          | Description                                                                                                                                                                                                                                                                                                                                                                                                                | Province | Setting        | Intervention Goals                                                                              | Timing       | Organization                                                       |
|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|----------------|-------------------------------------------------------------------------------------------------|--------------|--------------------------------------------------------------------|
| <b>ASPIRES smart prescribing</b>           | Vancouver Coastal Health Authority conducted an authority wide stewardship program including the development of clinical practice guidelines, audit and feedback of anti-infective prescriptions, nurse education, and development of clinical tools.                                                                                                                                                                      | BC       | Healthcare     | Improve patient care, reduce inappropriate anti-infective use, prevent antimicrobial resistance | 2013         | Vancouver Coastal Health                                           |
| <b>EQIP</b>                                | The Ministry of Health used administrative data to provide individual feedback on UTI and URTI prescribing to doctors.                                                                                                                                                                                                                                                                                                     | BC       | Healthcare     | Improve physician prescribing                                                                   | Not reported | BC Ministry of Health                                              |
| <b>LTC Training</b>                        | Academic detailing provided by Ministry of Health to Long Term Care staff and doctors about diagnosing UTI and not treating asymptomatic bacteria.                                                                                                                                                                                                                                                                         | BC       | Long Term Care | To reduce treatment of asymptomatic bacteria                                                    | Not reported | BC Ministry of Health                                              |
| <b>Champlain LHIN Stewardship Campaign</b> | Developed a program focused on leadership commitments, accountability, drug expertise, monitoring, reporting, and education, that distributed guidelines from the Ottawa Hospital, developed a tool for sharing data between pharmacists, corresponded with pharmacists about ON's provincial program and new resources. Conducted educational sessions with one hospital, and weekly ASP rounds with a separate hospital. | ON       | Hospital       | Support and assist in meeting individual hospital goals                                         | 2014         | The Ottawa Hospital; Champlain LHIN                                |
| <b>LTC A&amp;F</b>                         | Audit and Feedback to LTC facilities                                                                                                                                                                                                                                                                                                                                                                                       | ON       | Long Term Care | Not reported                                                                                    | 2018         | Institute for Clinical Evaluative Sciences; Health Quality Ontario |

## 6.6 Discussion

### 6.6.1 Principal findings

AMR is among the top global threats facing humanity, of such significance and severity that it is often compared to climate change. Yet the efforts identified in this environmental scan are too few, too small, and too uncoordinated to meaningfully address this global threat. Our scan suggests that 10 years of AMR efforts in Canada have mostly consisted of a disjointed series of small projects that are inadequate to meet the Government of Canada's own AMR goals. Governments at all levels have prioritized small, education-based programs, rather than making use of the more powerful regulatory, fiscal and legislative policy levers at their disposal. Furthermore, the programs identified are not all based on scientific evidence or evaluated using rigorous scientific methods.

While AMR efforts in Canada have mostly consisted of programs to educate and raise awareness about AMR among physicians and the public, there is only limited evidence that public awareness campaigns are effective at reducing antimicrobial use in the long-term [25, 26], and no evidence that shows what program elements make an effective public awareness campaign [7]. Indeed, at least one study showed that passively providing patients with information through posters and leaflets is ineffective [27]. While education to improve awareness of AMR may reduce patient demand for antimicrobials and could be one component of an effective AMR response [28], it is only one aspect of the prescribing equation and should not be the majority of any country's AMR response.

We believe Accreditation Canada's regulatory approach — which requires all hospitals and long-term care facilities to implement antimicrobial stewardship programs in order to obtain accreditation — will potentially be more effective at reducing long-term antimicrobial use. While evidence that accreditation leads to improved care is weak [29], there is strong evidence that antimicrobial stewardship is effective [30]. A rigorous evaluation of Accreditation Canada's program would be useful, particularly if it could identify the most effective components of a stewardship program. Other evidence-informed actions are the service provision efforts by the

British Columbia Ministry of Health and Health Quality Ontario to provide audit and feedback on antimicrobial use to health professionals and long-term care facilities [31].

We found relatively few references to clinical practice guidelines in this scan, although these are an essential part of the AMR response. Guidelines are an important component of an AMR response, although the simple production of guidelines without corresponding dissemination and implementation efforts, are insufficient to address AMR [19, 32]. To respond to growing AMR, guidelines need to be regularly updated and rapidly adopted by health professionals, yet research shows that uptake is slow when guidelines are insufficiently disseminated [19].

Most of the interventions we identified had no published or planned evaluations of policy or program effectiveness. Nor, in many cases, was it clear why an intervention was expected to work. For example, to the best of our knowledge, there is no evidence to suggest that placing warning labels about the potential for the development of AMR on product monographs will change either patient or professional behaviour. While experimenting with new policies and strategies is an essential part of responding to AMR, if these policies are planned without clear theories of change and never evaluated, they are unlikely to be effective.

Our findings suggest a surprising lack of engagement and action on AMR from key actors including health professional associations, regulatory colleges, and provincial and territorial governments. The Association of Medical Microbiology & Infectious Disease Canada is involved in many AMR efforts across Canada, and the College of Family Physicians of Canada has partnered with Choosing Wisely Canada on the Antibiotics Wisely campaign. Beyond these examples, we found only a few policy documents and statements of concern released by the medical associations, and a guideline statement from the Canadian Dental Association. An effective, coordinated AMR response will require substantially more effort to integrate professional associations and bodies from medicine, dentistry, nursing, and pharmacy.

The federated nature of the Canadian health system limits the federal government's regulatory powers on human health aspects of AMR, leaving the provinces and territories responsible for regulating health professionals and antimicrobial use. However, we saw limited evidence that Canadian provinces were independently pursuing regulatory approaches to addressing AMR. Provincial government responses to AMR have largely focused on educational campaigns and

prescribing guidelines, and, as far as we are aware, only Quebec is developing a provincial AMR action plan. The lack of action or action plans from other provinces and territories emphasizes the need for increased action, coordination and collaboration among federal, provincial and territorial actors. While the Public Health Agency has been designated the federal lead on AMR, Health Canada and the Canadian Food Inspection Agency were conspicuously absent from our environmental scan. There are opportunities for these agencies to show leadership, even where they do not have direct regulatory authority. For example, Health Canada is likely the only agency that can coordinate with provincial and regulatory bodies to develop a regulatory framework. The forthcoming Pan-Canadian Action Plan on AMR should provide a platform for increasing collaboration across levels of government; however, fulfilling the obligations of this action plan will require more action from provinces and territories than has been seen to date.

#### 6.6.2 Policy implications

Despite the activities catalogued in this environmental scan, the rates of community antimicrobial use in Canada have been stable since 2013, while rates of methicillin resistant *Staphylococcus aureus* infections, vancomycin resistant blood stream infections, and resistant *Neisseria gonorrhea* infections have continued to rise [33]. Increasing resistance highlights the extent to which the resources committed to AMR are incommensurate with the scale of the collective action problem. As AMR represents a major threat to the sustainability of the Canadian healthcare system and to the continued availability of healthcare services, it requires substantially more focused investment and attention than has thus far been provided. While Canada has taken on AMR leadership roles abroad, the level of political engagement, funding, regulatory and legislative action on AMR in Canada appears to be limited. PHAC provides routine funding for AMR surveillance and awareness campaigns, our scan did not identify any announcements of new domestic AMR funding beyond CIHR research grants.

The framing of AMR as a health threat related to individual patient and prescriber behaviours has unsurprisingly led to a series of AMR responses focused on simple educational messaging around taking fewer antimicrobials. This strategy rests on the recognition that providers are more likely to prescribe antibiotics when patients request them [34-36] ; however, research suggests that while patients expect something from their physician (check-up, reassurance,

medical certificate, guidance on symptom management) they do not necessarily expect antibiotics [37]. Antibiotic prescribing is also shaped by a series of health systems factors and social determinants of health, such as healthcare access, clinic volume, socio-economic status, and patient-provider trust [38-40]. Recent reviews show there are many more policy approaches available that have yet to be tried in the Canadian context [7]. Among these, legal, regulatory, and fiscal strategies represent important components of a public health strategy for AMR. To effectively address AMR, public health actors in Canada need to make full use of these potentially more powerful strategies to build a much more coordinated, evidence-based suite of programs and policies and address AMR at multiple-levels. Recent calls from CIHR and JPIAMR to fund social science and behaviour change research on AMR may lead to useful new strategies in this respect, and all policy interventions should be paired with appropriately rigorous evaluation plans to better inform resource allocation and shared learning across provinces and territories. As a starting point, provinces and territories should focus on improving and harmonizing the collection of data on AMR and antimicrobial use across the country, which will facilitate future evaluation efforts.

Going forward, concerted action will be needed from all actors to ensure that new policies and programs focus on advancing evidence-informed action, and do not prioritize the appearance of action over actual action. We hope that the forthcoming Pan-Canadian Action Plan on AMR will provide the necessary platform for ensuring cooperation and will allow the federal and provincial governments to move forward with a much more effective and ambitious AMR strategy. Future AMR action will need to move beyond simply integrating existing public communications campaigns and tools, and towards effective, integrated, regulatory, legislative, and fiscal measures.

### 6.6.3 Strengths and limitations

To the best of our knowledge, this is the first review of the state of AMR policy action in Canada in many years; the most recent published study on this topic included only national level interventions between 1995-2010 [12]. By surveying experts across Canada, we have not only captured data on AMR policy efforts at the national level but have also identified programs and policies at the provincial and territorial government level, and those organized by academics and

civil society. Although we aimed to be comprehensive through our combination of questionnaire, grey literature and published literature searching, we are aware that some policies and programs may not have been captured. Our purposive sampling strategy focused on experts who currently hold positions where they would be aware of AMR programs in Canada. However, although many of the experts we contacted have been engaged in AMR for more than 10 years, it is possible that we missed earlier programs as a result of staff turnover. We did not attempt to contact people who had moved on from their expert positions in the public health community. Similarly, the nature of online grey literature searching also privileges recent sources over older documentation. We have attempted to overcome these limitations by combining research strategies and to the best of our ability, verifying our information through other sources.

## **6.7 Conclusions**

AMR is a major threat to public health and healthcare in Canada. Our review suggests that the AMR interventions in Canada over the past 10 years have been too few, too small, and too uncoordinated to adequately address the threat posed by AMR. Increased commitment to AMR, including one-health inter-agency cooperation and funding are needed to ensure that future interventions are effective, evidence-informed, and sufficient for Canada to overcome this looming threat.

## **6.8 Declarations**

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**Ethics approval:** Not required

## **6.9 Conflict of interest**

SJH is Scientific Director of CIHR's Institute of Population & Public Health. The views expressed in this article are those of the authors and do not necessarily reflect those of CIHR or the Government of Canada.

## **6.10 List of supplemental files**

The following can be found in the supplemental information for Chapter 6:

|      |                                 |
|------|---------------------------------|
| A6-1 | List of grey literature sources |
|------|---------------------------------|

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## **7 Strengthening the science of addressing antimicrobial resistance: A framework for planning, conducting, and disseminating antimicrobial resistance intervention research**

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## 7.1 Preface

This manuscript describes a framework for strengthening the science of addressing antimicrobial resistance which addresses the third objective of my dissertation: to evaluate and propose analytic strategies for improving research on population health interventions on antimicrobial use and resistance.

I conceived of this project with Drs. Hoffman and Grimshaw. I collected the data, developed the framework and led the writing of the manuscript. Drs. Hoffman and Grimshaw supervised the project, and Drs. Taljaard, Mendelson, and Tam provided subject matter expertise. All authors contributed to the revision of the framework and have critically revised the manuscript which has been prepared for submission to *Health Research Policy and Systems*.

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**Ethics approval:** Not required

## **7.2 Abstract**

Antimicrobial resistance (AMR) has the potential to threaten tens of millions of lives and poses major global economic and development challenges. As the AMR threat grows, it is increasingly important to strengthen the scientific evidence base on AMR policy interventions, to learn from existing policies and programs, and integrate scientific evidence into the global AMR response. However, while rigorous evaluations of AMR policy interventions are the ideal, they are far from the current reality. To strengthen this evidence base, we describe a framework for planning, conducting and disseminating research on AMR policy interventions. The framework identifies challenges in AMR research, areas for enhanced coordination and cooperation with decision-makers, and best-practices in the design of impact evaluations for AMR policies. This framework offers a path forward, enabling increased local and global cooperation, and overcoming common limitations in existing research on AMR policy interventions.

### 7.3 Introduction

Antimicrobial resistance (AMR) — the process by which microbes acquire resistance to antimicrobial medicines — is widely recognized as a serious threat to global public health. The likelihood of drug resistance increases when microbes are exposed to antimicrobials, and, unlike previous generations, we can no longer count on the development of new drugs to overcome this threat [1-3]. The development of resistance has been accelerated by overuse of antimicrobials for medical and agricultural purposes. AMR now threatens tens of millions of lives [4], in addition to posing major global economic and development challenges [5].

AMR is politically, economically, and microbially difficult to tackle from a policy perspective. Efforts to evaluate AMR interventions would be significantly improved by increasing investments in monitoring and surveillance for antimicrobial resistance. Controlling AMR will require a suite of effective antimicrobial stewardship and conservation strategies to ensure the appropriate use of antimicrobials [6], in addition to substantial international cooperation on the regulation and surveillance of antimicrobials and their use [7-11]. Substantial research is needed to generate evidence on the effects and effectiveness of various possible AMR policies and to ensure that health system investments in AMR are evidence-informed. Existing research has created little clarity about what interventions are best suited to achieve AMR goals across contexts, cultures and health systems. Many efforts to reduce AMR are designed as policies to reduce the use of antimicrobials; in this manuscript, when we refer to *AMR policy*, we refer also to these antimicrobial use policies. Policy recommendations for AMR have changed little since the late 1990s [4, 12-16]. Worldwide, millions of dollars are invested annually in public programs to raise awareness about AMR, educate health professionals on appropriate prescribing, and decrease antimicrobial consumption in the health and agricultural sectors. Despite major financial and political investments it has been difficult to link these programs to concrete improvements in antimicrobial use, resistance or health outcomes more generally [6, 17], particularly as major surveillance and information gaps impede the global response to AMR [18](Box 7-1).

As the threat posed by AMR grows, it is increasingly important to strengthen the scientific evidence base on AMR policy interventions, to learn from existing policies and programs, and

integrate scientific evidence into the global AMR response [6]. The goal of this paper is to develop a framework that facilitates the strengthening of this evidence base. This paper is not intended as a formal research prioritization process, but rather, builds upon the findings from recent systematic reviews of interventions to reduce antimicrobial consumption [6, 17, 19, 20] and efforts by others to strengthen research on AMR and public health [17, 21-26], to draw insights for improving the planning, conduct and dissemination of research to evaluate AMR policy interventions (Figure 7-1). The framework identifies challenges in AMR evaluation research, areas for enhanced coordination and cooperation with policy-makers, and best-practices for overcoming common limitations in evaluating AMR policies. Some of these challenges are specific to AMR, while others are shared with other areas of health research.

#### BOX 7-1: Current state of the evidence base on AMR policy interventions

Around the world, 129 governments are currently in the process of developing or implementing a National Action Plan to address antimicrobial resistance [27].

Global capacity for AMR surveillance is lacking; discrepancies between methods and monitoring systems, data quality concerns, and lack of representativeness make it challenging to compare AMR data between countries [28].

Many evaluations of AMR policy interventions are conducted retrospectively by academics who were not involved in the design or implementation of the intervention [29].

A systematic review of experimental and quasi-experimental studies evaluating government policy interventions to reduce the use of antimicrobials [29] found that 30 of the 69 studies used low-quality study designs, such as uncontrolled before-after designs, which severely limits the validity of their findings. Among these 69 studies, only 4 used a randomized controlled design which is considered the gold standard for evaluating interventions.

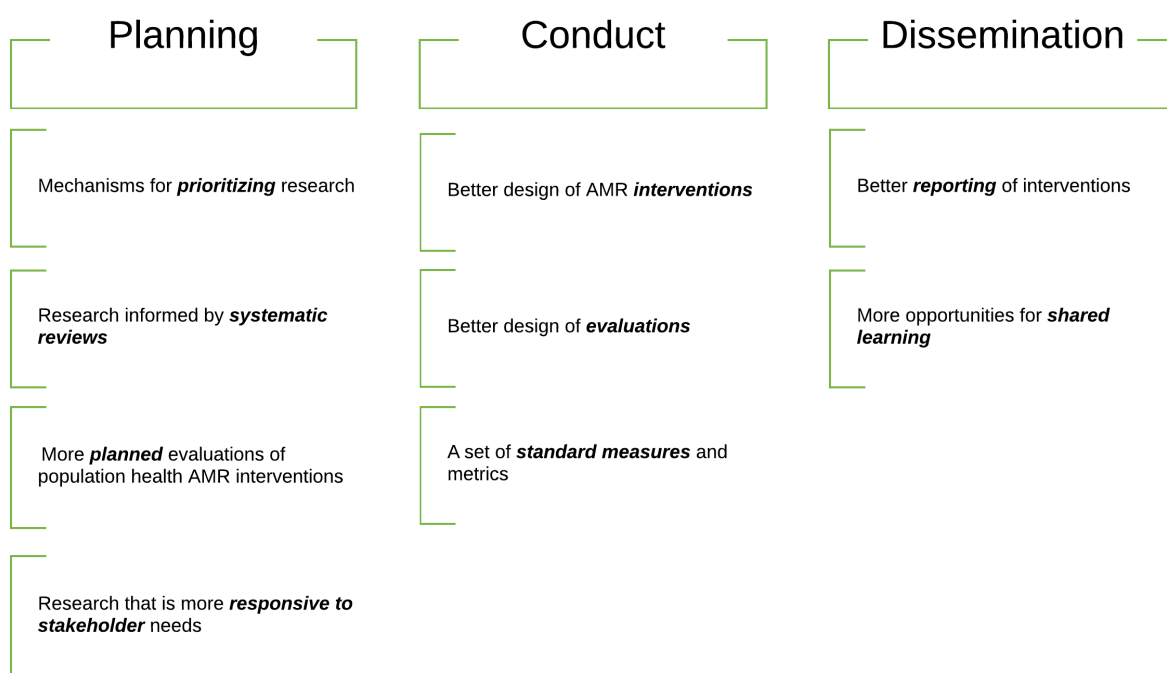
Another systematic review of 221 interventions for improving antibiotic prescribing among hospital inpatients found the quality of the reporting for the 163 non-randomised studies was so poor that it was difficult for professionals to use the research findings or to implement interventions that were shown to be useful. Further, this systematic review found that no useful evidence could be gleaned from studies using controlled before-after and non-randomized trial designs [17].

Reporting of AMR policy intervention studies is weak; studies often fail to describe the intervention in sufficient detail for replication, and many do not report the reason the intervention is expected to work [19].

In the broader field of public health, researchers have estimated that at least 50% of published research is not sufficiently clear, complete, or accurate for others to interpret or use [30, 31].

There are no standardized measures and metrics for AMR research. Many AMR intervention studies report antimicrobial use in Defined Daily Dose (DDD) per 1000 population, or a simple prescribing rate.

Figure 7-1: Framework for prioritizing, conducting, and disseminating AMR policy interventions



## 7.4 Research planning

### 7.4.1 Prioritizing research

**AMR researchers need to prioritize the study of *what* works, *when* it works, *why* it works, and *what* elements are necessary for its success.**

AMR needs better mechanisms for prioritizing important research questions that can shape effective action. There has already been substantial research on the root social and microbial causes of AMR [32-34] and we argue that attention now needs to be focused on determining which interventions are effective at addressing the underlying root causes of AMR, why these interventions work, what elements are necessary to their success, and in what contexts and circumstances these interventions work. More evidence on all four questions would be invaluable for policy planning [6, 17]. As the majority of existing research evidence focuses on interventions in high-income settings, additional research on these questions would particularly benefit low- and middle- income countries (LMICs) and other resource limited settings to identify policy interventions that can be adapted to meet local needs and priorities.

More formally, research prioritization can be improved by undertaking structured prioritization and consensus processes in collaboration with stakeholder groups including policymakers at different levels of government, civil society, health professionals, and research funders. Research funders can support this work through opportunities for strategically funded research to address AMR rather than relying on researcher-led operating grants. For example, the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) recently funded an international workshop and formal consensus process to develop 10 research priorities for behavioural approaches to develop more impactful hospital antimicrobial stewardship programs [25]. The James Lind Alliance in the United Kingdom, which provides a platform for priority setting partnerships between clinicians, patients, and carers has produce a guidebook that outlines their method for identifying research uncertainties and producing an agreed list of research priorities [35]. Research prioritization processes can also highlight the differences between research priorities in different contexts. Economic, political and cultural differences between countries and regions are likely to introduce new priorities. A recent prioritization exercise looking at

global health trial methodology found different research priorities in LMICs compared with the UK [36]. The Cochrane Collaboration has previously published a special series on priority setting which offers guidance on topics such as applying an equity lens to priority setting [37] and effective stakeholder participation in priority setting [38]. Formal prioritization processes would help drive research agendas at the international level, such as those of JPIAMR, the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), and the World Organisation for Animal Health (OIE). Recently, the WHO has engaged in formal priority setting exercises for AMR research and development, first through a multi-criteria decision analysis exercise to develop its list of priority pathogens for research and development of new antimicrobials [39], and more recently through the Global Antibiotic Research & Development Partnership (GARDP). At the country level, such prioritization processes can help drive national research funding, prompt updates to AMR national action plans, and support maximal learning from national AMR actions.

#### 7.4.2 Systematic reviews

**Researchers need to use rigorous systematic reviews to inform research prioritization and to summarize the effectiveness of policy interventions.**

Rigorous systematic reviews and evidence gap maps can support the planning of policy interventions by ensuring that they are adequately supported by evidence. However, to be useful, these reviews must be high quality and regularly updated. Health Systems Evidence has appraised and catalogued more than 50 systematic reviews related to health systems and antimicrobial use dating back to the year 2000, and this database shows that the rigour and quality of these reviews is mixed [40].

Conducting systematic reviews to summarize what we currently know is an essential input for research prioritization. Reviews can collate empirical evidence to answer a specific research question [41], but they can also map the availability of evidence to identify evidence gaps. The Campbell Collaboration and others have recently developed methodological guidance for creating evidence gap maps [42]. Systematic reviews need to be regularly updated to include new evidence as it arises, to determine whether research gaps have been addressed, and to determine

whether the research question has been satisfactorily answered, or whether future, more refined research is needed. Given that the current evidence base is weak, policy decisions in the near-future will be informed on relatively weak signals from the research base, which reinforces the need for further evaluation.

Systematic reviews can also ensure that research efforts are not wasted on questions that have already been definitively answered [22, 43]. Although replication is key to science, there is a point at which additional replication holds little additional value [21]. For example, it has been definitively shown that hospital antimicrobial stewardship interventions are effective at reducing antimicrobial use compared to control, and should be a standard part of the AMR response [17]. Future research can, instead, focus on optimizing stewardship for different contexts in order to maximize effects. This includes opportunities to embrace a philosophy of radical incrementalism, where a series of small evaluated changes one after the other result in radical cumulative change [44].

#### 7.4.3 More planned evaluations

**Researchers need to work with stakeholders to ensure that rigorous evaluations of all new AMR programs are the norm.**

Researchers can actively advance progress on AMR by ensuring that evaluations of policies become the norm. While rigorous evaluations of all AMR interventions would be ideal, at present we are very far from this reality [19]. Policy responses to AMR — from legislation and government regulation to public awareness campaigns — have played a major role in responding to AMR, yet these policies are rarely conceptualized as population health interventions, and, as a result, are rarely pilot-tested, reviewed, or evaluated with sufficient rigour to expand the AMR evidence base.

Without a culture of evaluation, we risk implementing, maintaining, and even spreading ineffective or inefficient AMR policies, at great financial cost and opportunity cost. And, though policymakers do not always see their added value, there are political advantages in conducting good impact evaluations; evaluation puts policymakers in the politically attractive position of continuous policy improvement, enables them to ensure that research assessing their initiative is

appropriate, and reduces political risk because they can acknowledge that they are operating with imperfect information [45]. Where possible, researchers should advise and partner with policymakers to raise the rigour of evaluations, simultaneously making progress on scientific questions. In particular, researchers should advocate for the development of protocols and evaluation plans *a priori*, which will help minimize waste of public resources in ineffective programs by ensuring that the data collected is appropriate to answer key policymaker questions, while also supporting implementation and future improvements in practice by ensuring that data is internationally comparable, and can feed into future evidence syntheses of similar policy interventions.

#### 7.4.4 Research that is responsive to stakeholder needs

**Research needs to be planned to address policymakers' questions about effectiveness, implementation, costs, and equity.**

Moving from evidence to policy inevitably involves consideration of pragmatic and ideological factors beyond evidence of effectiveness [46]. Researchers can support evidence-informed policymaking by considering, in advance, the likely information needs of policymakers. In addition to effectiveness, decisions to pursue or pass over various AMR policy interventions are likely to be informed by their perceived cost-effectiveness, equity and differential impacts based on gender, race and socioeconomic status, implementation challenges, and acceptability to diverse social groups. This is particularly true in the case of LMICs, where resources are scarce and where the level of evidence required before investing in policy action may be substantially higher [45].

One simple and intuitive tool for enabling policymaker engagement in research planning is to use the APEASE criteria (Box 7-2). Originally created as a framework for evaluating ideas for interventions, APEASE offers a useful structure for framing research questions and evidence needs in partnership with stakeholders, and for communicating policy relevant research findings. APEASE addresses many common stakeholder concerns including equality and equity considerations, acceptability across a wide range of groups, and the feasibility and practicality of an intervention in a given context, while recognizing important trade-offs. Consider, for

example, that both the clinical effectiveness and cost-effectiveness of an intervention is irrelevant if the intervention is unaffordable or infeasible given funding and resource constraints in a given context. In addition to the feasibility of implementation, it is useful to consider whether the intervention should be, or can be, equally applied across the whole population, and whether it will reach its target population and intended beneficiaries. Again, the inclusion of these additional research questions in the planning phase will particularly benefit policymakers in lower-resource settings, who must consider whether interventions from high-income settings could translate effectively to their setting, given the staff and resource limitations particular to their context.

Box 7-2: The APEASE Criteria [47]

**A**ffordability

**P**racticability

**E**ffectiveness/Cost-Effectiveness

**A**ceptability – Public, Professional, Political

**S**ide-effects/safety

**E**quality

## 7.5 Research conduct

### 7.5.1 Better design of AMR interventions

**Researchers need to use theory, frameworks, and logic models to design more coherent AMR policy interventions.**

Unfortunately, to date, the approach to designing AMR policy interventions has been ad hoc, and seems to be guided by the “it seemed like a good idea at the time” principle, rather than by an explicit process that considers the determinants of the problem, relevant theory and available empirical evidence [17, 19]. This strategy has often resulted in poorly considered AMR policies that — although designed to change attitudes, beliefs and practices around antimicrobial use — cannot clearly articulate how their intervention will successfully bring about this change. Poorly designed policies may also fail to recognize and address key AMR determinants, leading to ineffective or sub-optimally effective interventions.

Researchers can improve the design of AMR policy interventions by employing, and advocating for the inclusion of theory, frameworks, and logic models in the early stages of intervention design to describe how and why an intervention is expected to work. These steps can substantially address the common tendency in AMR to re-invent the “square” wheel rather than build on existing evidence from behavioural and implementation science. When planned without the use of theory, interventions are more likely to be unclear in the behaviours and outcomes targeted, and the means by which the intervention will achieve its intended effect [27]. The process of building such models can encourage researchers to consider all aspects of the intervention and the existing AMR evidence base. The UK Medical Research Council has published a useful framework for developing and evaluating complex interventions [48, 49]. Other useful frameworks include the Behaviour Change Wheel [43] to guide intervention development, the Theoretical Domains Framework to assess factors that impact behaviour, and the Behaviour Change Techniques taxonomy [50] which considers individual component strategies employed to change behaviour (e.g., feedback on behaviour, goal setting, prompts and cues) under the umbrella of a larger intervention [51]. Finally, the use of theories, frameworks

and logic models also facilitate research communication and dissemination, making clear the considerations and circumstances that drove the initial hypothesis.

### 7.5.2 Better design of evaluations

**Researchers need to ensure that policy interventions are evaluated using the most rigorous designs feasible in the given circumstances.**

When promoting a culture of AMR policy evaluation, improving and strengthening the design of evaluations should also be considered. One challenge in AMR research has been a lack of differentiation between *program* evaluation (i.e., evaluating whether the local program achieved its goals) and *research* evaluation (i.e., addressing generalizable concerns about what, when, how, and why an intervention works). While program evaluation is important, policymaking needs to be guided by robust evidence generated using rigorous study designs. AMR policy intervention research has been plagued by poor quality and inappropriate evaluation methods. In a recent systematic review, 30 of 69 included studies used uncontrolled before-after designs and simple descriptive methods that cannot control for important design concerns including bias, confounding, and secular trends, and are generally uninterpretable [6, 52, 53].

Overall, interventions should be evaluated using the most rigorous study designs feasible in the given circumstances, in order to minimize bias and maximize generalizability of findings. Choice of evaluation design will be guided by numerous factors, such as whether it is feasible to randomize intervention sites, whether there is a requirement to introduce the intervention at all sites, the acceptability of having a no-intervention control group, and the number of available intervention sites (Figure 7-2).

The focus on education, attitudes and behaviour change in AMR research, and the associated high likelihood of contamination, will likely preclude the use of RCTs randomized at the individual level in much of AMR policy intervention research. In most cases, a cluster randomized controlled trial (cRCT) should be considered the gold standard for AMR policy intervention evaluations [54]. Cluster randomization can be done at numerous levels, although trade-offs exist between the number of available units (e.g., regional level) and the risk of contaminations (e.g., provider level). Cluster randomized trials can take many forms, including

two arm trials, multi-arm trials, and factorial designs where two or more interventions can be carried out simultaneously. Another cluster design, the stepped wedge trial — where all sites start in the control arm and end in the intervention arm, crossing over to intervention sequentially and in random order [55] — may have many practical benefits for large policy evaluations where roll-out of an intervention to all sites within a health system or community is a requirement [56]. Figure 7-3 illustrates these recommended evaluation designs.

Where random allocation is not feasible (either due to an inadequate number of randomization units being available or because simultaneous implementation across the health system is required) interrupted time series (ITS) methods are the strongest study design for AMR research [57]. However, adding a control group [58], or additional sites with staggered implementation of interventions (multiple baselines ITS design [59]) can strengthen this design. Researchers should pay particular attention to whether an ITS design is appropriate for their study. ITS designs are best used for evaluating AMR interventions that have been implemented at a *clearly defined point in time* [57]; many AMR studies have inappropriately used this design to measure complex interventions rolled out in stages across several months or years. deKraker et al. have carefully considered the validity and bias concerns associated with these study designs and have published two excellent guides for evaluating antimicrobial stewardship interventions, which are also highly relevant to other AMR policy interventions [52, 54].

Uncontrolled before-after study designs, which historically, have been common in AMR research, should be avoided completely. The apparent effects of an intervention using these designs are completely confounded by secular trends and concurrent events. Even controlled-before-after studies, which mitigate this threat of confounding to a limited extent, should be avoided unless there are at least two intervention sites and two control sites, at which point, other more rigorous study designs may be feasible. Controlled-before-after studies and non-randomized trials are an option when randomization is not possible and there is insufficient data to conduct an ITS, however, these designs should only be considered as hypothesis generating. Figure 7-2 outlines some of the methodological considerations for choosing a prospective evaluation design.

Researchers can advocate for the use of more rigorous study designs, and partner with policymakers to ensure that evaluations are appropriately conducted. To move beyond effectiveness, research evaluations need to incorporate opportunities for addressing the other important questions described earlier, namely, *why* interventions work and *what* elements are necessary for their success. Once the initial effectiveness of an intervention has been shown, there is an opportunity to conduct controlled head-to-head comparisons of interventions in the interest of optimization, either through sequential trials comparing variations of the intervention, or using factorial designs to evaluate whether the addition of co-interventions meaningfully changes the intervention's effectiveness. These head-to-head designs are far more efficient than conducting a systematic review to compare intervention variations and can be facilitated by the development of implementation laboratories which involve close collaboration between research teams and health systems delivering implementation strategies at scale [56]. Head-to-head trials can also be designed to enhance the generalizability of evaluation by including fidelity sub-studies to determine whether an intervention was delivered and received as designed, mechanistic sub-studies to determine whether the intervention acted through the hypothesized pathways, qualitative process evaluations to investigate experience and acceptability, and economic evaluations [61].

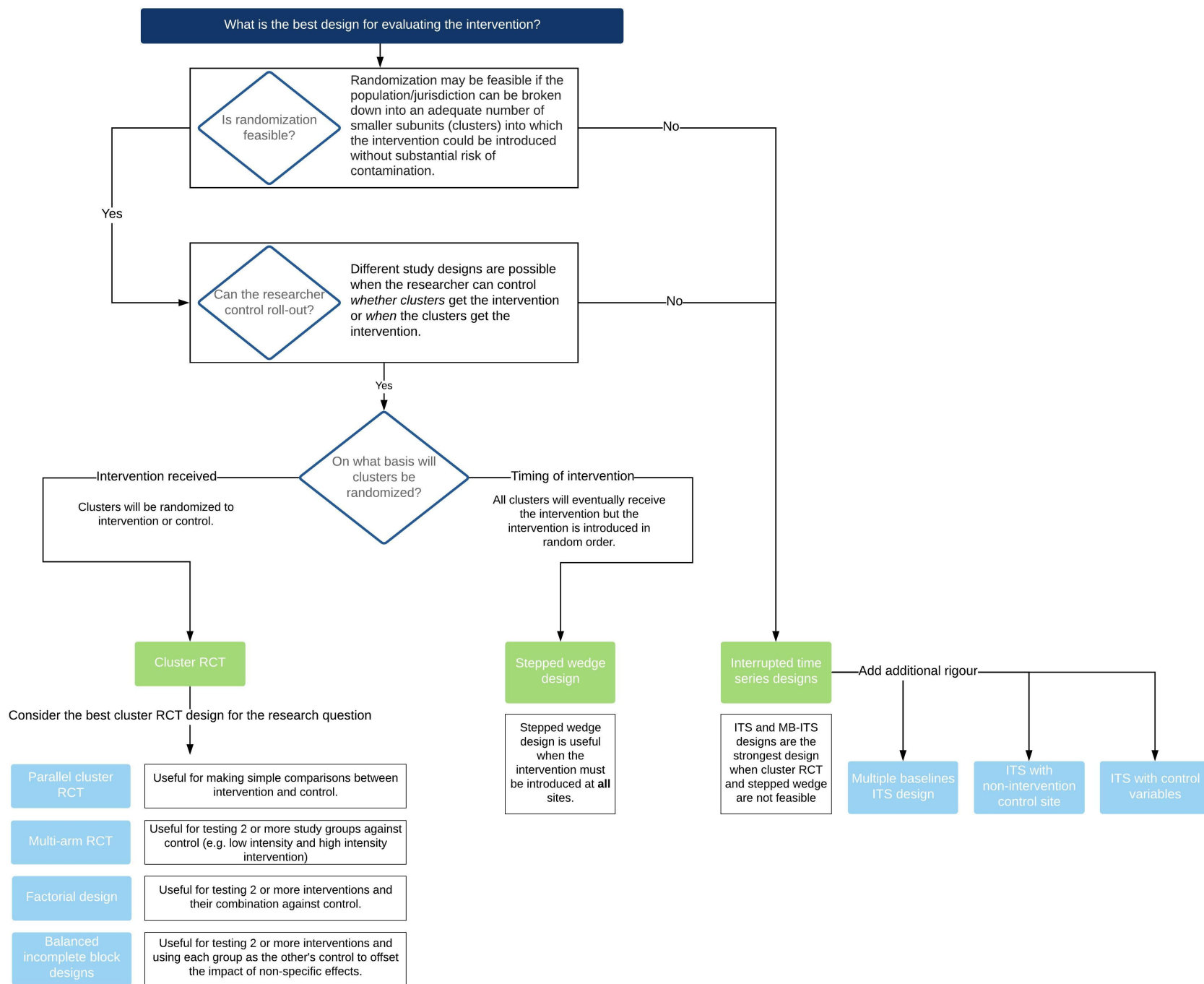
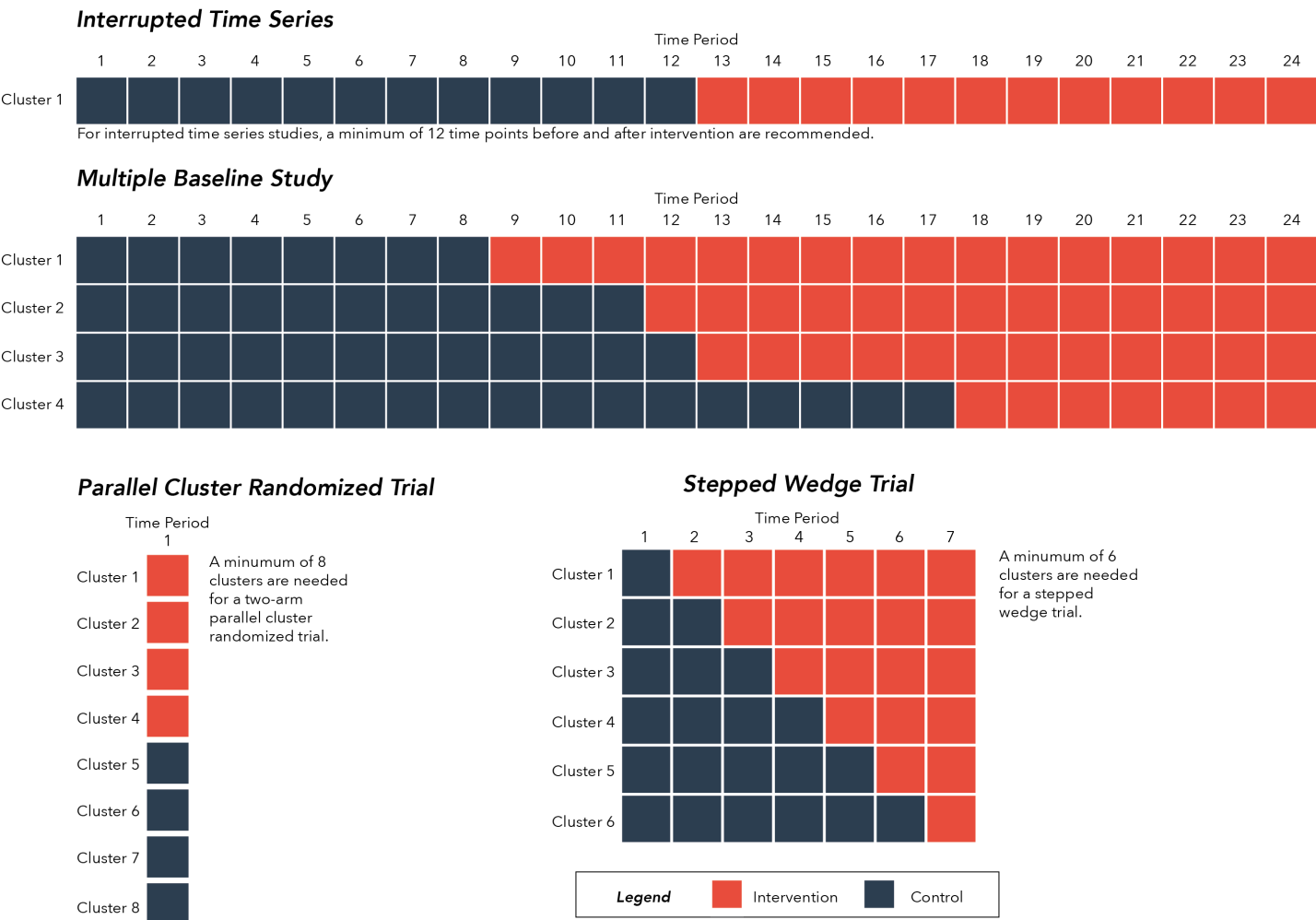


Figure 7-2.  
Considerations  
when choosing  
a prospective  
evaluation  
design for AMR  
policy  
interventions.

Figure 7-3. Recommended study designs for evaluating AMR policy interventions.



### 7.5.3 A set of standard measures and metrics

**Researchers need to define a set of core outcome measures for AMR research that address appropriate antimicrobial prescribing, development of antimicrobial resistance, and cost-effectiveness of policy interventions.**

AMR lacks both an agreed-upon metric for evaluating progress, and a common system for measuring the scope of the problem. Researchers can have a significant impact in these ongoing conversations by developing measures that facilitate data sharing; for example, through an agreed minimum dataset for collecting intervention data, and a core outcome set of measures to facilitate evaluations. Consideration should also be given as to whether a core outcome set can feed into AMR and antimicrobial use surveillance to facilitate the use of routinely collected data in impact evaluations.

A harmonized set of measures for conducting and evaluating interventions serves three purposes. First, it creates consistency between evaluations that facilitates systematic reviews to inform evidence-informed policymaking. Lack of a shared outcome measure is a common challenge in public health systematic reviews and one which limits the amount of evidence that can be rigorously synthesized [62]. Second, creating a harmonized set of methods offers the opportunity to include, as a requirement, metrics beyond impact that are relevant to stakeholders, such as equity considerations and cost-effectiveness. Finally, developing a set of harmonized measures offers an opportunity to consider common barriers to AMR policy implementation and to develop standard measures and indicators that also address these needs.

While there are substantial political and economic barriers to improving data collection and evaluation, from a metrics viewpoint, there are numerous successful initiatives that have adopted research governance principles to improve data collection and comparability of research studies, including the Core Outcome Measures in Effectiveness Trials (COMET) group [63], and ESSENCE for Health Research [64]. Outcome Measures in Rheumatology (OMERACT), for example, uses a data driven, iterative process to choose shared outcome measures across 4 domains, and each selected measure must meet 3 criteria: truth, discrimination, and feasibility [65]. The recently released (May 2019) tripartite monitoring and evaluation framework from the

WHO, FAO, and OIE suggests a number of indicators and is a useful starting point for these efforts [66].

## **7.6 Research dissemination**

### **7.6.1 Better reporting of interventions**

**Researchers need to register research protocols and evaluation trials, and use reporting guidelines and checklists to improve reporting quality.**

An effective and coherent global response to AMR requires full and transparent reporting of all aspects of AMR intervention studies. Unfortunately, public health research as a whole, and AMR specifically, faces challenges in this domain. Inaccessible research, partial reporting, and publication bias are all common in AMR research [19, 67] and limit opportunities for researchers and policymakers to learn from experiences in other contexts.

Researchers should register protocols, primary evaluations of policy interventions (both RCTs and quasi-experiments) and systematic reviews in trial registers. Pre-registration of an evaluation helps address the tendency to avoid publishing the results of research with neutral or negative findings, which is common to much of scientific research, and may be particularly common in policy research where government partners may feel that they lose credibility if a policy intervention is found to be less effective than expected. The fields of clinical trials and systematic reviewing — which both use protocol registration to reduce publication bias, and to enable other researchers to see whether a research study on a particular topic is ongoing — have benefited from the support of research funders, journals and research ethics boards to promote these efforts to improve research reporting [67]. Along with trial registration, researchers, governments, and other implementing organizations should commit to full and transparent reporting of study results in open-access journals, and to making datasets available to other researchers.

Researchers should also embrace the use of reporting guidelines and checklists to overcome common reporting challenges such as: not describing the intervention specifically enough to allow replication [19, 51]; using the same description to represent different types of interventions [68]; using different terminology to represent the same content [69, 70]; and repetition without

improvement [71]. The TIDieR tool [72] for describing and replicating interventions, and its extension TIDieR-PHP [73] for population health and policy studies, are both useful tools for researchers to ensure that their intervention has been thoroughly described. The SQUIRE checklist [74] for quality improvement interventions, and the CONSORT statement [75] for RCTs and its many extensions to cRCTs [76], stepped wedge trials [56], pilot studies [77], and pragmatic trials [78] are all useful tools to ensure the full reporting of methods and findings within a study report.

### 7.6.2 Shared learning opportunities

**Researchers need to embrace open-data and open-access opportunities to widely disseminate research findings.**

The principle of shared learning is familiar to researchers and embedded in much of health research. A key question facing the field is how best to promote this ideal when working with stakeholders to develop effective and efficient AMR policy interventions. There is an opportunity, however, as many governments embrace nudge units, innovation hubs, and radical incrementalism [44], for researchers to reiterate the substantial benefits of shared learning. Many new methodological tools can support these efforts: data sharing platforms and open-access information repositories will both go a long way to ensuring the evidence generated from policy experiments and intervention evaluations can support shared learning. Likewise, living systematic reviews — which are continually updated as new evidence is generated [79] — will also help ensure that new policies are planned based on current evidence.

## 7.7 Discussion

Although the threat posed by AMR has been well-known for many decades, recent escalation in multi- and extensively drug-resistant bacterial infections has elevated AMR to a more prominent position on the international political agenda. Substantial work is ongoing at the national level to address domestic AMR concerns [27], and, there are robust conversations at the international level about pursuing more large-scale, coordinated efforts to mitigate the AMR threat, such as an international legal treaty on AMR [8, 11, 80-82]. Innovative approaches have been taken to

research funding (e.g., JPIAMR [83]), health systems strengthening (e.g., Accreditation Canada [84]), and global policy monitoring (e.g., WHO [31]).

These national and international efforts require substantially more evidence for the effectiveness and feasibility of AMR policy interventions than is currently available. This gap, however, provides an opportunity for researchers to engage in a meaningful conversation about the importance of evidence-informed policymaking for AMR. Mitigating the threat posed by AMR will also require substantial collaboration among researchers and policymakers. Table 7-1 describes many of the ways in which research funders, publishers, and policymakers can jointly support researchers and facilitate action across the priorities identified in this framework. With their ability to strategically fund innovative research, encourage researchers to use rigorous study designs and reporting checklists, and facilitate shared learning, these partners have an opportunity to amplify researchers' calls for better AMR practice.

As we have highlighted, it is increasingly important to strengthen the scientific evidence base on AMR policy interventions, to learn from existing policies and programs, and integrate scientific evidence into the global AMR response [6]. This framework offers a path forward, increasing local and global cooperation, and overcoming common limitations in existing research on AMR policy interventions.

Table 7-1. Framework and recommendations for planning, conducting and disseminating evaluations of AMR policy interventions.

|                                                              | Researchers                                                                                                                                       | Policymakers                                                                                                                            | Research Funders                                                                                                                                                   | Publishers                                                                                                                                                              |
|--------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Mechanisms for prioritizing research</b>                  | Prioritize research to study <i>what</i> works, <i>when</i> it works, <i>why</i> it works, and <i>what elements</i> are necessary to its success. | Engage with the research community and make your evidence needs clear.                                                                  | Funding support for formal prioritization processes.<br><br>Targeted grant competitions to drive research in priority areas.                                       | Require that research reports summarize the evidence what was already known on a topic and show systematic review evidence that supports the conduct of an intervention |
| <b>Systematic reviews</b>                                    | Inform interventions using rigorous systematic reviews.                                                                                           | Partner with researchers to do evidence syntheses to inform policymaking.                                                               | Strategic funding support for systematic reviews, evidence syntheses, living systematic reviews.<br><br>Require evaluations to be justified by systematic reviews. | Support the publication of Systematic review protocols, systematic reviews, evidence syntheses, and living systematic reviews                                           |
| <b>More planned evaluations</b>                              | Work with other stakeholders to make rigorous evaluations of all AMR programs the norm.                                                           | Working with researchers, plan the evaluation strategy for a program or policy <i>before</i> launching the program or policy.           | Strategic funding support for evaluations of policy interventions and for policy-research partnerships to facilitate this research.                                | Require authors to register study protocols.                                                                                                                            |
| <b>Research that is more responsive to stakeholder needs</b> | Ensure that research addresses all informational needs of policy makers (e.g. including equity and cost-effectiveness)                            | Decide in advance what information and evidence you need to inform policymaking.                                                        | Encourage integrated knowledge translation and collaboration with stakeholders when awarding grants to support AMR policy research                                 | Ensure timely peer-review and publication of research to ensure that evidence is available to support stakeholders.                                                     |
| <b>Better design of AMR Interventions</b>                    | Use theory, frameworks, and logic models in the intervention design phase to frame how and why an intervention is expected to work.               | Use theory, frameworks, and logic models when planning policy interventions to clarify how and why an intervention is expected to work. | Do not fund interventions that do not employ theory, frameworks or logic models to describe how and why the intervention is expected to work.                      | Require authors to report on their use of theory, frameworks, and logic in the design and conduct of AMR interventions.                                                 |

|                                               |                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                              |                                                                                                                                                                                         |                                                                                                                                                  |
|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Better design of evaluations</b>           | Use the most rigorous possible evaluation designs to minimize bias and maximize generalizability.                                                                                                                                                                        | Embrace research evaluation.<br><br>Promote radical incrementalism (based on rigorous evaluation) to enhance the effectiveness of extant policies.                                                                                                                           | Studies using weak study designs (e.g. uncontrolled before and after designs) should not be funded.                                                                                     | Refrain from publishing studies that use poor quality methods such as uncontrolled before and after studies for evaluation of AMR interventions. |
| <b>A set of standard measures and metrics</b> | Develop a set of core outcome measures for AMR research                                                                                                                                                                                                                  | Partner with researchers to ensure that core-outcome measures address your key evidence needs.                                                                                                                                                                               | Funding support for the development of an AMR core-outcome set.<br><br>Require use of core-outcome measures in funded applications                                                      | Require researchers to use the core-outcome measures in published evaluations.                                                                   |
| <b>Better reporting of interventions</b>      | Commit to full and transparent reporting of studies.<br><br>Use reporting guidelines and checklists to fully report a study.<br><br>Register intervention protocols to reduce the risk of publication bias.<br><br>Avoid ‘spin’ especially with weak evaluative designs. | Publish or make available reports on the effectiveness of policy interventions and efforts to improve them.                                                                                                                                                                  | Make public the details of funded interventions.<br><br>Require full and transparent reporting of studies.<br><br>Require researchers to register the protocols of their interventions. | Require authors to use the relevant research reporting guidelines and checklists.<br><br>Publish research with neutral and negative results.     |
| <b>More opportunities for shared learning</b> | Disseminate research widely and embrace open-data and open-access opportunities.<br><br>Make datasets available to other researchers through data repositories.<br><br>Develop cross program collaborations to encourage learning and efficient knowledge generation.    | Take advantage of opportunities to borrow and adapt policy interventions from other contexts.<br><br>Make available data on policy interventions in your setting to promote uptake in other contexts and ensure that ineffective policy is not duplicated in other settings. | Provide funding for open access publishing, open data sharing platforms, cross program collaborations, and living systematic reviews.                                                   | Increased commitment and support for open-access publication                                                                                     |

## 7.8 Declarations

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## 7.9 List of supplemental files

There are no supplemental files for this manuscript.

## 7.10 Citations

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## 8 Integrated Discussion

The rise of antimicrobial resistance has significant implications for the health, security, and economic development of countries around the world [1, 2]. Efforts to stave off this growing infectious disease threat and conserve the effectiveness of antimicrobials have traditionally focused on education and communication to change the behaviour of individual patients and prescribers rather than addressing the health system and societal level barriers and enablers to lower prescribing [3, 4]. This individual approach neglects the evidence from a long and successful history of using policy and regulatory approaches to improve public health. Many of our most successful public health efforts — mass vaccination programs, tobacco control [5, 6], and seatbelt laws [7] among many others — have relied on policy and regulatory strategies to achieve their goals. Furthermore, there is evidence to suggest that health protection interventions (e.g. vaccination) and legislative interventions have the highest return on investment among public health interventions [8]. This makes policy and regulatory interventions an important part of the toolkit for governments around the world that have a responsibility to protect the health of their citizens.

AMR is currently enjoying a high level of political attention on the global stage, helped in part by leadership from the WHO [9], the United Nations [10], and the government of the UK [1]. Recent AMR scares, including the emergence of new resistant pathogens such as NDM-1 [11], artemisinin resistant malaria [12], and *C. auris* [13] have also helped bring AMR to the forefront of global health discussions. This focus on AMR offers a new opportunity to achieve meaningful action in the face of this global threat. Yet, public policy and program recommendations for AMR have changed little since the late 1990s and offer few concrete suggestions for reducing antimicrobial use [1, 14, 15].

Some aspects of AMR, such as hospital-based interventions to reduce prescribing, have received substantial research attention in recent years. A Cochrane review of interventions to improve antimicrobial prescribing in hospitals included 66 studies in 2005 [16], 89 studies in 2013 [17] and an impressive 221 studies in 2017 [3]. Policy interventions, however, have not received the same level of attention or evaluation. Limitations in AMR and antimicrobial use surveillance, including discrepancies between methods and monitoring systems and a lack of

representativeness have made evaluations of existing policies difficult [18] and without substantial improvements there is a real danger of implementing, maintaining and even spreading ineffective AMR strategies. As such, the goal of this dissertation was to examine the evidence on policy and regulatory interventions for AMR, and to strengthen the scientific evidence base by exploring and appraising the evidence and developing recommendations and best practices.

## **8.1 Summary of Research Findings**

An underlying goal of this dissertation was to inform the development of national action plans on AMR with evidence from rigorously evaluated, evidence-based policies. It was with these needs and users in mind that I developed the protocol for a systematic review and meta-analysis outlined in Chapter 2. The intent was to conduct two closely related reviews that would speak to the evidence needs of government policy-makers: a *descriptive review* to identify and describe any government policy interventions that had been implemented and evaluated with the objective of changing human antimicrobial use, and an *effectiveness review* to assess the impact of these government policy interventions on reducing human antimicrobial use. By synthesizing the evidence on previously evaluated government policy interventions, our goal was to inform the development, prioritization and adoption of new policies to reduce human antimicrobial use.

In this respect, a key finding of this dissertation is the need for better evidence to support policymakers. Chapter 3, my systematic review and evidence map, reports the findings from this descriptive review. The main challenge in reviewing the literature in Chapter 3 was that many of the identified policy options were not rigorously evaluated, and due to the poor-quality methods employed, their effectiveness is unknown. The goal of Chapter 5, our effectiveness review, was to better understand the effectiveness of various government policy interventions, and we limited the included studies to those rigorous evaluations using experimental or quasi-experimental methods. This decision substantially reduced the available evidence on policy interventions and the remaining studies were predominantly evaluated in Europe and North America. The study did find evidence for the effectiveness of particular policy approaches in particular settings and contexts, but the identified interventions were too disparate to comment on their likely

effectiveness if implemented in other contexts, and it was not possible to conduct a meta-analysis on any of the policy options.

In spite of these challenges with the quality of both reviews, there is good news on three fronts: first, there are numerous policy options available to policymakers that can address AMR, second, it is possible to conduct rigorous policy evaluations of AMR policy, and third, there is evidence that diverse policy approaches have been successful in bringing about reductions in antimicrobial use in particular settings and contexts. Chapter 3, which I have conceptualized as a “menu” of options for policymakers, identifies and describes the range of previously evaluated policies and finds 17 unique policy options that governments could try in order to reduce human antimicrobial use. These 17 options included some commonly discussed approaches, such as public awareness campaigns and guidelines, and some more innovative approaches, such as vaccination programs and changes at the health system level. Chapter 5 found 18 examples of rigorous policy evaluations which point to the potential effectiveness of programs such as antimicrobial guidelines in high income countries, long-term national public awareness campaigns in high income countries, and banning over-the-counter sales of antimicrobials in Latin America. Ideally Chapters 3 and 5 will act as a starting point for policymakers looking to develop new approaches to reduce antimicrobial use, particularly as many countries are not yet implementing their national action plans [19].

Chapter 4 is an additional analysis that was not described in our initial systematic review protocol. Recognizing however, that reporting quality is a challenge in much of public health research and that there is a growing body of literature exploring the quality of scientific reporting [20-25], we decided to apply this lens and evaluate the quality of reporting among studies captured in our systematic review and evidence map (Chapter 2). We found that reporting quality among these studies was poor, creating challenges for interpreting and replicating study results. Of particular concern, considering the importance of shared learning and using these studies as an evidence base for future evaluations, was that 80% of included studies did not report the elements of the intervention in sufficient detail for replication, and 75% did not clearly articulate why they thought this intervention was likely to work. The failure to report — or to use — theories of change in the design of the interventions was particularly troubling. Our findings

of weak reporting for the rationale and description of the intervention, are supported by research that suggests interventions planned without the use of theory often result in interventions that are unclear about the behaviours and outcomes being targeted and the means by which the intervention will achieve their intended effects [28].

Chapters 2-5 investigated the existing evidence base and focused on published impact evaluations of AMR policies. At this point however, we were already aware of additional policy interventions that had not been captured by our systematic review because they had not been evaluated, had not been evaluated with respect to antimicrobial use, or had not been reported in peer-reviewed or grey literature. To further explore these unpublished policy interventions, we conducted a case study of policy interventions in the Canadian context (Chapter 6). While we identified at least one program in most Canadian jurisdictions, these were often limited to public awareness campaigns or stewardship efforts, and we found few examples of other policy strategies including fiscal measures, guidelines, and regulations. Overall, we found that AMR efforts in Canada have been too few, too small and too uncoordinated to address this global threat. Investments and policy action on AMR in Canada have also been woefully inadequate and many of the existing programs were not supported by scientific evidence. The findings from this environmental scan also point to a level of policy activity on AMR that did not get picked up by our systematic review; our survey identified a number of communication and guidelines programs that aimed to change knowledge and behaviour related to AMR that were never evaluated for effectiveness. The small scale of these interventions and the lack of consistent data on antimicrobial prescribing across Canada [26] may explain the lack of evaluations. WHO data shows that Canada sits middle-of-the-pack in terms of global AMR efforts [19, 27], so it is reasonable to hypothesise that there are many small AMR programs and policies in other countries which have gone similarly un-evaluated. This highlights the urgent need for more investment and action on AMR, data collection, and evaluation to ensure that we learn from the successes and failures of existing AMR policies.

Chapters 2-6 allowed me to identify a number of challenges to evidence-informed decision making on AMR, and in Chapter 7 I integrated these findings to develop a framework for improving the evidence in this field. Building on the previous chapters, we identified areas for

improvement in three phases: the intervention planning phase, conducting the study, and disseminating the findings. The first section on intervention planning offers advice and best practices on mechanisms for prioritizing research, better design of interventions by incorporating insights from previous research (systematic reviews) and jurisdictional barriers to AMR action and behavioural and organisational science, planning intervention evaluations a priori, and developing research evidence that is responsive to stakeholder needs. Drawing on the literature reviewed in Chapters 3 and 5 (and other published systematic reviews), the conduct section offers advice for designing AMR interventions, an overview and guide to rigorous methods for evaluating interventions and discusses the need for a standard set of measures and metrics for AMR evaluations. Finally, drawing heavily on the findings from Chapter 4 and 5, the section on dissemination highlights the need for better reporting of interventions and expanding the opportunities for shared learning in AMR interventions. The majority of the framework speaks directly to researchers and analysts who are conducting evaluations of AMR research; however, the discussion also offers a number of action steps for policymakers, research funders and publishers on each of the framework's 9 components. Taken together, the framework offers a path forward for increasing local and global cooperation and overcoming key limitations in order to strengthen the evidence-base for future AMR policy development.

## **8.2 Implications for policymakers**

To adequately address the threat posed by AMR, governments and international actors need to bring about widespread decreases in antimicrobial use. As we have outlined in Chapter 5, promising strategies for achieving this goal include guidelines, stopping over-the-counter sales of antimicrobials, and long-term, recurring, public awareness campaigns. To ensure efficient use of public resources and maximize opportunities for shared learning, policymakers should also develop rigorous evaluation plans alongside these interventions to measure local effectiveness. Government policymakers need to consider how these strategies, and other innovative strategies as outlined in Chapter 3, can be combined into a comprehensive national strategy for AMR. As we have highlighted in the Canadian context (Chapter 6), the implementation of many small, ad hoc AMR policies is insufficient to meet national goals. These national strategies need to ground their policies in scientific evidence and consider the relevance, feasibility and affordability of

different interventions in their setting; as we have shown in Chapter 5, the success of many AMR interventions depends on ability and willingness to implement and maintain the intervention over time. Substantial collaboration and coordination are needed between different local and national governments, and the One Health nature of the AMR threat demands collaboration between human, animal and environmental health actors.

Maximizing global learning from AMR policy across different jurisdictions will require a greater commitment to evaluating government policies. Although rigorous policy evaluations are the ideal, they are not currently the norm in AMR research which has led to a great deal of research waste. Nearly three-quarters of the AMR impact evaluations identified in Chapter 3 could not be used in the effectiveness review in Chapter 5 as a result of poor study design, and Chapter 4 showed that many of these studies did not report why they believed the intervention was likely to work in the first place. Chapter 7 describes a number of approaches for strengthening the evidence base on AMR, but achieving this goal will require substantial support from all corners. Government policy makers need to be committed to engaging researchers in the design and evaluation of their policy interventions from the beginning so that interventions and evaluations can be planned in tandem. Furthermore, funders and publishers of scientific research need to commit to funding and publishing only high-quality research that can inform the results of new systematic reviews and push the evidence-base further.

Developing the scientific evidence-base will take time, but in the short-term, there are many improvements to AMR interventions that can be made on the basis of existing knowledge from implementation science and behaviour change literature, and the lack of AMR specific research in these areas need not present a barrier to improving interventions. There is substantial literature on how to design interventions [28-30], change healthcare provider behaviour [31-33], improve guideline development and dissemination [34-36], conduct audit and feedback [37-39], and evaluate policy interventions [40-46]. Developing and evaluating new policies in accordance with this literature is a good first-step for expanding the AMR evidence-base.

Although the OECD estimates that the majority of deaths from AMR could be averted with an investment of only 2 USD per person per year [47], there are many gaps in the evidence base that prevent us from knowing how best to allocate these resources. These important gaps in the

evidence base, including challenges in data quality, limited or no evidence on effective AMR policies from entire regions of the world, and very limited consideration of equity all pose challenges in this respect, all of which must be overcome in order to mitigate the threat posed by AMR. As we have noted in previous chapters, successful policies from the global north are not likely to work the same in the global south, particularly as differences in health systems will change the type of policies that governments have at their disposal. For example, rather than changes in prescribing behaviour, some LMIC countries may find that the most impactful AMR policies are in fact investments in water and sanitation. With this in mind, every effort should be made to develop knowledge on AMR interventions across diverse global settings. Governments can avoid wasting public resources by ensuring that future antimicrobial resistance policy interventions are rigorously evaluated, published, and that all future policies are planned in accordance with the evidence.

This thesis has focused on the evidentiary inputs necessary to build strong governmental AMR policies. To achieve its intended impact however, this evidence needs to be integrated into government policies and enacted. Despite a shift towards evidence-informed policymaking, conventional knowledge translation efforts have been more successful in changing clinical behaviour than in changing public policy [48]. Decision-making authority within a government is diffused, involves complex hierarchies, and is increasingly shaped by non-governmental actors including the private sector, civil society actors [48, 49]. Moving the evidence from this dissertation into practice will therefore require engagement with a diverse array of actors from across these groups, including a discussion of the role of vested interests, such as the pharmaceutical industry, in AMR policymaking; defining the role of the pharmaceutical industry in AMR policy making will be particularly difficult given the need to stimulate innovation while regulating and reducing antimicrobial use [50].

### **8.3 Limitations**

The most important limitation of this research is its exclusive focus on human health. Antimicrobial use in humans represents only a fraction of total global antimicrobial use; the

same antimicrobials used in human healthcare are used in much higher quantities in agriculture for growth promotion and the treatment of sick animals. The nature of AMR and the mechanisms through which pathogens pass resistance genes has rendered it difficult to tease out the respective impacts of human and agricultural antimicrobial use on the increase in resistance. AMR is a One Health problem; mitigating the threat posed by AMR and improving public health outcomes will require policies and regulations that tie together human, animal, and environmental health. Although it was beyond the scope of this dissertation to explore the policy and regulatory interventions used to reduce antimicrobial use in agriculture, it is worth noting that many such policies exist (e.g. [51-54]). Policies which balance One Health obligations will not be easy to develop — for example, from an animal rights point of view, simply banning antimicrobial use in animals would be ethically unjustifiable. The policies presented in this dissertation largely focus on human health which, in some respects renders them simpler to implement, yet ethical questions will still arise about the need to balance access to antimicrobials for people in resource limited settings who currently lack access to these lifesaving drugs and conservation of antibiotics in order to secure the pool of effectiveness for future generations [55]. Research on this topic should emphasize the importance of the environmental and agricultural uses of antimicrobials, particularly as they are also ripe for policy and regulatory intervention, and in particular, explore the One Health implications of various packages of policies, and the ways in which packages of policy interventions might include elements from human health, agriculture and the environment.

This dissertation takes a broad conservation lens on the challenge of antimicrobial resistance. As direct measurements of changes in AMR are difficult, we have chosen to focus on reducing antimicrobial use and misuse, which is one of the key steps in the causal pathway for AMR. This choice means that many of the policies we engage with are reactive; we have captured policies that deal with decreasing antimicrobial use, largely in high-income countries. There are, however, other lenses on the challenge of AMR that we have not engaged with. For example, there is substantially more that could be done to reduce AMR at the level of infection prevention and control. The design of our systematic search strategy — with its focus on measured reductions in antimicrobial use — rarely captures these interventions. Our systematic review

captured only one study that looked at the effectiveness of vaccination campaigns. Vaccination campaigns are more likely to have been measured in terms of reductions in consultations for particular outcomes — the impact of the influenza vaccine for example, is commonly measured in terms of reductions in consultations for upper respiratory tract infections (URTI). Antibiotics are often prescribed inappropriately for URTI and reductions in this measure are likely an upstream indicator of reduced antibiotic use. Approaching AMR with the lens of infection prevention and control and using an outcome measure that captures reductions in consultations for illnesses where antibiotic overprescribing is common, would be a useful addition to our “menu” of policy options for AMR, and might yield several new strategies for reducing antimicrobial use, although the primary research may not have used antimicrobial use as their outcome measure of interest. This focus on conservation efforts also means that we do not engage with issues surrounding research and development for new antimicrobials and alternative therapies. There has been substantial theoretical discussion in the academic literature on policy mechanisms to encourage the development of new antimicrobials, and there have been strategic investments in new diagnostic tools as illustrated in Chapter 6 and by the UK’s Longitude Prize, but to the best of our knowledge, tools and drugs resulting from these policies and investments have not yet reached a point where they would be evaluated in terms of antimicrobial use. As has been discussed in the case of a legal agreement on AMR [55], it is likely that a comprehensive strategy for addressing AMR will require consideration of all three of these aspects: access, conservation, and innovation. More research will be needed to determine what policy mechanisms can most effectively be used to promote the access and innovations aspects of this tripod.

In line with our goal to inform the development of national action plans and strategies for AMR, in Chapters 2 through 5 we focused on government policies to reduce antimicrobial use.

Although we cast a wide net for government — including all levels of government and studies where government was an implementing partner — we recognize that there are other organizations in a position to take a policy approach to AMR. Governments have policy levers at their disposal (e.g. legislation) that are not available for to other policymakers, and although they do not have a monopoly on other policy levers that we studied (e.g. regulation and

communication) it is likely that other actors use these levers differently. Professional associations and colleges, for example, have a different relationship to those they regulate than the government. We recognize that excluding policies from these groups might have limited the number of studies we were able to include in Chapters 3 through 5. However, given the many differences that already exist in the organization of governments and health care systems we chose not to add this additional level of complexity, and instead focused our analyses exclusively on government.

Finally, there are a number of limitations to this body of research related to the availability of evidence and the existing evidence base. First, as in much of previous AMR research, we have focused on the impact of reducing antimicrobial use as a proxy measure for reducing AMR. To what extent antimicrobial use is a good proxy measure remains to be seen; temporally and geographically linking antimicrobial use to resistance has proved difficult [56, 57]. Furthermore, the development of resistance is not linearly related to antimicrobial use — any use of antimicrobials offers the potential for resistance to develop. Much of current data on antimicrobial use is still collected at a high level or using sentinel sites [18]. As surveillance of both antimicrobial use and AMR improves it will be important to elucidate this link and carry evaluations forward, or at least model the potential impact of interventions on resistance.

Second, despite our best efforts to include research across the breadth of AMR, much of the available research focuses exclusively on antibiotic resistance and fails to consider the importance of antifungal, antiviral, and anti-parasitics. Given the new threats posed by resistance to other antimicrobial drugs (e.g. malaria and *C. auris*) this represents a significant gap in the literature. Finally, we note that gender and equity considerations are rarely included in the existing evidence. This oversight is problematic: any policies that limit access to antimicrobial drugs are likely to have differential impacts based on gender and socioeconomic status, and these elements should be considered in the design and evaluation of AMR policies.

## **8.4 Conclusion**

Governments around the world have committed to respond to AMR, however, rigorous evidence to inform their policy and regulatory strategies is lacking. This dissertation examines the evidence on policy and regulatory interventions for AMR, and aims to strengthen the scientific

evidence base by exploring and appraising the evidence and developing recommendations for best practices. It is clear that the implementation of small, ad hoc policies is insufficient to meet national and global goals. As the threat posed by AMR grows, it is increasingly important to strengthen the scientific evidence base on AMR policy interventions, to learn from existing policies and programs, and integrate scientific evidence in to the global AMR response.

Governments have a variety of policy options at their disposal and should consider how these approaches can be coordinated to create a feasible and effective AMR response for their local context and setting.

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## Supplemental information - Chapter 2

### A2-1. PRISMA-P checklist: recommended items to address in a systematic review protocol<sup>1</sup>

| Section/topic              | #  | Checklist item                                                                                                                                                                                                            | Information reported                |                          | Line number(s) |
|----------------------------|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|----------------|
|                            |    |                                                                                                                                                                                                                           | Yes                                 | No                       |                |
| ADMINISTRATIVE INFORMATION |    |                                                                                                                                                                                                                           |                                     |                          |                |
| Title                      |    |                                                                                                                                                                                                                           |                                     |                          |                |
| Identification             | 1a | Identify the report as a protocol of a systematic review                                                                                                                                                                  | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 1              |
| Update                     | 1b | If the protocol is for an update of a previous systematic review, identify as such                                                                                                                                        | <input type="checkbox"/>            | <input type="checkbox"/> | N/A            |
| Registration               | 2  | If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract                                                                                                                  | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 62 and 132     |
| Authors                    |    |                                                                                                                                                                                                                           |                                     |                          |                |
| Contact                    | 3a | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author                                                                             | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 4-29           |
| Contributions              | 3b | Describe contributions of protocol authors and identify the guarantor of the review                                                                                                                                       | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 372-377        |
| Amendments                 | 4  | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments                           | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 130            |
| Support                    |    |                                                                                                                                                                                                                           |                                     |                          |                |
| Sources                    | 5a | Indicate sources of financial or other support for the review                                                                                                                                                             | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 365-370        |
| Sponsor                    | 5b | Provide name for the review funder and/or sponsor                                                                                                                                                                         | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 365            |
| Role of sponsor/funder     | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol                                                                                                                        | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 370-371        |
| INTRODUCTION               |    |                                                                                                                                                                                                                           |                                     |                          |                |
| Rationale                  | 6  | Describe the rationale for the review in the context of what is already known                                                                                                                                             | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 66-124         |
| Objectives                 | 7  | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)                                                                  | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                |
| METHODS                    |    |                                                                                                                                                                                                                           |                                     |                          |                |
| Eligibility criteria       | 8  | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 154-195        |

<sup>1</sup> PRISMA Checklist is formatted as it was published by the journal. Line numbers do not correspond to line numbers in this dissertation.

| Section/topic                             | #   | Checklist item                                                                                                                                                                                                                              | Information reported                |                          | Line number(s)  |
|-------------------------------------------|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|-----------------|
|                                           |     |                                                                                                                                                                                                                                             | Yes                                 | No                       |                 |
| <b>Information sources</b>                | 9   | Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage                                                        | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 196-215         |
| <b>Search strategy</b>                    | 10  | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated                                                                                                  | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 387             |
| <b>STUDY RECORDS</b>                      |     |                                                                                                                                                                                                                                             |                                     |                          |                 |
| Data management                           | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review                                                                                                                                                | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 130-139         |
| Selection process                         | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)                                                 | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 216-227         |
| Data collection process                   | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators                                                        | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 130-139         |
| <b>Data items</b>                         | 12  | List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications                                                                                       | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 390             |
| <b>Outcomes and prioritization</b>        | 13  | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale                                                                                                        | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 188-195         |
| <b>Risk of bias in individual studies</b> | 14  | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis                        | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 240-247         |
| <b>DATA</b>                               |     |                                                                                                                                                                                                                                             |                                     |                          |                 |
| <b>Synthesis</b>                          | 15a | Describe criteria under which study data will be quantitatively synthesized                                                                                                                                                                 | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 255-296         |
|                                           | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., $I^2$ , Kendall's tau) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 255-296         |
|                                           | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)                                                                                                                                         | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 252 and 255-293 |
|                                           | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned                                                                                                                                                          | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 252 and 291     |
| <b>Meta-bias(es)</b>                      | 16  | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)                                                                                                                 | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 255-296         |
| <b>Confidence in cumulative evidence</b>  | 17  | Describe how the strength of the body of evidence will be assessed (e.g., GRADE)                                                                                                                                                            | <input checked="" type="checkbox"/> | <input type="checkbox"/> | 307-311         |

## A2-2. Additional Search Strategies

### MEDLINE Search Strategy

1. Anti-Bacterial Agents/
2. Anti-infective Agents/
3. 1 or 2
4. ((antibiotic? or alamethicin? or amdinocillin? or amdinocillin pivoxil? or amikacin? or amoxicillin? or amoxicillin-potassium clavulanate combination? or amphotericin? or ampicillin? or anisomycin? or antimycin? or aurodox? or azithromycin? or azlocillin? or aztreonam? or bacitracin? or bacteriocin? or bambarmycin? or bongkreikic acid? or brefeldin? or butirosin sulfate? or calcimycin? or candidin? or capreomycin? or carbenicillin? or carfecillin? or cefaclor? or cefadroxil? or cefamandole? or cefatrizine? or cefazolin? or cefixime? or cefmenoxime? or cefmetazole? or cefonicid? or cefoperazone? or cefotaxime? or cefotetan? or cefotiam? or cefoxitin? or cefsulodin? or ceftazidime? or ceftizoxime? or ceftriaxone? or cefuroxime? or cephradine? or cephaloglycin? or cephaloridine? or cephalosporin? or cephalothin? or cephamycin? or cephapirin? or cephradine? or chloramphenicol? or chlortetracycline? or citrinin? or clarithromycin? or clavulanic acid? or clavulanic acid? or clindamycin? or cloxacillin? or colistin? or cyclacillin? or dactinomycin? or daptomycin? or demeclocycline? or dibekacin? or dicloxacillin? or dihydrostreptomycin sulfate? or diketopiperazine? or distamycin? or doxycycline? or echinomycin? or edeine? or enviomycin? or erythromycin? or erythromycin estolate? or erythromycin ethylsuccinate? or filipin? or floxacillin? or fluoroquinolone? or fosfomycin? or framycetin? or fusidic acid? or gentamicin? or gramicidin? or hygromycin? or imipenem? or josamycin? or kanamycin? or kitasamycin? or lactam? or lasalocid? or leucomycin? or lincomycin? or lincosamide? or lucensomycin? or lymecycline? or mepartricin? or methacycline? or methicillin? or mezlocillin? or mikamycin? or minocycline? or miocamycin? or moxalactam? or mupirocin? or mycobacillin? or nafcillin? or natamycin? or nebramycin? or neomycin? or netilmicin? or netropsin? or nigericin? or nisin? or norfloxacin? or novobiocin? or nystatin? or ofloxacin? or oleandomycin? or oligomycin? or oxacillin? or oxytetracycline? or paromomycin? or penicillanic acid? or penicillic acid? or penicillin?? or piperacillin? or pivampicillin? or polymyxin b? or polymyxin? or pristnamycin? or prodigiosin? or ribostamycin? or rifabutin? or rifamycin? or ristocetin? or rolitetracycline? or roxarsone? or roxithromycin? or rutamycin? or sirolimu? or sisomicin? or spectinomycin? or spiramycin? or streptogramin?? or streptomycin? or streptovaricin? or sulbactam? or sulbenicillin? or sulfamerazine? or sulfamethoxypyridazine? or talampicillin? or teicoplanin? or tetracycline? or thiamphenicol? or thienamycin? or thiostrepton? or ticarcillin? or tobramycin? or troleandomycin? or tunicamycin? or tylosin? or tyrocidine? or tyrothricin? or valinomycin? or vancomycin? or vernamycin? or viomycin? or virginiamycin? or beta-lactams) adj2 (use\* or misuse or consume or consumption or intake or dose or dosage or prescription\* or prescrib\* or overprescrib\* or sale\* or rate\*)).ab,ti.
5. 3 and 4
6. (adjust\* or alter\* or change or changes or changing or control\* or decreas\* or limit\* or modify or modified or modifying or reduce or reducing or reduction\* or restrict\* or appropriate or inappropriate or rational\* or irrational\*).ab,ti.
7. exp policy/
8. exp policy making/
9. exp legislation as Topic/
10. exp Government/
11. Government Regulation/
12. (program\* or campaign\* or policy or policies or guideline\* or ban or banned or Regulat\* or law or laws or prohibit\* or restrict\* or legislat\* or report\* or tax\* or audit\* or formular\* or expenditure\* or spending or label\* or market\* or advertis\* or consultation\*).ab,ti.
13. (health\$ adj2 (policy or policies or planning or priorit\$)).ab,ti.
14. 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 5 and 6 and 14
16. exp animals/ not humans.sh.
17. 15 not 16

## EMBASE Search Strategy

1. exp antiinfective agent/
2. exp antibiotic resistance/
3. ((antibiotic? or alamethicin? or amdinocillin? or amdinocillin pivoxil? or amikacin? or amoxicillin? or amoxicillin-potassium clavulanate combination? or amphotericin? or ampicillin? or anisomycin? or antimycin? or aurodox? or azithromycin? or azlocillin? or aztreonam? or bacitracin? or bacteriocin? or bambermycin? or bongkreikic acid? or brefeldin? or butirosin sulfate? or calcimycin? or candidin? or capreomycin? or carbenicillin? or carfecillin? or cefaclor? or cefadroxil? or cefamandole? or cefatrizine? or cefazolin? or cefixime? or cefmenoxime? or cefmetazole? or cefonicid? or cefoperazone? or cefotaxime? or cefotetan? or cefotiam? or cefoxitin? or cefsulodin? or ceftazidime? or ceftizoxime? or ceftriaxone? or cefuroxime? or cephradine? or cephaloglycin? or cephaloridine? or cephalosporin? or cephalothin? or cephamycin? or cephradine? or chloramphenicol? or chlortetracycline? or citrinin? or clarithromycin? or clavulanic acid? or clavulanic acid? or clindamycin? or cloxacillin? or colistin? or cyclacillin? or dactinomycin? or daptomycin? or demeclocycline? or dibekacin? or dicloxacillin? or dihydrostreptomycin sulfate? or diketopiperazine? or distamycin? or doxycycline? or echinomycin? or edeine? or enviomycin? or erythromycin? or erythromycin estolate? or erythromycin ethylsuccinate? or filipin? or floxacillin? or fluoroquinolone? or fosfomycin? or framycetin? or fusidic acid? or gentamicin? or gramicidin? or hygromycin? or imipenem? or josamycin? or kanamycin? or kitasamycin? or lactam? or lasalocid? or leucomycin? or lincomycin? or lincosamide? or lucensomycin? or lymecycline? or mepartricin? or methacycline? or methicillin? or mezlocillin? or mikamycin? or minocycline? or miocamycin? or moxalactam? or mupirocin? or mycobacillin? or nafcillin? or natamycin? or nebramycin? or neomycin? or netilmicin? or netropsin? or nigericin? or nisin? or norfloxacin? or novobiocin? or nystatin? or ofloxacin? or oleandomycin? or oligomycin? or oxacillin? or oxytetracycline? or paromomycin? or penicillanic acid? or penicillic acid? or penicillin?? or piperacillin? or pivampicillin? or polymyxin b? or polymyxin? or pristinamycin? or prodigiosin? or ribostamycin? or rifabutin? or rifamycin? or ristocetin? or rolitetracycline? or roxarsone? or roxithromycin? or rutamycin? or sirolimu? or sisomicin? or spectinomycin? or spiramycin? or streptogramin?? or streptomycin? or streptovaricin? or sulbactam? or sulbenicillin? or sulfamerazine? or sulfamethoxypyridazine? or talampicillin? or teicoplanin? or tetracycline? or thiamphenicol? or thienamycin? or thiostrepton? or ticarcillin? or tobramycin? or troleandomycin? or tunicamycin? or tylosin? or tyrocidine? or tyrothricin? or valinomycin? or vancomycin? or vernamycin? or viomycin? or virginiamycin? or beta-lactams) adj2 (use\* or misuse or consume or consumption or intake or dose or dosage or prescription\* or prescrib\* or overprescrib\* or sale\* or rate\*)).ab,ti.
4. 1 or 2
5. 3 and 4
6. (adjust\* or alter\* or change or changes or changing or control\* or decreas\* or limit\* or modify or modified or modifying or reduce or reducing or reduction\* or restrict\* or appropriate or inappropriate or rational\* or irrational\*).ab,ti.
7. exp policy/
8. exp health care policy/
9. exp legislation, drug/
10. (program\* or campaign\* or policy or policies or guideline\* or ban or banned or Regulat\* or law or laws or prohibit\* or restrict\* or legislat\* or public or report\* or tax\* or audit\* or formular\* or feedback).ab,ti.
11. (health\$ adj3 (policy or policies or planning or priorit\$)).ab,ti.
12. 7 or 8 or 9 or 10 or 11
13. 5 and 6 and 12
14. exp animals/ not humans.sh.
15. 13 not 14

## Web of Science Search Strategy

- 1) TS=(antibiotic\* near/2 use\*) OR  
TS=(antibiotic\* near/2 misuse) OR  
TS=(antibiotic\* near/2 consume) OR  
TS=(antibiotic\* near/2 consumption) OR  
TS=(antibiotic\* near/2 intake) OR  
TS=(antibiotic\* near/2 dose) OR  
TS=(antibiotic\* near/2 dosage) OR  
TS=(antibiotic\* near/2 prescription\*) OR  
TS=(antibiotic\* near/2 prescrib\*) OR  
TS=(antibiotic\* near/2 overprescrib\*) OR  
TS=(antibiotic\* near/2 sale\*) OR  
TS=(antibiotic\* near/2 rate\*) OR  
TS=(antimicrobial\* near/2 use\*) OR  
TS=(antimicrobial\* near/2 misuse) OR  
TS=(antimicrobial\* near/2 consume) OR  
TS=(antimicrobial\* near/2 consumption) OR  
TS=(antimicrobial\* near/2 intake) OR  
TS=(antimicrobial\* near/2 dose) OR  
TS=(antimicrobial\* near/2 dosage) OR  
TS=(antimicrobial\* near/2 prescription\*) OR  
TS=(antimicrobial\* near/2 prescrib\*) OR  
TS=(antimicrobial\* near/2 overprescrib\*) OR  
TS=(antimicrobial\* near/2 sale\*) OR  
TS=(antimicrobial\* near/2 rate\*)
- 2) TS=(adjust\*) OR TS=(alter\*) OR TS=(change) OR TS=(changes) OR TS=(changing) OR TS=(control\*) OR  
TS=(decreas\*) OR TS=(limit\*) OR TS=(modify) OR TS=(modified) OR TS=(modifying) OR TS=(reduce) OR  
TS=(reducing) OR TS=(reduction\*) OR TS=(restrict\*) OR TS=(appropriate) OR TS=(inappropriate) OR  
TS=(rational\*) OR TS=(irrational\*)
- 3) TS=(program\* OR campaign\* OR policy OR policies OR guideline\* OR ban OR banned OR regulat\* OR law OR  
laws OR prohibit\* OR restrict\* OR legislat\* OR report\* OR tax\* or audit\* OR formular\* or expenditure\* or spending  
or label\* or maket\* or advertis\* or consultation\*) OR TS=(health\* NEAR/2 policy) OR TS=(health\* NEAR/2  
policies) OR TS=(health\* NEAR/2 planning) OR TS=(health\* NEAR2 priorit\*)
- 4) #1 AND #2 AND #3
- 5) TS=(resistan\*) OR TS=(steward\*)
- 6) #4 and #5
- 7) TS=( \*food\* OR aqua\* OR animal\* OR vetrinar\* OR livestock OR "live stock" OR agricultur\*)
- 8) #6 NOT #7

## CENTRAL Search Strategy

1. MeSH descriptor: [Anti-Infective Agents] explode all trees
2. ((antibiotic? or alamethicin? or amdinocillin? or amdinocillin pivoxil? or amikacin? or amoxicillin? or amoxicillin-potassium clavulanate combination? or amphotericin? or ampicillin? or anisomycin? or antimycin? or aurodox? or azithromycin? or azlocillin? or aztreonam? or bacitracin? or bacteriocin? or bambermycin? or bongkreikic acid? or brefeldin? or butirosin sulfate? or calcimycin? or candidin? or capreomycin? or carbenicillin? or carfecillin? or cefaclor? or cefadroxil? or cefamandole? or cefatrizine? or cefazolin? or cefixime? or cefmenoxime? or cefmetazole? or cefonicid? or cefoperazone? or cefotaxime? or cefotetan? or cefotiam? or cefoxitin? or cefsulodin? or ceftazidime? or ceftizoxime? or ceftriaxone? or cefuroxime? or cephradine? or cephaloglycin? or cephaloridine? or cephalosporin? or cephalothin? or cephamycin? or cephapirin? or cephradine? or chloramphenicol? or chlortetracycline? or citrinin? or clarithromycin? or clavulanic acid? or clavulanic acid? or clindamycin? or cloxacillin? or colistin? or cyclacillin? or dactinomycin? or daptomycin? or demeclocycline? or dibekacin? or dicloxacillin? or dihydrostreptomycin sulfate? or diketopiperazine? or distamycin? or doxycycline? or erythromycin? or erythromycin estolate? or erythromycin ethylsuccinate? or filipin? or floxacillin? or fluoroquinolone? or fosfomycin? or framycetin? or fusidic acid? or gentamicin? or gramicidin? or hygromycin? or imipenem? or josamycin? or kanamycin? or kitasamycin? or lactam? or lasalocid? or leucomycin? or lincomycin? or lincosamide? or lucensomycin? or lymecycline? or mepartricin? or methacycline? or methicillin? or mezlocillin? or mikamycin? or minocycline? or miocamycin? or moxalactam? or mupirocin? or mycobacillin? or nafcillin? or natamycin? or nebramycin? or neomycin? or netilmicin? or netropsin? or nigericin? or nisin? or norfloxacin? or novobiocin? or nystatin? or ofloxacin? or oleandomycin? or oligomycin? or oxacillin? or oxytetracycline? or paromomycin? or penicillanic acid? or penicillic acid? or penicillin?? or piperacillin? or pivampicillin? or polymyxin b? or polymyxin? or pristinamycin? or prodigiosin? or ribostamycin? or rifabutin? or rifamycin? or ristocetin? or rolitetracycline? or roxarsone? or roxithromycin? or rutamycin? or sirolimu? or sisomicin? or spectinomycin? or spiramycin? or streptogramin?? or streptomycin? or streptovaricin? or sulbactam? or sulbenicillin? or sulfamerazine? or sulfamethoxypyridazine? or talampicillin? or teicoplanin? or tetracycline? or thiamphenicol? or thienamycin? or thiostrepton? or ticarcillin? or tobramycin? or troleandomycin? or tunicamycin? or tylosin? or tyrocidine? or tyrothricin? or valinomycin? or vancomycin? or vernamycin? or viomycin? or virginiamycin? or beta-lactams) adj2 (use\* or misuse or consume or consumption or intake or dose or dosage or prescription\* or prescrib\* or overprescrib\* or sale\* or rate\*))
3. #1 and #2
4. (adjust\* or alter\* or change or changes or changing or control\* or decreas\* or limit\* or modify or modified or modifying or reduce or reducing or reduction\* or restrict\* or appropriate or inappropriate or rational\* or irrational\*)
5. MeSH descriptor: [Policy] explode all trees
6. MeSH descriptor: [Legislation as Topic] explode all trees
7. MeSH descriptor: [Government] explode all trees
8. MeSH descriptor: [Government Regulation] explode all trees
9. MeSH descriptor: [Policy Making] explode all trees
10. (program\* or campaign\* or policy or policies or guideline\* or ban or banned or Regulat\* or law or laws or prohibit\* or restrict\* or legislat\* or report\* or tax\* or audit\* or formular\* or expenditure\* or spending or label\* or market\* or advertis\* or consultation\*)
11. (health\$ near/2 (policy or policies or planning or priorit\$))
12. #5 or #6 or #7 or #8 or #9 or #10 or #11
13. #3 and #4 and #12

## CINAHL Search Strategy

1. (MH "Antiinfective Agents+")
2. (TI antibiotic\* N2 use\*) OR (AB antibiotic\* N2 use\*) OR (HW antibiotic\* N2 use\*) OR (TI antibiotic\* N2 misuse) OR (AB antibiotic\* N2 misuse) OR (HW antibiotic\* N2 misuse) OR (TI antibiotic\* N2 consume ) OR (AB antibiotic\* N2 consume ) OR (HW antibiotic\* N2 consume ) OR (TI antibiotic\* N2 consumption) OR (AB antibiotic\* N2 consumption) OR (HW antibiotic\* N2 consumption) OR (TI antibiotic\* N2 intake ) OR (AB antibiotic\* N2 intake ) OR (HW antibiotic\* N2 intake ) OR (TI antibiotic\* N2 dose ) OR (AB antibiotic\* N2 dose ) OR (HW antibiotic\* N2 dose ) OR (TI antibiotic\* N2 dosage ) OR (AB antibiotic\* N2 dosage ) OR (HW antibiotic\* N2 dosage) OR (TI antibiotic\* N2 prescription\* ) OR (AB antibiotic\* N2 prescription\* ) OR (HW antibiotic\* N2 prescription\* ) OR (TI antibiotic\* N2 prescrib\* ) OR (AB antibiotic\* N2 prescrib\* ) OR (HW antibiotic\* N2 prescrib\* ) OR (TI antibiotic\* N2 overprescrib\* ) OR (AB antibiotic\* N2 overprescrib\* ) OR (HW antibiotic\* N2 overprescrib\* ) OR (TI antibiotic\* N2 sale\* ) OR (AB antibiotic\* N2 sale\* ) OR (HW antibiotic\* N2 sale\* )
3. (TI antibiotic\* N2 rate\* ) OR (AB antibiotic\* N2 rate\* ) OR (HW antibiotic\* N2 rate\* ) OR (TI antimicrobial\* N2 use\*) OR (AB antimicrobial\* N2 use\*) OR (HW antimicrobial\* N2 use\*)
4. (TI antimicrobial\* N2 misuse) OR (AB antimicrobial\* N2 misuse) OR (HW antimicrobial\* N2 misuse) OR (TI antimicrobial\* N2 consume ) OR (AB antimicrobial\* N2 consume ) OR (HW antimicrobial\* N2 consume ) OR (TI antimicrobial\* N2 consumption) OR (AB antimicrobial\* N2 consumption) OR (HW antimicrobial\* N2 consumption) OR (TI antimicrobial\* N2 intake ) OR (AB antimicrobial\* N2 intake ) OR (HW antimicrobial\* N2 intake ) OR (TI antimicrobial\* N2 dose ) OR (AB antimicrobial\* N2 dose ) OR (HW antimicrobial\* N2 dose ) OR (TI antimicrobial\* N2 dosage ) OR (AB antimicrobial\* N2 dosage ) OR (HW antimicrobial\* N2 dosage ) OR (TI antimicrobial\* N2 prescription\* ) OR (AB antimicrobial\* N2 prescription\* ) OR (HW antimicrobial\* N2 prescription\* ) OR (TI antimicrobial\* N2 prescrib\* ) OR (AB antimicrobial\* N2 prescrib\* ) OR (HW antimicrobial\* N2 prescrib\* ) OR (TI antimicrobial\* N2 overprescrib\* ) OR (AB antimicrobial\* N2 overprescrib\* ) OR (HW antimicrobial\* N2 overprescrib\* ) OR (TI antimicrobial\* N2 sale\* ) OR (AB antimicrobial\* N2 sale\* ) OR (HW antimicrobial\* N2 sale\* ) OR (TI antimicrobial\* N2 rate\* ) OR (AB antimicrobial\* N2 rate\* ) OR (HW antimicrobial\* N2 rate\* )
5. (TI adjust\* ) OR (AB adjust\* ) OR (TI alter\* ) OR (AB alter\* ) OR (TI change ) OR (AB change ) OR (TI changes ) OR (AB changes ) OR (TI changing ) OR (AB changing ) OR (TI control\* ) OR (AB control\* ) OR (TI decreas\* ) OR (AB decreas\* ) OR (TI limit\* ) OR (AB limit\* ) OR (TI modify ) OR (AB modify ) OR (TI modified ) OR (AB modified ) OR (TI modifying ) OR (AB modifying ) OR (TI reduce ) OR (AB reduce ) OR (TI reducing ) OR (AB reducing ) OR (TI reduction\* ) OR (AB reduction\* ) OR (TI restrict\* ) OR (AB restrict\* ) OR (TI appropriate ) OR (AB appropriate ) OR (TI inappropriate ) OR (AB inappropriate ) OR (TI rational\* ) OR (AB rational\* ) OR (TI irrational\* ) OR (AB irrational\* )
6. (MH "Hospital Policies")
7. (MH "Health Policy Studies")
8. (MH "Policy Studies")
9. (MH "Public Policy+")
10. (MH "Policy Making")
11. (MH "Legislation, Drug")
12. (TI program\* ) OR (AB program\* ) OR (TI campaign\* ) OR (AB campaign\* ) OR (TI policy ) OR (AB policy ) OR (TI policies ) OR (AB policies ) OR (TI guideline\* ) OR (AB guideline\* ) OR (TI ban ) OR (AB ban ) OR (TI banned ) OR (AB banned ) OR (TI Regulat\* ) OR (AB Regulat\* ) OR (TI law ) OR (AB law ) OR (TI laws ) OR (AB laws ) OR (TI prohibit\* ) OR (AB prohibit\* ) OR (TI restrict\* ) OR (AB restrict\* ) OR (TI legislat\* ) OR (AB legislat\* ) OR (TI report\* ) OR (AB report\* ) OR (TI tax\* ) OR (AB tax\* ) OR (TI audit\* ) OR (AB audit\* ) OR (TI formular\* ) OR (AB formular\* ) OR (TI expenditure\* ) OR (AB expenditure\* ) OR (TI spending ) OR (AB spending ) OR (TI label\* ) OR (AB label\* ) OR (TI market\* ) OR (AB market\* ) OR (TI advertis\* ) OR (AB advertis\* ) OR (TI consultation\* ) OR (AB consultation\* ) OR (TI health\* N2 policy) OR (AB health\* N2 use\*) OR (TI health\* N2 policies ) OR (AB health\* N2 policies ) OR (TI health\* N2 planning ) OR (AB health\* N2 planning ) OR (TI health\* N2 priorit\* ) OR (AB health\* N2 priorit\* )
13. 12 AND (5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11) AND (3 AND 4 AND 12)

### PAIS Index Search Strategy

(ti(((antibiotic\* OR antimicrobial\*) NEAR/2 (use\* OR misuse OR consume OR consumption OR intake OR dose OR dosage OR prescription\* OR prescrib\* OR overprescrib\* OR sale\* OR rate\*))) OR ab(((antibiotic\* OR antimicrobial\*) NEAR/2 (use\* OR misuse OR consume OR consumption OR intake OR dose OR dosage OR prescription\* OR prescrib\* OR overprescrib\* OR sale\* OR rate\*)))) AND (ti(adjust\* or alter\* or change or changes or changing or control\* or decreas\* or limit\* or modify or modified or modifying or reduce or reducing or reduction\* or restrict\* or appropriate or inappropriate or rational\* or irrational\*) OR ab(adjust\* or alter\* or change or changes or changing or control\* or decreas\* or limit\* or modify or modified or modifying or reduce or reducing or reduction\* or restrict\* or appropriate or inappropriate or rational\* or irrational\*)) AND (ti(program\* or campaign\* or policy or policies or guideline\* or ban or banned or Regulat\* or law or laws or prohibit\* or restrict\* or legislat\* or report\* or tax\* or audit\* or formular\* or expenditure\* or spending or label\* or market\* or advertis\* of consultation\*) OR ab(program\* or campaign\* or policy or policies or guideline\* or ban or banned or Regulat\* or law or laws or prohibit\* or restrict\* or legislat\* or public or report\* or tax\* or audit\* or formular\* or expenditure\* or spending or label\* or market\* or advertis\* of consultation\*)) OR (ti(health\* NEAR/2 (policy or policies or planning or priorit\*)) OR ab(health\* NEAR/2 (policy or policies or planning or priorit\*)))

### A1-2-7 MEDLINE NOT PUBMED Search Strategy

(((((Anti-Bacterial Agents[MeSH Terms]) OR Anti-infective Agents[MeSH Terms])) AND ((antibiotic?[Title/Abstract] OR alamethicin?[Title/Abstract] OR aminocillin?[Title/Abstract] OR aminocillin pivoxil?[Title/Abstract] OR amikacin?[Title/Abstract] OR amoxicillin?[Title/Abstract] OR amoxicillin-potassium clavulanate combination?[Title/Abstract] OR amphotericin?[Title/Abstract] OR ampicillin?[Title/Abstract] OR anisomycin?[Title/Abstract] OR antimycin?[Title/Abstract] OR aurodox?[Title/Abstract] OR azithromycin?[Title/Abstract] OR azlocillin?[Title/Abstract] OR aztreonam?[Title/Abstract] OR bacitracin?[Title/Abstract] OR bacteriocin?[Title/Abstract] OR bambarmycin?[Title/Abstract] OR bongkreikic acid?[Title/Abstract] OR brefeldin?[Title/Abstract] OR butirosin sulfate?[Title/Abstract] OR calcimycin?[Title/Abstract] OR candidin?[Title/Abstract] OR capreomycin?[Title/Abstract] OR carbenicillin?[Title/Abstract] OR carfecillin?[Title/Abstract] OR cefaclor?[Title/Abstract] OR cefadroxil?[Title/Abstract] OR cefamandole?[Title/Abstract] OR cefatrizine?[Title/Abstract] OR cefazolin?[Title/Abstract] OR cefixime?[Title/Abstract] OR cefmenoxime?[Title/Abstract] OR cefmetazole?[Title/Abstract] OR cefonicid?[Title/Abstract] OR cefoperazone?[Title/Abstract] OR cefotaxime?[Title/Abstract] OR cefotetan?[Title/Abstract] OR cefotiam?[Title/Abstract] OR ceftazidime?[Title/Abstract] OR ceftizoxime?[Title/Abstract] OR ceftriaxone?[Title/Abstract] OR cefuroxime?[Title/Abstract] OR cephaloridine?[Title/Abstract] OR cephalixin?[Title/Abstract] OR cephaloglycin?[Title/Abstract] OR cephaloridine?[Title/Abstract] OR cephalosporin?[Title/Abstract] OR cephalothin?[Title/Abstract] OR cephamycin?[Title/Abstract] OR cephapirin?[Title/Abstract] OR cephradine?[Title/Abstract] OR chloramphenicol?[Title/Abstract] OR chlortetracycline?[Title/Abstract] OR citrinin?[Title/Abstract] OR clarithromycin?[Title/Abstract] OR clavulanic acid?[Title/Abstract] OR clavulanic acid?[Title/Abstract] OR clindamycin?[Title/Abstract] OR cloxacillin?[Title/Abstract] OR colistin?[Title/Abstract] OR cyclacillin?[Title/Abstract] OR dactinomycin?[Title/Abstract] OR daptomycin?[Title/Abstract] OR demeclocycline?[Title/Abstract] OR dibekacin?[Title/Abstract] OR dicloxacillin?[Title/Abstract] OR dihydrostreptomycin sulfate?[Title/Abstract] OR diketopiperazine?[Title/Abstract] OR distamycin?[Title/Abstract] OR doxycycline?[Title/Abstract] OR echinomycin?[Title/Abstract] OR edeine?[Title/Abstract] OR enviomycin?[Title/Abstract] OR erythromycin?[Title/Abstract] OR erythromycin estolate?[Title/Abstract] OR erythromycin ethylsuccinate?[Title/Abstract] OR filipin?[Title/Abstract] OR floxacillin?[Title/Abstract] OR fluoroquinolone?[Title/Abstract] OR fosfomycin?[Title/Abstract] OR framycetin?[Title/Abstract] OR fusidic acid?[Title/Abstract] OR gentamicin?[Title/Abstract] OR gramicidin?[Title/Abstract] OR hygromycin?[Title/Abstract] OR imipenem?[Title/Abstract] OR josamycin?[Title/Abstract] OR kanamycin?[Title/Abstract] OR kitasamycin?[Title/Abstract] OR lactam?[Title/Abstract] OR lasalocid?[Title/Abstract] OR leucomycin?[Title/Abstract] OR lincomycin?[Title/Abstract] OR lincosamide?[Title/Abstract] OR lucensomycin?[Title/Abstract] OR lymecycline?[Title/Abstract] OR

mepartricin?[Title/Abstract] OR methacycline?[Title/Abstract] OR methicillin?[Title/Abstract] OR mezlocillin?[Title/Abstract] OR mikamycin?[Title/Abstract] OR minocycline?[Title/Abstract] OR miocamycin?[Title/Abstract] OR moxalactam?[Title/Abstract] OR mupirocin?[Title/Abstract] OR mycobacillin?[Title/Abstract] OR nafcillin?[Title/Abstract] OR natamycin?[Title/Abstract] OR nebramycin?[Title/Abstract] OR neomycin?[Title/Abstract] OR netilmicin?[Title/Abstract] OR netropsin?[Title/Abstract] OR nigericin?[Title/Abstract] OR nisin?[Title/Abstract] OR norfloxacin?[Title/Abstract] OR novobiocin?[Title/Abstract] OR nystatin?[Title/Abstract] OR ofloxacin?[Title/Abstract] OR oleandomycin?[Title/Abstract] OR oligomycin?[Title/Abstract] OR oxacillin?[Title/Abstract] OR oxytetracycline?[Title/Abstract] OR paromomycin?[Title/Abstract] OR penicillanic acid?[Title/Abstract] OR penicillic acid?[Title/Abstract] OR penicillin?[Title/Abstract] OR piperacillin?[Title/Abstract] OR pivampicillin?[Title/Abstract] OR polymyxin b?[Title/Abstract] OR polymyxin?[Title/Abstract] OR pristinamycin?[Title/Abstract] OR prodigiosin?[Title/Abstract] OR ribostamycin?[Title/Abstract] OR rifabutin?[Title/Abstract] OR rifamycin?[Title/Abstract] OR ristocetin?[Title/Abstract] OR rolitetracycline?[Title/Abstract] OR roxarsone?[Title/Abstract] OR roxithromycin?[Title/Abstract] OR rutamycin?[Title/Abstract] OR sirolimu?[Title/Abstract] OR sisomicin?[Title/Abstract] OR spectinomycin?[Title/Abstract] OR spiramycin?[Title/Abstract] OR streptogramin?[Title/Abstract] OR streptomycin?[Title/Abstract] OR streptovaricin?[Title/Abstract] OR sulbactam?[Title/Abstract] OR sulbenicillin?[Title/Abstract] OR sulfamerazine?[Title/Abstract] OR sulfamethoxypyridazine?[Title/Abstract] OR talampicillin?[Title/Abstract] OR teicoplanin?[Title/Abstract] OR tetracycline?[Title/Abstract] OR thiamphenicol?[Title/Abstract] OR thienamycin?[Title/Abstract] OR thioestrepton?[Title/Abstract] OR ticarcillin?[Title/Abstract] OR tobramycin?[Title/Abstract] OR troleandomycin?[Title/Abstract] OR tunicamycin?[Title/Abstract] OR tylosin?[Title/Abstract] OR tyrocidine?[Title/Abstract] OR tyrothricin?[Title/Abstract] OR valinomycin?[Title/Abstract] OR vancomycin?[Title/Abstract] OR vernamycin?[Title/Abstract] OR viomycin?[Title/Abstract] OR virginiamycin?[Title/Abstract] OR beta-lactams[Title/Abstract])) AND ((use\*[Title/Abstract] OR misuse[Title/Abstract] OR consume[Title/Abstract] OR consumption[Title/Abstract] OR intake[Title/Abstract] OR dose[Title/Abstract] OR dosage[Title/Abstract] OR prescription\*[Title/Abstract] OR prescrib\*[Title/Abstract] OR overprescrib\*[Title/Abstract] OR sale\*[Title/Abstract] OR rate\*[Title/Abstract])) AND ((adjust\*[Title/Abstract] OR alter\*[Title/Abstract] OR change[Title/Abstract] OR changes[Title/Abstract] OR changing[Title/Abstract] OR control\*[Title/Abstract] OR decreas\*[Title/Abstract] OR limit\*[Title/Abstract] OR modify[Title/Abstract] OR modified[Title/Abstract] OR modifying[Title/Abstract] OR reduce[Title/Abstract] OR reducing[Title/Abstract] OR reduction\*[Title/Abstract] OR restrict\*[Title/Abstract] OR appropriate[Title/Abstract] OR inappropriate[Title/Abstract] OR rational\*[Title/Abstract] OR irrational\*[Title/Abstract])) AND (((((policy[MeSH Terms]) OR policy making[MeSH Terms]) OR legislation as Topic[MeSH Terms]) OR Government[MeSH Terms]) OR Government Regulation[MeSH Terms]) OR (program\*[Title/Abstract] OR campaign\*[Title/Abstract] OR policy[Title/Abstract] OR policies[Title/Abstract] OR guideline\*[Title/Abstract] OR ban[Title/Abstract] OR banned[Title/Abstract] OR Regulat\*[Title/Abstract] OR law[Title/Abstract] OR laws[Title/Abstract] OR prohibit\*[Title/Abstract] OR restrict\*[Title/Abstract] OR legislat\*[Title/Abstract] OR report\*[Title/Abstract] OR tax\*[Title/Abstract] OR audit\*[Title/Abstract] OR formular\*[Title/Abstract] OR expenditure\*[Title/Abstract] OR spending[Title/Abstract] OR label\*[Title/Abstract] OR market\*[Title/Abstract] OR advertis\*[Title/Abstract] OR consultation\*[Title/Abstract])) AND (in process[sb] OR medline[sb])) AND 2017/03/01"[Entrez Date]:"3000"[Entrez Date]) Schema: all Schema: all

## Supplemental information – Chapter 3

### A3-1. Intervention and study design summary table of all included studies

| Study                                                         | Country                  | Policy Level | Enacting Government                                 | Intervention Summary                                                                                                                                                           | Methods                                              | Outcome                                                            | Policy Strategy | Policy Option            | BCW Intervention Function | Impact   | Target Audience                 |
|---------------------------------------------------------------|--------------------------|--------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|--------------------------------------------------------------------|-----------------|--------------------------|---------------------------|----------|---------------------------------|
| <b>D'Acremont V, et al. Malaria Journal. 2011;10:107.</b>     | Tanzania                 | Regional     | City Medical Office and Municipal Health Department | Provision of guidelines and education for use of anti-malarial drugs with rapid malaria diagnostic testing.                                                                    | Cluster RCT using routinely collected data.          | Monthly number of anti-malarial or antibiotic doses issued         | Guidelines      | Antimicrobial Guidelines | Education                 | Expected | Health Care Worker <sup>2</sup> |
| <b>Finkelstein JA, et al. Pediatrics. 2008;121(1):e15-23.</b> | United States of America | Regional     | Massachusetts Department of Public Health           | Annual public and provider education campaign "REACH Mass" during cold and influenza season.                                                                                   | Cluster RCT using health insurance claims data.      | Number of oral antibiotic dispensed per person-year of observation | Communication   | Public Awareness         | Education                 | Expected | Community; Health Care Worker   |
| <b>Hallsworth M, et al. Lancet. 2016;387(10029):1743-52.</b>  | England                  | National     | Department of Health – Chief Medical Officer        | Feedback letter from England's Chief Medical Officer informing high using practitioners that they were prescribing antibiotics at a higher rate than 80% of practices in their | A 2x2 factorial RCT using national prescribing data. | Prescriptions per 1000 STAR-PU                                     | Guidelines      | Feedback                 | Education; Persuasion     | Expected | Health Care Worker              |

<sup>2</sup> The intended effect column is based upon the authors' conclusions of the papers and was coded as: expected, neutral, opposite.

|                                                                 |         |          |                                               |                                                                                                                                                              |                                                                                                                                                |                                                                       |                     |                              |           |                    |           |  |
|-----------------------------------------------------------------|---------|----------|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|---------------------|------------------------------|-----------|--------------------|-----------|--|
|                                                                 |         |          |                                               | region; and provider education materials                                                                                                                     |                                                                                                                                                |                                                                       |                     |                              |           |                    |           |  |
|                                                                 |         |          |                                               |                                                                                                                                                              | Cluster RCT using data from health centre information system, a household survey, a village clinic survey and a township health centre survey. |                                                                       |                     |                              |           |                    |           |  |
| <b>Yip W, et al. Health affairs. 2014;33(3):502-10.</b>         | China   | Regional | Government of Ningxia                         | Pilot program changing fee-for-services to pay-for-performance in rural healthcare settings.                                                                 | Prescription Rate                                                                                                                              | Fiscal Measures                                                       | Pay for Performance | Environmental restructuring; | Expected  | Health Care Worker |           |  |
|                                                                 |         |          |                                               |                                                                                                                                                              |                                                                                                                                                |                                                                       |                     |                              |           |                    |           |  |
| <b>Bauraind I, et al. JAMA. 2004;292(20):2468-70.</b>           | Belgium | National | Belgian Scientific Institute of Public Health | Two public campaigns using booklets, handouts, posters and television to promote rational use of antibiotics and reduce overuse and misuse in the community. | DDD                                                                                                                                            | Communication                                                         | Public Awareness    | Education                    | Expected  | Community          |           |  |
|                                                                 |         |          |                                               |                                                                                                                                                              |                                                                                                                                                |                                                                       |                     |                              |           |                    |           |  |
| <b>Bernier A, et al. Antimicrobial Agents and Chemotherapy.</b> | France  | National | French National Health Insurance              | National public health campaign "Antibiotics Are Not Automatic!" repeated every winter.                                                                      | Interrupted time-series analysis using data from the French National Health                                                                    | Outpatient antibiotics prescribed and reimbursed per 1000 inhabitants | Communication       | Public Awareness             | Education | Expected           | Community |  |

|                                                                                                   |                          |          |                                            |                                                                                                                                                                                                  |                                                                                                                        |                                                              |               |                          |                        |          |                    |
|---------------------------------------------------------------------------------------------------|--------------------------|----------|--------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|---------------|--------------------------|------------------------|----------|--------------------|
| <b>2014;58(1):71-7.</b>                                                                           |                          |          |                                            |                                                                                                                                                                                                  | Insurance Database.                                                                                                    |                                                              |               |                          |                        |          |                    |
| <b>Dommergues MA, Hentgen V. Scandinavian Journal of Infectious Diseases. 2012;44(7):495-501.</b> | France                   | National | French National Health Insurance           | National public health campaign "Antibiotics Are Not Automatic!" repeated every winter.                                                                                                          | Time-series analysis using data from a permanent survey of medical prescriptions.                                      | Prescription Rate                                            | Communication | Public Awareness         | Education              | Expected | Community          |
| <b>Dowell D, et al. American Journal of Public Health. 2012;102(1):148-55.</b>                    | United States of America | Regional | Centers for Disease Control and Prevention | Publication and circulation of revised CDC guidelines for the treatment of gonorrhea through MMWR, state and local health departments, a dear colleague letter, and a national press conference. | Interrupted time-series using data from a national network of health departments conducting enhanced STD surveillance. | Percentage of Infections treated with antibiotic             | Guidelines    | Antimicrobial Guidelines | Education              | Expected | Health Care Worker |
| <b>Hernandez-Santiago V, et al. Journal of Antimicrobial Chemotherapy. 2015;70(8):2397-404.</b>   | Scotland                 | Regional | National Health Service Tayside            | National policy changes including guidelines, educational interventions and feedback for practices, and information leaflets to explain                                                          | Interrupted time-series analysis using administrative data.                                                            | Quarterly rate of 4C antibiotics dispensed per 1000 patients | Guidelines    | Antimicrobial Guidelines | Education; Persuasion; | Expected | Health Care Worker |

|                                                                                  |        |                |                                               |                                                                                                                                                                                                   |                                                                         |                                        |            |                          |                       |          |                    |
|----------------------------------------------------------------------------------|--------|----------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------|------------|--------------------------|-----------------------|----------|--------------------|
|                                                                                  |        |                |                                               | prescribing changes to individuals.                                                                                                                                                               |                                                                         |                                        |            |                          |                       |          |                    |
| <b>Mamdani M, et al. American Journal of Medicine. 2007;120(10):893-900.</b>     | Canada | State/Province | Government of Ontario                         | Formulary change to restrict the use of fluoroquinolones requiring prescribers to indicate the reason for fluoroquinolone use.                                                                    | Time series analysis using administrative healthcare databases.         | Prescriptions per 1000 persons/quarter | Regulation | Restricted Use           | Restriction           | Expected | Health Care Worker |
| <b>Manns B, et al. BMC Health Services Research. 2012;12:290.</b>                | Canada | State/Province | Alberta Health and Wellness                   | Regulation requiring physicians to submit additional paperwork in order for patients to have their quinolone prescription reimbursed unless they registered as a designated quinolone prescriber. | Interrupted time-series analysis using administrative drug claims data. | Prescription Rate                      | Regulation | Restricted Reimbursement | Restriction; Coercion | Neutral  | Health Care Worker |
| <b>Marra F, et al. Journal of Antimicrobial Chemotherapy. 2005;55(1):95-101.</b> | Canada | State/Province | British Columbia Government                   | Formulary change delisting and later relisting clarithromycin, and adding valaciclovir and famciclovir to the formulary.                                                                          | Interrupted time series using BC PharmaNet data.                        | DDDs per 1000 population/day           | Regulation | Formulary Change         | Restriction;          | Expected | Health Care Worker |
| <b>Marshall D, et al. Journal of Health Services Research &amp;</b>              | Canada | State/Province | Ontario Ministry of Health and Long-term Care | Limitation on reimbursement of two fluoroquinolones to patients for whom                                                                                                                          | Interrupted time-series analysis using data from                        | Prescribing volume                     | Regulation | Restricted Reimbursement | Restriction;          | Opposite | Health Care Worker |

|                                                                                |        |                |                                  |                                                                                                                                                                                                                                                         |                                                                                                                    |                                                             |               |                          |                                                                         |          |                               |  |
|--------------------------------------------------------------------------------|--------|----------------|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|---------------|--------------------------|-------------------------------------------------------------------------|----------|-------------------------------|--|
| Policy.<br>2006;11(1):13-20.                                                   |        |                |                                  | second line antibiotics were indicated, while other patients would be reimbursed for first-line drugs only.                                                                                                                                             | Bayer Health Inc.                                                                                                  |                                                             |               |                          |                                                                         |          |                               |  |
| Sabuncu E, et al. Plos Medicine.<br>2009;6(6).                                 | France | National       | French National Health Insurance | Nationwide public health campaign “Antibiotics Are Not Automatic!” targeting the general public and health care professionals.                                                                                                                          | Interrupted time series analysis using administrative data from the national health insurance programme.           | Weekly rate of antibiotic prescriptions per 100 inhabitants | Communication | Public Awareness         | Education                                                               | Expected | Community; Health Care Worker |  |
| Sun J, et al. Journal of Global Antimicrobial Resistance.<br>2015;3(2):95-102. | China  | National       | Ministry of Health China         | Multifaceted national intervention to promote rational use of antibiotics including target setting, monitoring, prescribing restrictions, training and revoking prescribing rights for prescribers who continuously do not meet the hospital's targets. | Interrupted time-series using data from the National Antimicrobial Clinical Use and Resistance Monitoring Network. | Prescription Rate                                           | Regulation    | Complex Intervention     | Coercion; Restriction; Environmental Restructuring; Education; Training | Expected | Health Care Worker            |  |
| Weiss K, et al. Clinical Infectious Diseases.                                  | Canada | State/Province | Quebec Government                | Provincial educational program provided graphic guidelines on antibiotic use for                                                                                                                                                                        | Interrupted time series using IMS Health data.                                                                     | Number of antibiotic prescriptions                          | Guidelines    | Antimicrobial Guidelines | Education; Persuasion;                                                  | Expected | Health Care Worker            |  |

2011;53(5):43

3-9.

common conditions

per 1000

in outpatient settings

inhabitants

which were sent to

all physicians and

pharmacists,

accompanied by a

letter from key

provincial

stakeholders.

Interrupted

time series

using

consumer

reported use

of antibiotics

for colds and

flu, and data

from Medicare

Australia and

the Drug

Utilization

Sub-

Committee

(DUSC) of the

Pharmaceutica

I Benefits

Advisory

Committee.

Wutzke SE, et  
al. Health  
promotion  
international.  
2007;22(1):53-  
64.

Australia

National

NPS is an  
independent,  
non-profit  
organization  
funded by the  
Australian  
Government  
Department of  
Health and  
Ageing

Educational  
intervention for  
patients and health  
professionals:  
'Common colds need  
common sense'  
using TV, radio and  
magazines.

Median  
original  
scripts/1000  
consultations/  
GP/year

Communicatio  
n

Public  
Awareness

Education

Expected

Community;  
Health Care  
Worker

Bou-Antoun S,  
et al. Journal  
of  
Antimicrobial  
Chemotherap

England

National

NHS England

NHS England Quality  
Premium: Financial  
incentives for Clinical  
Commissioning  
Groups to reduce

Interrupted  
time series  
analysis using  
data from the  
Clinical

Antibiotic  
items per 1000  
RTI  
consultations

Fiscal  
Measures

Pay for  
Performance

Incentivisation  
;

Expected

Health Care  
Worker

|                                                                                                       |        |          |                                                                                |                                                                                                                                                                                                                 |                                                                                                                          |                                                                                                                                                                                                                    |                    |                             |                                        |          |                       |
|-------------------------------------------------------------------------------------------------------|--------|----------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------------------|----------------------------------------|----------|-----------------------|
| y.<br>2018;73(10):2<br>883-92.                                                                        |        |          |                                                                                | antibiotic prescribing<br>in primary care                                                                                                                                                                       | Practice<br>Research<br>Datalink.                                                                                        |                                                                                                                                                                                                                    |                    |                             |                                        |          |                       |
| Ellegard LM,<br>Dietrichson J,<br>Anell A.<br>Health<br>Economics.<br>2018;27(1):e3<br>9-e54.         | Sweden | Regional | County Health<br>Authorities in<br>Sweden                                      | Pay-for-performance<br>(P4P), monetary<br>incentives to reach<br>predefined targets in<br>antibiotic prescribing                                                                                                | Difference-in-<br>differences<br>(DID) model<br>using data<br>from the<br>Swedish<br>Prescribed<br>Drug Register         | PcV share: the<br>number of<br>narrow-<br>spectrum<br>penicillin V<br>prescriptions<br>divided by the<br>total number<br>of RTI<br>antibiotics<br>prescriptions<br>to children<br>between 0 and<br>6 years of age. | Fiscal<br>Measures | Pay for<br>Performance      | Incentivisation<br>;                   | Expected | Health Care<br>Worker |
| Kelly AA, et al.<br>A Infection<br>control and<br>hospital<br>epidemiology.<br>2017;38(5):51<br>3-20. | USA    | National | Department of<br>Veterans Affairs<br>(VA) Veterans<br>Health<br>Administration | A Veterans Health<br>Administration<br>National<br>Antimicrobial<br>Stewardship<br>Initiative including<br>continuing<br>education, disease-<br>specific guidelines,<br>and development of<br>example policies. | Interrupted<br>time series<br>analysis using<br>resource<br>utilization data<br>from the<br>corporate data<br>warehouse. | Days of<br>therapy per<br>1,000 in<br>patient bed<br>days of care                                                                                                                                                  | Guidelines         | Antimicrobial<br>Guidelines | Education;<br>Enablement;<br>Modelling | Expected | Health Care<br>Worker |
| Ouldali N, et<br>al. Clinical<br>infectious<br>diseases.                                              | France | National | French Agency<br>for the safety of<br>Health Products                          | Introduction of<br>national guidelines<br>(2011) on antibiotic<br>prescriptions for<br>acute respiratory                                                                                                        | Interrupted<br>time series<br>analysis using<br>routinely                                                                | Antibiotic<br>prescription<br>rate for ARI                                                                                                                                                                         | Guidelines         | Antimicrobial<br>Guidelines | Education;                             | Expected | Health Care<br>Worker |

|                                                                                                    |           |          |                                  |                                                                                                                                                                                                                                     |                                                                                                                                          |                                              |               |                     |                                              |          |                       |  |
|----------------------------------------------------------------------------------------------------|-----------|----------|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|---------------|---------------------|----------------------------------------------|----------|-----------------------|--|
| 2017;65(9):14<br>69-76.                                                                            |           |          |                                  | tract infection in<br>pediatric emergency<br>departments.                                                                                                                                                                           | collected<br>hospital data.                                                                                                              | per 1000 PED<br>visits                       |               |                     |                                              |          |                       |  |
| Tang YQ, et al.<br>Cost<br>Effectiveness<br>and Resource<br>Allocation.<br>2018;16.                | China     | National | Government of<br>China           | Chinese government<br>issued administrative<br>rules for the clinical<br>use of antibiotics<br>which included the<br>creation of restricted<br>groups of antibiotics<br>and penalties for<br>violating the<br>administrative rules. | Controlled ITS<br>with a<br>difference-in-<br>difference<br>approach                                                                     | Volume of<br>procured<br>medicines in<br>DDD | Regulation    | Restricted Use      | Coercion;<br>Education;<br>Restriction       | Expected | Health Care<br>Worker |  |
| Walker AJ,<br>Curtis HJ,<br>Goldacre B.<br>Journal of<br>Antimicrobial<br>Chemotherapy<br>2019.    | England   | National | NHS England                      | Five year<br>antimicrobial<br>stewardship strategy<br>and a suite of actions<br>taken by the Chief<br>Medical Officer                                                                                                               | Interrupted<br>time series<br>analysis using<br>the<br>Prescription<br>Cost Analysis<br>Dataset from<br>NHS Digital.                     | Prescriptions<br>per 1000<br>STAR-PU         | Guidelines    | Stewardship         | Environmental<br>Restructuring;<br>Education | Expected | Health Care<br>Worker |  |
| Wu J, et al.<br>The Journal of<br>international<br>medical<br>research.<br>2018;46(4):13<br>26-38. | Australia | National | NPS<br>Medicinewise<br>Australia | NPS Medicinewise: a<br>series of nationwide<br>educational and<br>advertising<br>interventions for<br>general practitioners<br>and consumers.                                                                                       | Bayesian<br>structural time<br>series model<br>using<br>prescriber<br>level data from<br>PBS and the<br>Medicare<br>Benefit<br>Schedule. | Total number<br>of dispensed<br>scripts      | Communication | Public<br>Awareness | Education                                    | Expected | Health Care<br>Worker |  |

|                                                                                      |                   |                |                                                                        |                                                                                                                                                         |                                                                              |                                   |               |                          |                       |          |                               |
|--------------------------------------------------------------------------------------|-------------------|----------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------|---------------|--------------------------|-----------------------|----------|-------------------------------|
| Zhen L, Jin C, Xu H-N. BMC health services research. 2018;18(1):77.                  | China             | National       | Huangdao Bureau of Health                                              | Rural Clinics<br>Prescription Commitment: creation of antibiotic guidelines with audit and feedback to rural prescribers.                               | Interrupted time series analysis using data from electronic medical records. | Total number of dispensed scripts | Guidelines    | Feedback                 | Education;            | Expected | Health Care Worker            |
| Fuertes EI, et al. Canadian Journal of Public Health. 2010;101(4):304-8.             | Canada            | State/Province | BC Centres for Disease Control; Provincial Government British Columbia | Provincial public education campaign "Do Bugs Need Drugs?" targeting school children and healthcare professionals.                                      | Interrupted time-series analysis using data from BC PharmaNet.               | DDD per 1000 population/day       | Communication | Public Awareness         | Education             | Expected | Community; Health Care Worker |
| Santa-Ana-Tellez Y, et al. PLoS one. 2013;8(10):e75550.                              | Mexico and Brazil | National       | Governments of Mexico and Brazil                                       | Restriction on the sale of antibiotics without a prescription in pharmacies, and introduction of a fine on the owners of pharmacies for non-compliance. | Interrupted time-series analysis using IMS Health data.                      | DDD per 1000 inhabitants/day      | Regulation    | Prescription Requirement | Restriction; Coercion | Expected | Community; Health Care Worker |
| Santa-Ana-Tellez Y, et al. Antimicrobial agents and chemotherapy. 2015;59(1):105-10. | Mexico and Brazil | National       | Governments of Mexico and Brazil                                       | Restriction on the sale of antibiotics without a prescription in pharmacies, and introduction of a fine on the owners of pharmacies for non-compliance. | Interrupted time-series analysis using IMS Health data.                      | DDD per 1000 inhabitants/day      | Regulation    | Prescription Requirement | Restriction; Coercion | Expected | Community; Health Care Worker |

|                                                                                          |                                       |                   |                                                           |                                                                                                                                                |                                                                                     |                                                                  |               |                          |                                   |          |                               |
|------------------------------------------------------------------------------------------|---------------------------------------|-------------------|-----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------|---------------|--------------------------|-----------------------------------|----------|-------------------------------|
| <b>Wirtz VJ, et al. Tropical Medicine &amp; International Health. 2013;18(6):665-73.</b> | Chile, Columbia, Mexico and Venezuela | Multiple Policies | Governments of Chile, Colombia, and Venezuela             | Banning over-the-counter antibiotics sales and requiring retention of prescriptions and inspections of pharmacies.                             | Interrupted time-series using IMS Health data.                                      | DDD per 1000 inhabitants/day                                     | Regulation    | Prescription Requirement | Restriction; Coercion; Education; | Expected | Community; Health Care Worker |
| <b>Formoso G, et al. BMJ. 2013;347:f5391.</b>                                            | Italy                                 | Regional          | Emilia-Romagna Regional Agency for Health and Social Care | Provincial information campaign "Antibiotics, solution or problem" using social marketing and consumer research and communication techniques.  | Controlled non-randomized trial using regional prescribing databases.               | DDD per 1000 inhabitants/day                                     | Communication | Public Awareness         | Education                         | Expected | Community                     |
| <b>Gonzales R, et al. Health Services Research. 2005;40(1):101-16.</b>                   | United States of America              | State/Province    | Colorado Department of Public Health and Environment      | State public education campaign "Be S.M.A.R.T. about Antibiotics" with brochures, educational information, and posters.                        | A controlled non-randomized trial using administrative claims data.                 | Prescription Rate                                                | Communication | Public Awareness         | Education                         | Expected | Community                     |
| <b>Hennessy TW, et al. Clinical Infectious Diseases. 2002;34(12):1543-50.</b>            | United States of America              | Regional          | Centers for Disease Control and Prevention                | Public and provider education campaign including workshops for community-health aides and physicians, follow-up visits to the community-health | Cluster non-randomized trial using individual medical records from village clinics. | Number of courses of antibiotics per respiratory infection visit | Communication | Public Awareness         | Education; Training;              | Expected | Community; Health Care Worker |

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|                                                                                           |          |                |                                                 | aides to review the principals of appropriate use, and village-wide educational meetings.                                                                              |                                                                                          |                                             |            |                                      |                                        |          |                    |
| <b>Bastiaens GJH, et al. Malaria Journal. 2011;10:76.</b>                                 | Tanzania | Regional       | Tanzanian Ministry of Health and Social Welfare | Pilot test of replacing microscopy with malaria rapid diagnostic testing and restricting treatment to RDT positive patients in order to tackle malaria over-diagnosis. | Controlled before and after study using questionnaire data.                              | Prescription Rate                           | Guidelines | Antimicrobial Guidelines             | Restriction; Education; Training       | Expected | Health Care Worker |
| <b>Duval M, Desrosiers M. Otolaryngology-- Head and Neck Surgery. 2007;136(2):258-60.</b> | Canada   | State/Province | Government of Quebec                            | Mailout of guidelines for acute bacterial rhinosinusitis along with information cards, supported by a press conference and media campaign.                             | Controlled before and after study using data from IMS Health.                            | Number of antibiotic prescriptions          | Guidelines | Antimicrobial Guidelines             | Education                              | Expected | Health Care Worker |
| <b>Gong Y, et al. Health Policy and Planning. 2016;31(1):21.</b>                          | China    | National       | Chinese Ministry of Health                      | Multifaceted National Chinese Essential Medicines Policy covering drug production, pricing, distribution, procurement, prescribing,                                    | Controlled before and after study using data from a nationwide community health services | Percent of prescriptions with an antibiotic | Regulation | National Essential Medicines Program | Education; Environmental Restructuring | Expected | Health Care Worker |

|                                                                                                      |                          |          |                                |                                                                                                                                                                                                                                           |                                                                                       |                                         |               |                                      |                                                    |          |                               |
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|                                                                                                      |                          |          |                                | payment, monitoring and evaluation.                                                                                                                                                                                                       | monitoring project.                                                                   |                                         |               |                                      |                                                    |          |                               |
| Lambert MF, et al. Journal of Antimicrobial Chemotherapy. 2007;59(3):537-43.                         | United Kingdom           | Regional | North East Primary Care Trusts | Regional mass media campaign "Antibiotics- tracking down the truth" supported by information materials in GP offices.                                                                                                                     | Controlled before and after study using data from the prescription pricing authority. | Prescriptions per 1000 STAR-PU          | Communication | Public Awareness                     | Education                                          | Expected | Community                     |
| Perz JF, Craig AS, Coffey CS, Jorgensen DM, Mitchel E, Hall S, et al. JAMA. 2002;287(23):3103-9.     | United States of America | Regional | Knox County Health Department  | Regional education campaign to decrease unnecessary antibiotic use in children, including lectures, staff meetings and grand rounds for providers, and pamphlets for parents, and the public along with TV, radio and newspaper coverage. | Controlled before and after study using data from computerized Medicaid files.        | Prescription Rate                       | Communication | Public Awareness                     | Education                                          | Expected | Community; Health Care Worker |
| Wei X, Yin J, Walley JD, Zhang Z, Hicks JP, Zhou Y, et al. Tropical medicine & international health. | China                    | National | Government of China            | Chinese National Essential Medicines Policy and zero-markup on prescriptions policy                                                                                                                                                       | A controlled pre-post natural experiment analysis using data from the hospital        | Outpatient antibiotic prescription rate | Regulation    | National Essential Medicines Program | Restriction; Coercion; Environmental Restructuring | Expected | Health Care Worker            |

2017;22(9):11

66-74.

information

system.

Yang L, et al.  
Health Policy  
and Planning.  
2013;28(7):75  
0-60.

China

National

Multifaceted  
National Chinese  
Essential Medicines  
Chinese  
Ministry of  
Health, National  
Development  
and Reform  
Commission  
and seven other  
agencies  
Policy which  
implemented  
policies and  
procedures  
addressing selection,  
production, supply  
and use of essential  
medicine, pricing,  
payment, monitoring  
and evaluation  
arrangements.

Controlled  
before and  
after study  
using data  
from health  
centre  
databases in  
Hubei  
province.

Percentage of  
prescriptions  
requiring  
antibiotics

Regulation

National  
Essential  
Medicines  
Program

Education;  
Environmental  
Restructuring

Neutral

Health Care  
Worker

Eythorsson E,  
et al. BMC  
Infectious  
Diseases.  
2018;18:10.

Iceland

National

Iceland  
Department of  
Health  
The 10-valent  
pneumococcal non-  
typeable Haemophi-  
lus influenzae  
protein D-conjugate  
vaccine (PHiD-CV10,  
SynflorixTM) was  
introduced into the  
Icelandic paediatric  
vaccination program  
without a catch-up  
for all children born  
in 2011 and later.

Whole  
population  
observational  
cohort study  
using data  
from National  
Prescription  
Database

Incidence  
rates of  
antimicrobial  
prescriptions  
per 100  
person-years  
at risk

Guidelines

Vaccination  
Guidelines

Environmental  
restructuring;

Expected

Community

Belongia EA,  
et al.  
Emerging  
Infectious

United  
States of  
America

Regional

Wisconsin  
Division of  
Public Health

Establishment of  
Wisconsin Antibiotic  
Resistance Network:  
public and physician

Retrospective  
cohort study

Prescription  
Rate

Communication

Public  
Awareness

Education

Neutral

Community;  
Health Care  
Worker

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| Diseases.<br>2005;11(6):91<br>2-20.                                                                   |                |          |                                                          | educational activities<br>and a media<br>campaign.                                                                                                                                 | using IMS<br>Health data.                                                                                       |                                         |                   |                                          |             |          |                       |  |
| Altunsoy A, et<br>al.<br>International<br>Journal of<br>Medical<br>Sciences.<br>2011;8(4):339-<br>44. | Turkey         | National | Turkish Ministry<br>of Health                            | Nationwide<br>restriction on use of<br>particular antibiotics<br>without approval by<br>an infectious disease<br>specialist.                                                       | Uncontrolled<br>before and<br>after study<br>using hospital<br>pharmacy<br>databases and<br>IMS Health<br>data. | Weight in<br>grams                      | Regulation        | Restricted Use                           | Restriction | Expected | Health Care<br>Worker |  |
| Chang SC, et<br>al. Journal of<br>the Formosan<br>Medical<br>Association.<br>2001;100(3):1<br>55-61.  | Taiwan         | National | National health<br>insurance<br>system in<br>Taiwan      | Implementation of a<br>regulation on<br>physician<br>reimbursement<br>where physicians did<br>not receive payment<br>if antibiotic<br>prescriptions did not<br>follow regulations. | Uncontrolled<br>before and<br>after study<br>using data<br>from public<br>health<br>stations.                   | Prescription<br>Rate                    | Regulation        | Reimburseme<br>nt Penalty<br>(Physician) | Coercion    | Neutral  | Health Care<br>Worker |  |
| Curry M, et al.<br>The New<br>Zealand<br>Medical<br>Journal.<br>2006;119(123<br>3):U1957.             | New<br>Zealand | National | Pharmaceutical<br>Management<br>Agency<br>(PHARMAC)      | National public<br>education campaign<br>"Wise Use of<br>Antibiotics<br>Campaign."                                                                                                 | Uncontrolled<br>before and<br>after study<br>using data<br>from a<br>telephone<br>questionnaire.                | Patient<br>reported<br>antibiotic use   | Communicatio<br>n | Public<br>Awareness                      | Education   | Expected | Community             |  |
| Ho M, et al.<br>International<br>Journal of<br>Antimicrobial<br>Agents.                               | Taiwan         | National | Department of<br>Health, Bureau<br>of National<br>Health | Reimbursement<br>regulation forbidding<br>the use of<br>antimicrobials in<br>ambulatory patients                                                                                   | Uncontrolled<br>before and<br>after study<br>using national<br>health                                           | DDD per 1,000<br>inhabitants<br>per day | Regulation        | Restricted<br>Reimburseme<br>nt          | Coercion    | Expected | Health Care<br>Worker |  |

|                                                                                      |                |          |                                                                                                                                                                                  |                                                                                                                                                        |                                                                                                    |                                      |             |                             |                                 |          |                       |
|--------------------------------------------------------------------------------------|----------------|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|--------------------------------------|-------------|-----------------------------|---------------------------------|----------|-----------------------|
| 2004;23(5):43<br>8-45.                                                               |                |          |                                                                                                                                                                                  | with upper<br>respiratory infections<br>(URI) without<br>evidence of bacterial<br>infection.                                                           | insurance<br>data.                                                                                 |                                      |             |                             |                                 |          |                       |
| Kliemann BS,<br>et al. PLoS<br>One.<br>2016;11(12).                                  | Brazil         | National | Government of<br>Brazil                                                                                                                                                          | Law abolishing over-<br>the-counter sales of<br>antibiotics in private<br>pharmacies and<br>requiring a copy of<br>the prescription to<br>be retained. | Interrupted<br>time-series<br>analysis using<br>IMS Health<br>data.                                | DDD per 1000<br>inhabitants/day      | Legislation | Prescription<br>Requirement | Restriction;                    | Expected | Community             |
| Kurt H, et al.<br>Chemotherapy.<br>2010;56(5):35<br>9-63.                            | Turkey         | National | Government of<br>Turkey:<br>Ministries of<br>Health and<br>Finance, SSK,<br>Health<br>Department of<br>the Army, and<br>scientific<br>committees of<br>the Ministry of<br>Health | Restricted<br>reimbursement of<br>antibiotics without<br>prescription or<br>approval by an<br>infectious disease<br>specialist.                        | Uncontrolled<br>before and<br>after study<br>using IMS<br>Health data.                             | DDD per 1,000<br>inhabitants/<br>day | Regulation  | Restricted<br>Reimbursement | Coercion;<br>Restriction        | Expected | Health Care<br>Worker |
| Lee YS, et al.<br>Archives of<br>Pharmacal<br>Research.<br>2014;37(10):1<br>295-300. | South<br>Korea | National | Health<br>Insurance<br>Review and<br>Assessment<br>Services                                                                                                                      | Introduction of a<br>requirement for<br>public disclosure of<br>antibiotic prescribing<br>rates online.                                                | Uncontrolled<br>before and<br>after study<br>using national<br>health<br>insurance<br>claims data. | DDD per 1000<br>inhabitants/day      | Regulation  | Disclosure                  | Environmental<br>restructuring; | Expected | Health Care<br>Worker |

|                                                                                          |             |                |                                                                                                                             |                                                                                                                                                                  |                                                                                             |                                   |             |                          |                                           |          |                    |
|------------------------------------------------------------------------------------------|-------------|----------------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------|-------------|--------------------------|-------------------------------------------|----------|--------------------|
| <b>Ma XD, et al. BMC Infectious Diseases. 2016;16.</b>                                   | China       | National       | Chinese Ministry of Health                                                                                                  | National policies to improve the intelligent use of antibiotics including restrictions on the type of antibiotics used, and hospital targets for antibiotic use. | Uncontrolled before and after study using hospital data.                                    | DDD per 100 occupied bed days     | Regulation  | Stewardship              | Environmental restructuring; Restriction; | Expected | Health Care Worker |
| <b>MacCara ME, et al. The Annals of pharmacotherapy. 2001;35(7-8):852-8.</b>             | Canada      | State/Province | Nova Scotia Department of Health and Wellness                                                                               | Reimbursement guidelines for the use of fluoroquinolones.                                                                                                        | Uncontrolled before and after study using administrative drug claims data.                  | Number of prescription claims     | Regulation  | Restricted Reimbursement | Coercion                                  | Expected | Health Care Worker |
| <b>Molstad S, Cars O. Scandinavian Journal of Infectious Diseases. 1999;31(2):191-5.</b> | Sweden      | National       | Swedish Institute for Infectious Disease Control, Swedish Medical Products Agency, the National Board on Health and Welfare | Development of guidelines for the use of antibiotics in respiratory tract infections, and the development of regional expert groups to provide advice.           | Uncontrolled before and after intervention using data from the Nordic Council on Medicines. | DDD per 1,000 inhabitants per day | Guidelines  | Committee Development    | Education; Environmental Restructuring    | Expected | Health Care Worker |
| <b>Park S, et al. Health Policy and Planning. 2005;20(5):302-9.</b>                      | South Korea | National       | Government of Korea                                                                                                         | National law prohibiting doctors from dispensing drugs and                                                                                                       | Uncontrolled before and after study using data from the                                     | Prescription Rate                 | Legislation | Professional Regulation  | Restriction                               | Expected | Health Care Worker |

|                                                                                                                   |         |          |                                                                   |                                                                                                                             |                                                                                                                        |                                                                        |            |                                        |                                                |          |                                     |
|-------------------------------------------------------------------------------------------------------------------|---------|----------|-------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|------------|----------------------------------------|------------------------------------------------|----------|-------------------------------------|
|                                                                                                                   |         |          |                                                                   | pharmacists from<br>prescribing drug.                                                                                       | Korean<br>National<br>Health<br>Insurance<br>Claims<br>Database.                                                       |                                                                        |            |                                        |                                                |          |                                     |
| <b>Steffensen FH,<br/>et al. Clinical<br/>Microbiology<br/>and Infection.<br/>1997;3(6):653-<br/>7.</b>           | Denmark | Regional | National Health<br>Service                                        | Reimbursement for<br>antibiotics was<br>reduced by 50% for<br>subsidized antibiotics<br>and withdrawn for<br>tetracyclines. | Uncontrolled<br>before and<br>after study<br>using data<br>from a<br>pharmacy<br>computerized<br>accounting<br>system. | DDD                                                                    | Regulation | Reimburseme<br>nt Penalty<br>(Patient) | Coercion                                       | Expected | Community;<br>Health Care<br>Worker |
| <b>Tao JH, et al.<br/>Therapeutic<br/>Innovation &amp;<br/>Regulatory<br/>Science.<br/>2013;47(1):23-<br/>31.</b> | China   | National | Ministry of<br>Health China                                       | A series of Ministry<br>of Health policies on<br>rational use of<br>antibiotics in China<br>from 2008 to 2011               | Uncontrolled<br>before and<br>after study<br>using data<br>from the<br>Menet<br>Database.                              | DDD per<br>patient                                                     | Regulation | Restricted Use                         | Restriction;<br>Environmental<br>Restructuring | Expected | Health Care<br>Worker               |
| <b>Thornhill MH,<br/>et al. BMJ.<br/>2011;342:d23<br/>92.</b>                                                     | England | National | National<br>Institute for<br>Health and<br>Clinical<br>Excellence | Clinical guidelines for<br>dental and other<br>invasive procedures                                                          | Uncontrolled<br>before and<br>after study<br>using data<br>from the NHS<br>prescription<br>pricing<br>division.        | Monthly<br>number of<br>prescriptions<br>for antibiotic<br>prophylaxis | Guidelines | Antimicrobial<br>Guidelines            | Education                                      | Expected | Health Care<br>Worker               |

|                                                                                                                                         |       |          |                          |                                                                                                                                                                                                             |                                                                                                         |                                                                   |            |                                      |                                        |          |                    |
|-----------------------------------------------------------------------------------------------------------------------------------------|-------|----------|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|------------|--------------------------------------|----------------------------------------|----------|--------------------|
| <b>Xiao YH, et al.</b><br><b>International Journal of Antimicrobial Agents.</b><br><b>2016;48(4):409-14.</b>                            | China | National | Government of China      | Implementation and dissemination of National Essential Drugs List in primary health care settings.                                                                                                          | Uncontrolled before and after study using data from health centre records.                              | Percentage of outpatient prescriptions that contained antibiotics | Regulation | National Essential Medicines Program | Education; Environmental Restructuring | Neutral  | Health Care Worker |
| <b>Zhang W, et al.</b><br><b>Pharmacoepidemiology and Drug Safety.</b><br><b>2008;17(3):306-11.</b>                                     | China | National | Ministry of Health China | Guidelines for antibacterial use in clinical practice dividing antibiotics into non-restricted use, restricted use and special use categories.                                                              | Uncontrolled before and after study using data from hospital databases.                                 | DDD per 100 bed days                                              | Guidelines | Antimicrobial Guidelines             | Restriction; Education                 | Neutral  | Health Care Worker |
| <b>Zou XX, et al.</b><br><b>Journal of Huazhong University of Science and Technology-Medical Sciences.</b><br><b>2014;34(3):456-63.</b> | China | National | Ministry of Health China | Multifaceted nationwide campaign to overhaul the clinical use of antibiotics dividing antibiotics into non-restricted use, restricted use and special use categories and launching targets for prescribing. | Uncontrolled before and after study using data from hospital administrative and prescription databases. | DDD per 100 inpatient days                                        | Regulation | Restricted Use                       | Restriction; Education                 | Expected | Health Care Worker |
| <b>Bavestrello F L, Cabello M A.</b> <i>Revista medica de Chile.</i>                                                                    | Chile | National | Ministry of Health Chile | Restriction on sale of antibiotics without a prescription in pharmacies.                                                                                                                                    | Descriptive time-series using IMS Health data.                                                          | DDD per 1,000 inhabitants per day                                 | Regulation | Prescription Requirement             | Education                              | Expected | Community          |

|                                                                                                                                  |        |          |                                  |                                                                                                                                                                             |                                                                                           |                                          |               |                          |                              |          |                               |
|----------------------------------------------------------------------------------------------------------------------------------|--------|----------|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|------------------------------------------|---------------|--------------------------|------------------------------|----------|-------------------------------|
| <b>Bavestrello L, et al. Revista chilena de infectologia. 2002;130(11):1265-72.</b>                                              | Chile  | National | Ministry of Health Chile         | Restriction on the sale of antibiotics without a prescription in pharmacies, supported by a poster, radio and television campaign.                                          | Uncontrolled before and after study using IMS Health data.                                | DDD per 1,000 inhabitants per day        | Regulation    | Prescription Requirement | Restriction; Education       | Expected | Community                     |
| <b>Chahwakilian P, et al. The Journal of Antimicrobial Chemotherapy. 2011;66(12):2872-9.</b>                                     | France | National | French National Health Insurance | National public health campaign "Antibiotics Are Not Automatic!" repeated every winter.                                                                                     | Observational time-series analysis using IMS Health data.                                 | Ambulatory antibiotic prescription rates | Communication | Public Awareness         | Education                    | Expected | Community; Health Care Worker |
| <b>Fan Q, et al. Proceedings of the International Conference on Electronics, Mechanics, Culture and Medicine. 2016;45:654-8.</b> | China  | Regional | Chinese Ministry of Health       | National policies to improve the intelligent use of antibiotics including the establishment of hospital drug therapeutic committees and targets for antibiotic prescribing. | Retrospective, one group post-test study using data from the hospital information system. | DDD / 100 patient days                   | Regulation    | Stewardship              | Environmental restructuring; | Expected | Health Care Worker            |

|                                                                                                              |          |                |                                         |                                                                                                                                                                                                                         |                                                                              |                                     |                   |                          |                                    |          |                               |
|--------------------------------------------------------------------------------------------------------------|----------|----------------|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-------------------------------------|-------------------|--------------------------|------------------------------------|----------|-------------------------------|
| <b>Furst J, et al. Expert Review of Anti-Infective Therapy. 2015;13(2):279-89.</b>                           | Slovenia | National       | Health Insurance Institute of Slovenia  | Suite of education, engineering, economics and enforcement interventions, including workshops, guidelines, prescribing restrictions, and public education.                                                              | Uncontrolled before and after study using data from a prescription database. | DDD per 1000 inhabitants/day        | Regulation        | Restricted Use           | Education; Restriction; Persuasion | Expected | Health Care Worker            |
| <b>Lambert ML, et al. BMJ Open. 2015;5(2).</b>                                                               | Belgium  | National       | Government of Belgium                   | Financial and technical support for hiring antimicrobial management teams at acute care hospitals.                                                                                                                      | Descriptive time-series analysis using hospital administrative data.         | DDD per 100 days of hospitalization | Service Provision | Funding                  | Enablement; Training;              | Neutral  | Health Care Worker            |
| <b>McKay RM et al. Canadian Journal of Infectious Diseases &amp; Medical Microbiology. 2011;22(1):19-24.</b> | Canada   | State/Province | Province of British Columbia Government | Provincial public education campaign "Do Bugs Need Drugs?" including a media campaign, print education material, and educational curricula for school children, parents and older adults in assisted-living facilities. | Descriptive time-series using BC PharmaNet data.                             | DDD per 1,000 inhabitants per day   | Communication     | Public Awareness         | Education                          | Expected | Community; Health Care Worker |
| <b>Moura ML, et al. Medicine. 2015;94(38).</b>                                                               | Brazil   | National       | Government of Brazil                    | Law imposed restricting over-the-counter sales of antimicrobials in                                                                                                                                                     | Descriptive time-series of pharmacy                                          | DDD per 1,000 inhabitants per day   | Legislation       | Prescription Requirement | Restriction                        | Expected | Community                     |

|                                                                                                               |             |          |                                                            |                                                                                                                                                                                                                                                                                             |                                                                                                                                |                                  |            |                          |            |          |                    |  |
|---------------------------------------------------------------------------------------------------------------|-------------|----------|------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|----------------------------------|------------|--------------------------|------------|----------|--------------------|--|
|                                                                                                               |             |          |                                                            | pharmacies and requiring a medical prescription for all antimicrobials sales.                                                                                                                                                                                                               | using IMS Health data.                                                                                                         |                                  |            |                          |            |          |                    |  |
|                                                                                                               |             |          |                                                            |                                                                                                                                                                                                                                                                                             | Descriptive time-series analysis using data from the Health Insurance Review and Assessment Services National Patients Sample. |                                  |            |                          |            |          |                    |  |
| Shin JY, et al. Pharmacoepidemiology and Drug Safety. 2014;23(12):1320-4.                                     | South Korea | National | Korean Regulatory Agency; Ministry of Food and Drug Safety | Release of guidelines for fluoroquinolone use in patients under 18 through a nationwide computerized drug utilization review system.                                                                                                                                                        |                                                                                                                                | Proportion Specific Abx          | Guidelines | Antimicrobial Guidelines | Education  | Expected | Health Care Worker |  |
|                                                                                                               |             |          |                                                            |                                                                                                                                                                                                                                                                                             |                                                                                                                                |                                  |            |                          |            |          |                    |  |
|                                                                                                               |             |          |                                                            |                                                                                                                                                                                                                                                                                             |                                                                                                                                |                                  |            |                          |            |          |                    |  |
| Long MJ, LaPlant BN, McCormick JC. Journal of the American Pharmacists Association : JAPhA. 2017;57(2):241-7. | USA         | National | Federal Bureau of Prisons                                  | A national antimicrobial stewardship program established and developed in the Federal Bureau of Prisons that includes a variety of approaches, including formulary restrictions, clinical guidelines, development of an antimicrobial stewardship group, and dissemination of a tool kit to | Descriptive study using data from electronic medical records.                                                                  | Rate and Number of prescriptions | Guidelines | Antimicrobial Guidelines | Education; | Expected | Health Care Worker |  |

|                                             |                |          |                                                            |                                                                             |                             |                                                                                                            |                                                                     |            |                             |                                              |          |                       |
|---------------------------------------------|----------------|----------|------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------|------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|------------|-----------------------------|----------------------------------------------|----------|-----------------------|
| Song SY, et al.<br>Plos One.<br>2017;12(5). | South<br>Korea | National | Health<br>Insurance<br>Review and<br>Assessment<br>Service | Restrictions on<br>prescribing<br>fluoroquinolones to<br>children under 18. | individual<br>institutions. | Descriptive<br>study using<br>data from the<br>Health<br>Insurance<br>Review and<br>Assessment<br>Service. | Annual<br>prescription<br>rate of FQ per<br>100,000<br>person-years | Guidelines | Antimicrobial<br>Guidelines | Education;<br>Environmental<br>restructuring | Expected | Health Care<br>Worker |
|                                             |                |          |                                                            |                                                                             |                             |                                                                                                            |                                                                     |            |                             |                                              |          |                       |

## A3-2. PRISMA Checklist

| Section/topic                      | #  | Checklist item                                                                                                                                                                                                                                                                                              | Reported in section               |
|------------------------------------|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| <b>TITLE</b>                       |    |                                                                                                                                                                                                                                                                                                             |                                   |
| Title                              | 1  | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                                                                                                                         | Title                             |
| <b>ABSTRACT</b>                    |    |                                                                                                                                                                                                                                                                                                             |                                   |
| Structured summary                 | 2  | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | Abstract                          |
| <b>INTRODUCTION</b>                |    |                                                                                                                                                                                                                                                                                                             |                                   |
| Rationale                          | 3  | Describe the rationale for the review in the context of what is already known.                                                                                                                                                                                                                              | Introduction ¶4                   |
| Objectives                         | 4  | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                                                                                                                  | Methods ¶1 and Search Strategy ¶2 |
| <b>METHODS</b>                     |    |                                                                                                                                                                                                                                                                                                             |                                   |
| Protocol and registration          | 5  | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                                                                                                               | Methods ¶1                        |
| Eligibility criteria               | 6  | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                                                                                      | Methods ¶1                        |
| Information sources                | 7  | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                                                                                                                  | Search Strategy ¶1                |
| Search                             | 8  | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                                                                                                               | Supplementary File 2              |
| Study selection                    | 9  | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                                                                                                                   | Search Strategy ¶2                |
| Data collection process            | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                                                                                                  | Protocol                          |
| Data items                         | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                                                                                                                       | Protocol                          |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.                                                                                      | N/A                               |
| Summary measures                   | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                                                                                                               | N/A                               |

| Section/topic                 | #  | Checklist item                                                                                                                                                                                           | Reported in section         |
|-------------------------------|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Synthesis of results          | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.                                                | Data Analysis ¶1            |
| Risk of bias across studies   | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).                                                             | N/A                         |
| Additional analyses           | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                         | N/A                         |
| <b>RESULTS</b>                |    |                                                                                                                                                                                                          |                             |
| Study selection               | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                          | Figure 1                    |
| Study characteristics         | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                             | Supplemental Table 1        |
| Risk of bias within studies   | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                | N/A                         |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | N/A                         |
| Synthesis of results          | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                  | Table 2                     |
| Risk of bias across studies   | 22 | Present results of any assessment of risk of bias across studies (see Item 15).                                                                                                                          | N/A                         |
| Additional analysis           | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).                                                                                    | N/A                         |
| <b>DISCUSSION</b>             |    |                                                                                                                                                                                                          |                             |
| Summary of evidence           | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                     | Principal Findings ¶1       |
| Limitations                   | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                                            | Strength and Limitations ¶2 |
| Conclusions                   | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                  | Conclusions ¶1              |
| <b>FUNDING</b>                |    |                                                                                                                                                                                                          |                             |
| Funding                       | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.                                                               | Role of the Funding Source  |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. www.prisma-statement.org.

### A3-3. Data Extraction Tool

#### General Information

|                           |               |                                                                               |
|---------------------------|---------------|-------------------------------------------------------------------------------|
| First Author Name         |               |                                                                               |
| Publication Year          |               |                                                                               |
| Journal Name              |               |                                                                               |
| Contact Details           | Name          |                                                                               |
|                           | Affiliation   |                                                                               |
|                           | Email Address |                                                                               |
| Publication Type          |               | CHOOSE:<br><b>Research Study</b><br><b>Abstract</b><br><b>Grey Literature</b> |
| Ethics Approval Received? |               |                                                                               |
| Funding Source            |               |                                                                               |
| Country of Implementation |               |                                                                               |

#### PICO Summary

|              |  |
|--------------|--|
| Population   |  |
| Intervention |  |
| Comparator   |  |

|         |  |
|---------|--|
| Outcome |  |
|---------|--|

CONTINUE?

|                                            |          |
|--------------------------------------------|----------|
| Does the study meet the PICO requirements? | YES / NO |
| Rationale for excluding at this stage      |          |

If yes, continue to next section; if no, stop.

### Study Characteristics

|                                  | Description             | Page # |
|----------------------------------|-------------------------|--------|
| Intervention Aim                 |                         |        |
| Study Aim                        |                         |        |
| Type of study                    |                         |        |
| Study Timing                     |                         |        |
| Population of interest           |                         |        |
| Data Source                      | Source                  |        |
|                                  | Description of data     |        |
| Inclusion Criteria               |                         |        |
| Exclusion Criteria               |                         |        |
| Outcome measure                  |                         |        |
| Sample Size                      | N of Participants       |        |
|                                  | Sample size calculation |        |
|                                  | Power calculation       |        |
| Method of recruitment            |                         |        |
| Randomization/Allocation Methods |                         |        |
| Notes                            |                         |        |

## Intervention Characteristics

|                                                                                                                           |                                  | Description | Page # |
|---------------------------------------------------------------------------------------------------------------------------|----------------------------------|-------------|--------|
| Enacting Government                                                                                                       |                                  |             |        |
| Description of Policy Intervention                                                                                        |                                  |             |        |
| Description of Intervention Groups                                                                                        |                                  |             |        |
| Number of Intervention Groups                                                                                             |                                  |             |        |
| Intervention Dates                                                                                                        |                                  |             |        |
| Intervention Duration                                                                                                     | Duration: Pre-Intervention       |             |        |
|                                                                                                                           | N of Pre-intervention timepoints |             |        |
|                                                                                                                           | Duration: Follow-up              |             |        |
|                                                                                                                           | N of follow-up timepoints        |             |        |
| Setting                                                                                                                   |                                  |             |        |
| Delivery (eg. Stages (sequential or simultaneous), timing, frequency, duration, intensity, fidelity – process indicators) |                                  |             |        |
| Notes                                                                                                                     |                                  |             |        |

## Results Summary

|                                  | Description | Page |
|----------------------------------|-------------|------|
| Main findings                    |             |      |
| Secondary Findings               |             |      |
| Key conclusions of study authors |             |      |
| Notes                            |             |      |

|                                                                                 |  |
|---------------------------------------------------------------------------------|--|
| Does the study design meet the inclusion criteria for the Effectiveness Review? |  |
|---------------------------------------------------------------------------------|--|

## Intervention Effects

### *For Uncontrolled Study Designs*

|                   | Description as stated in report/paper | Location in text or source ( <i>pg &amp; ¶/fig/table/other</i> ) |
|-------------------|---------------------------------------|------------------------------------------------------------------|
| Comparison        |                                       |                                                                  |
| Outcome           |                                       |                                                                  |
| Subgroup          |                                       |                                                                  |
| Describe Analysis |                                       |                                                                  |
| No. participants  |                                       |                                                                  |
| Results           |                                       |                                                                  |

### *For RCT/CCT*

#### *Continuous outcome*

|                                                                    | Description as stated in report/paper | Location in text or source ( <i>pg &amp; ¶/fig/table/other</i> ) |
|--------------------------------------------------------------------|---------------------------------------|------------------------------------------------------------------|
| Comparison                                                         |                                       |                                                                  |
| Outcome                                                            |                                       |                                                                  |
| Subgroup                                                           |                                       |                                                                  |
| Time point<br>( <i>specify from start or end of intervention</i> ) |                                       |                                                                  |
| Post-intervention or change from baseline?                         |                                       |                                                                  |

| Results                                                                                          | Intervention       |                                          |                  | Comparison |                                          |                  |  |
|--------------------------------------------------------------------------------------------------|--------------------|------------------------------------------|------------------|------------|------------------------------------------|------------------|--|
|                                                                                                  | Mean               | SD ( <i>or other variance, specify</i> ) | No. participants | Mean       | SD ( <i>or other variance, specify</i> ) | No. participants |  |
|                                                                                                  |                    |                                          |                  |            |                                          |                  |  |
| Any other results reported ( <i>e.g. mean difference, CI, P value</i> )                          |                    |                                          |                  |            |                                          |                  |  |
| No. missing participants                                                                         |                    |                                          |                  |            |                                          |                  |  |
| Reasons missing                                                                                  |                    |                                          |                  |            |                                          |                  |  |
| No. participants moved from other group                                                          |                    |                                          |                  |            |                                          |                  |  |
| Reasons moved                                                                                    |                    |                                          |                  |            |                                          |                  |  |
| Unit of analysis ( <i>individuals, cluster/ groups or body parts</i> )                           |                    |                                          |                  |            |                                          |                  |  |
| Statistical methods used and appropriateness of these ( <i>e.g. adjustment for correlation</i> ) |                    |                                          |                  |            |                                          |                  |  |
| Reanalysis required? ( <i>specify</i> )                                                          | Yes   No   Unclear |                                          |                  |            |                                          |                  |  |

|                      |                    |  |  |
|----------------------|--------------------|--|--|
| Reanalysis possible? | Yes   No   Unclear |  |  |
| Reanalysed results   |                    |  |  |
| Notes:               |                    |  |  |

***For Controlled Before-and-After study (CBA)***

|                                                                    |                                       |                                          |                                          |                                          |                                                                   |
|--------------------------------------------------------------------|---------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|-------------------------------------------------------------------|
|                                                                    | Description as stated in report/paper |                                          |                                          |                                          | Location in text or source ( <i>pg &amp; ¶ /fig/table/other</i> ) |
| Comparison                                                         |                                       |                                          |                                          |                                          |                                                                   |
| Outcome                                                            |                                       |                                          |                                          |                                          |                                                                   |
| Subgroup                                                           |                                       |                                          |                                          |                                          |                                                                   |
| Time point<br>( <i>specify from start or end of intervention</i> ) |                                       |                                          |                                          |                                          |                                                                   |
| Post-intervention or change from baseline?                         |                                       |                                          |                                          |                                          |                                                                   |
| No. participants                                                   | Intervention                          |                                          | Control                                  |                                          |                                                                   |
| Results                                                            | Intervention result                   | SE ( <i>or other variance, specify</i> ) | Control result                           | SE ( <i>or other variance, specify</i> ) |                                                                   |
|                                                                    |                                       |                                          |                                          |                                          |                                                                   |
|                                                                    | Overall results                       |                                          | SE ( <i>or other variance, specify</i> ) |                                          |                                                                   |
|                                                                    |                                       |                                          |                                          |                                          |                                                                   |
| Any other results reported                                         |                                       |                                          |                                          |                                          |                                                                   |

|                                                                           |                     |  |  |
|---------------------------------------------------------------------------|---------------------|--|--|
| No. missing participants                                                  |                     |  |  |
| Reasons missing                                                           |                     |  |  |
| No. participants moved from other group                                   |                     |  |  |
| Reasons moved                                                             |                     |  |  |
| Unit of analysis<br>( <i>individuals, cluster/ groups or body parts</i> ) |                     |  |  |
| Statistical methods used and appropriateness of these                     |                     |  |  |
| Reanalysis required?<br>( <i>specify</i> )                                | Yes   No<br>Unclear |  |  |
| Reanalysis possible?                                                      | Yes   No<br>Unclear |  |  |
| Reanalysed results                                                        |                     |  |  |
| Notes:                                                                    |                     |  |  |

*For Interrupted Time Series study (ITS)*

|            | Description as stated in report/paper | Location in text or source ( <i>pg &amp; ¶/fig/table/other</i> ) |
|------------|---------------------------------------|------------------------------------------------------------------|
| Comparison |                                       |                                                                  |
| Outcome    |                                       |                                                                  |

|                                                             |                            |                   |  |
|-------------------------------------------------------------|----------------------------|-------------------|--|
| Subgroup                                                    |                            |                   |  |
| Length of time points measured ( <i>e.g. days, months</i> ) |                            |                   |  |
| Total period measured                                       |                            |                   |  |
| No. participants measured                                   |                            |                   |  |
| No. missing participants                                    |                            |                   |  |
| Reasons missing                                             |                            |                   |  |
|                                                             | Pre-intervention           | Post-intervention |  |
| No. time points measured                                    |                            |                   |  |
| Mean value ( <i>with variance measure</i> )                 |                            |                   |  |
| Any other results reported                                  |                            |                   |  |
| Unit of analysis ( <i>individuals or cluster/ groups</i> )  |                            |                   |  |
| Statistical methods used and appropriateness of these       |                            |                   |  |
| Reanalysis required? ( <i>specify</i> )                     | Yes    No<br>ar      Uncle |                   |  |
| Reanalysis possible?                                        | Yes    No<br>ar      Uncle |                   |  |

|                               |                 |    |                 |    |  |
|-------------------------------|-----------------|----|-----------------|----|--|
| Individual time point results |                 |    |                 |    |  |
| Read from figure?             | Yes             |    |                 |    |  |
|                               | No              |    |                 |    |  |
| Reanalysed results            | Change in level | SE | Change in slope | SE |  |
|                               |                 |    |                 |    |  |
| Notes:                        |                 |    |                 |    |  |

## Additional Questions

|                                                                                           | Description | Page |
|-------------------------------------------------------------------------------------------|-------------|------|
| Beneficial Effects                                                                        |             |      |
| Adverse Effects                                                                           |             |      |
| Key conclusions of study authors                                                          |             |      |
| References to other relevant studies                                                      |             |      |
| Correspondence required for further study information ( <i>from whom, what and when</i> ) |             |      |
| Notes:                                                                                    |             |      |

## Supplemental information – Chapter 4

### A4-1. Decision guide for SQUIRE 2.0 Checklist

| SQUIRE ITEM               | Explanation in SQUIRE 2.0<br>(adapted from Goodman 2016)                                                                                                                                                                          | Decision Rules and Response Item                                                                                                                                                                                                                                                                                                                                           |
|---------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title and Abstract</b> |                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                            |
| Title                     | Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patient- centeredness, timeliness, cost, efficiency, and equity of healthcare).         | <b>Fully reported:</b> authors have indicated that the manuscript concerns an initiative (program or intervention) to change the use of antimicrobials.<br><b>Not fully reported:</b> the authors have not indicated that the manuscript concerns an initiative to change the use of antimicrobials.                                                                       |
| Abstract                  | a. Provide adequate information to aid in searching and indexing                                                                                                                                                                  | <b>Fully reported:</b> the authors have provided adequate information on the topic of the paper to allow readers to quickly decide if it is relevant to their work, and have included keywords and phrases that will allow for quick retrieval in a literature search.<br><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear. |
|                           | b. Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions | <b>Fully reported:</b> the authors have provided an appropriate summary of all aspects of the study including the purpose, methods, and scope of the intervention, and the results, conclusions and recommendations;<br><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.                                                   |
| <b>Introduction</b>       |                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                            |
| Problem Description       | Nature and significance of the local problem                                                                                                                                                                                      | <b>Fully reported:</b> the nature and significance of the problem are described with reference to the significance or impact on the region/province or state/nation;<br><b>Not fully reported:</b> the nature and significance of the problem are not reported/unclear;                                                                                                    |
| Available Knowledge       | Summary of what is currently known about the problem, including relevant previous studies.                                                                                                                                        | <b>Fully reported:</b> study summarizes current evidence on the problem with reference to other research in the field to provide background and support for this intervention;                                                                                                                                                                                             |

|                |                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                |                                                                                                                                                                                                                                  | <b>Not fully reported:</b> study does not refer to current evidence about the problem;                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Rationale      | Informal or formal frameworks, models, concepts and/or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s), and reasons why the intervention(s) was expected to work. | <p><b>Fully reported:</b> the authors make explicit their reasons for expecting that an intervention will work, which might include: providing an explanation, specifying underlying principles, hypothesizing processes or mechanisms of change, or producing a logic model;</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                     |
| Specific Aims  | Purpose of the project and of this report                                                                                                                                                                                        | <p><b>Fully reported:</b> the authors precisely state the aim of this intervention, which should align with the nature of the problem and reflect the rationale for the intervention.</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                                                                                                             |
| <b>Methods</b> |                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Context        | Contextual elements considered important at the outset of introducing the intervention.                                                                                                                                          | <p><b>Fully reported:</b> The authors consider from the outset the contextual elements such as the physical and sociocultural makeup of the local environment and the interpretation of these factors by the healthcare workers and patients, and how these might affect the effectiveness and generalizability of the intervention.</p> <p><b>Not fully reported:</b> the authors do not report the potential impact of contextual factors on the effectiveness or generalizability of the intervention.</p> |
| Intervention   | a. Description of the intervention(s) in sufficient detail that others could reproduce it                                                                                                                                        | <p><b>Fully reported:</b> the report provides a complete description of the activities and tools used in sufficient detail that others could reproduce it, including: the inputs, internal activities, outputs, and mechanisms by which these components are expected to produce change.</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                          |
|                | b. Specifics of the team involved in the work                                                                                                                                                                                    | <p><b>Fully reported:</b> The report provides specifics on the team that was involved in the work.</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                                                                                                                                                                                                |

|                           |                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|---------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study of the intervention | a. Approach chosen for assessing the impact of the intervention(s)                                                                                                                      | <p><b>Fully reported:</b> the authors report the study design and methods chosen to assess the impact of the intervention;</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                                                                                                                                                                                                                                                                            |
|                           | b. Approach used to establish whether the observed outcomes were due to the intervention(s)                                                                                             | <p><b>Fully reported:</b> the authors report the study design, methods, and/or statistics used to assess the impact of the intervention; the authors report whether the evaluative techniques used were performed by the authors themselves or by an outside team, and what relationship existed between the authors and the evaluators. The authors should also report the timing of the evaluation in comparison to the intervention (was the study evaluated prospectively, retrospectively etc.,)</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p> |
| Measures                  | a. Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability | <p><b>Fully reported:</b> the study reports the chosen process and outcomes measures along with their definitions, validity/reliability, and the rationale for choosing these measures</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                                                                                                                                                                                                                |
|                           | b. Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost                                          | <p><b>Fully reported:</b> the approach to the assessment of contextual elements is described;</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                                                                                                                                                                                                                                                                                                         |
|                           | c. Methods employed for assessing completeness and accuracy of data                                                                                                                     | <p><b>Fully reported:</b> the methods for assessing the completeness and accuracy of data are described;</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                                                                                                                                                                                                                                                                                              |
| Analysis                  | a. Qualitative and quantitative methods used to draw inferences from the data                                                                                                           | <p><b>Fully reported:</b> The qualitative and/or quantitative methods used to interpret the findings and data are described;</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                                                                                                                                                                                                                                                                          |

|                        |                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                        | <b>b.</b> Methods for understanding variation within the data, including the effects of time as a variable                                                                                        | <p><b>Fully reported:</b> The authors report the methods used to understand variation within the data;</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                                                                                                                        |
| Ethical Considerations | Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest           | <p><b>Fully reported:</b> the report considers the potential for harm, burden and cost to the stakeholders associated with the intervention, and, where applicable, reports formal ethics review and potential conflicts of interest.</p> <p><b>Not fully reported:</b> the authors do not consider the ethical aspects of implementing the study or does not report formal ethics review and conflicts of interest where applicable.</p> |
| <b>Results</b>         |                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Results                | <b>a.</b> Initial steps of the intervention(s) and their evolution over time (e.g., time-line diagram, flow chart, or table), including modifications made to the intervention during the project | <p><b>Fully reported:</b> the authors provide a timeline, flowchart, or table describing the the steps of the intervention and modifications that were made to the intervention during the project.</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                           |
|                        | <b>b.</b> Details of the process measures and outcome                                                                                                                                             | <p><b>Fully reported:</b> the authors provide tables and figures that adequately report both the process measures and outcomes of the study;</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                                                                                  |
|                        | <b>c.</b> Contextual elements that interacted with the intervention(s)                                                                                                                            | <p><b>Fully reported:</b> the authors describe in tables or in the text the contextual elements that may interact with the intervention such as structural variables.</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                                                         |
|                        | <b>d.</b> Observed associations between outcomes, interventions, and relevant contextual elements                                                                                                 | <p><b>Fully reported:</b> the authors describe in tables or in the text the associations between contextual elements, outcomes, and intervention.</p>                                                                                                                                                                                                                                                                                     |

|                   |                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                   |                                                                                                                                  | <b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.                                                                                                                                                                                                                                                                         |
|                   | <b>e.</b> Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s). | <b>Fully reported:</b> the authors report and describe any unintended benefits or consequences associated with the intervention;<br><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.                                                                                                                                     |
|                   | <b>f.</b> Details about missing data                                                                                             | <b>Fully reported:</b> the authors report the extent of missing data;<br><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.                                                                                                                                                                                                |
| <b>Discussion</b> |                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                          |
| Summary           | <b>a.</b> Key findings, including relevance to the rationale and specific aims                                                   | <b>Fully reported:</b> The authors summarize their key findings at their relevance at the beginning of the discussion section of the paper;<br><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.                                                                                                                          |
|                   | <b>b.</b> Particular strengths of the project                                                                                    | <b>Fully reported:</b> the authors describe the strengths of their intervention or analysis;<br><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.                                                                                                                                                                         |
| Interpretation    | <b>a.</b> Nature of the association between the intervention(s) and the outcomes                                                 | <b>Fully reported:</b> the authors describe the association between intervention and outcome, provide alternative explanations for these findings, and consider other factors that might have confounded the asserted relationship between intervention and outcome.<br><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear. |
|                   | <b>b.</b> Comparison of results with findings from other publications                                                            | <b>Fully reported:</b> the authors contextualize their results with findings from other relevant publications;<br><b>Not fully reported:</b> the authors do not contextualize their findings within the wider body of evidence.                                                                                                                                          |

|             |                                                                                                                                                 |                                                                                                                                                                                                                                                                                    |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|             | c. Impact of the project on people and systems                                                                                                  | <p><b>Fully reported:</b> the authors consider the impact of the intervention on people and health systems;</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                            |
|             | d. Reasons for any differences between observed and anticipated outcomes, including the influence of context                                    | <p><b>Fully reported:</b> the authors acknowledge differences between observed and anticipated outcomes, and consider reasons for the existence of these differences.</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>  |
|             | e. Costs and strategic trade-offs, including opportunity costs                                                                                  | <p><b>Fully reported:</b> the authors discuss the feasibility, sustainability, costs and trade-offs of their intervention.</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                             |
| Limitations | a. Limits to the generalizability of the work                                                                                                   | <p><b>Fully reported:</b> the authors report the extent to which the findings are generalizable;</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                       |
|             | b. Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis | <p><b>Fully reported:</b> the authors report on potential sources of confounding, bias, and imprecision in their study design, data collection and analysis;</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>           |
|             | c. Efforts made to minimize and adjust for limitations                                                                                          | <p><b>Fully reported:</b> the authors report whether they have made any efforts to minimize and adjust for the limitations in (b) and what adjustments have been made.</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p> |
| Conclusions | a. Usefulness of the work                                                                                                                       | <p><b>Fully reported:</b> the authors report on the impact/usefulness of this work as it relates to current debates in the field, gaps in the available body of evidence, changes in practice or other key issues;</p>                                                             |

|                          |                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                          |                                                                                                                                                     | <b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.                                                                                                                                                                                                                                                                  |
|                          | <b>b. Sustainability</b>                                                                                                                            | <p><b>Fully reported:</b> where applicable, the authors comment on the sustainability of the implemented intervention;</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                                |
|                          | <b>c. Potential for spread to other contexts</b>                                                                                                    | <p><b>Fully reported:</b> the authors discuss whether this intervention could be used in other contexts;</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                                              |
|                          | <b>d. Implications for practice and for further study in the field</b>                                                                              | <p><b>Fully reported:</b> the authors discuss the implications of this work for practice and further study;</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                                           |
|                          | <b>e. Suggested next steps</b>                                                                                                                      | <p><b>Fully reported:</b> the authors suggest next steps for this research;</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p>                                                                                                                                                                           |
| <b>Other information</b> |                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Funding</b>           | Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting | <p><b>Fully reported:</b> the authors report the sources of funding, role of the funding organization in the design, implementation, interpretation and reporting of the study, or report that the funding did not have such a role where applicable.</p> <p><b>Not fully reported:</b> one or more of the components of this item are not addressed/unclear.</p> |

## A4-2. Individual notes on reporting quality for each included study

| Altunsoy 2011                    |                                                                                                                                                                                                                                                                                                                |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                 |
| <b>Abstract</b>                  | Provided adequate information for searching and indexing<br>Did not provide a full summary of key information for the local problem, methods or recommendations.                                                                                                                                               |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                 |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                 |
| <b>Rationale</b>                 | Did not adequately refer to current evidence about the problem or report on support for the intervention.                                                                                                                                                                                                      |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                 |
| <b>Context</b>                   | Did not provide sufficient information on context or how context might affect the effectiveness and generalizability of the intervention.                                                                                                                                                                      |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it.<br>Did not report the specifics of the team involved in the work.                                                                                                                                                          |
| <b>Study of the Intervention</b> | Did not fully report the methods chosen to assess the impact of the intervention, they only report that the intervention was a quasi-experiment.                                                                                                                                                               |
| <b>Measures</b>                  | Did not report on the rationale for choice of measures, or validity and reliability.<br>Did not describe their approach to the assessment of contextual elements.<br>Did not report on the methods employed for assessing completeness and accuracy of data.                                                   |
| <b>Analysis</b>                  | Adequately reported quantitative methods used to draw inferences from the data.<br>Did not report on the effects of time as a variable.                                                                                                                                                                        |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                              |
| <b>Results</b>                   | Process measures and outcomes and observed associations between outcomes and interventions were adequately reported.<br>Did not report on contextual elements that interacted with the intervention.<br>Discussion of unintended consequences and costs is unclear. Did not report the extent of missing data. |
| <b>Summary</b>                   | Unclear description of key findings and particular strengths of the project.                                                                                                                                                                                                                                   |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes.<br>Did not report on the costs and strategic trade-offs.                                 |
| <b>Limitations</b>               | Did not report limits to the generalizability of the work.<br>Adequately reported on factors that limited internal validity.<br>Did not report on efforts made to minimize and adjust for limitations.                                                                                                         |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work.<br>Did not report on sustainability, potential for spread to other contexts.<br>Unclear reporting of implications and next step.                                                                                                                            |
| <b>Funding</b>                   | Did not report on the sources of funding or the role of the funding organization.                                                                                                                                                                                                                              |

| Bastiaens 2011                   |                                                                                                                                                                                                                                                                                |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing.<br>Adequately summarized key all key information from various sections of the text.                                                                                                                           |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Intervention</b>              | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Measures</b>                  | Did not report the rationale for choosing these measures or their operational definitions, validity and reliability.<br>Did not describe their approach to the assessment of contextual elements or missing data.                                                              |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Results</b>                   | Contextual elements, process measures and outcomes, and observed associations between outcomes and interventions were adequately reported.<br>Did not report the Initial steps of the intervention and their evolution over time or the extent of missing data.                |
| <b>Summary</b>                   | Adequately report key findings.<br>Unclear report of the strengths of the project.                                                                                                                                                                                             |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes.<br>Did not report on the costs and strategic trade-offs. |
| <b>Limitations</b>               | Did not report limits to the generalizability of the work or efforts to adjust for limitations.<br>Unclear discussion of factors that might have limited internal validity.                                                                                                    |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, sustainability, implications for further practice and suggested next steps.<br>Did not report on potential for spread to other contexts.                                                                                    |
| <b>Funding</b>                   | Did not report on the sources of funding or the role of the funding organization.                                                                                                                                                                                              |

| <b>Belongia 2005</b>             |                                                                                                                                                                                                                                                                                                                                                             |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                              |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing.<br>Did not summarize the all key information from various sections of the text.                                                                                                                                                                                                            |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                              |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                              |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                         |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                              |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                              |
| <b>Intervention</b>              | Intervention described in sufficient detail for replication.<br>Missing details on the team involved in the work including a description of who provided the training sessions.                                                                                                                                                                             |
| <b>Study of the Intervention</b> | Unclear description of the approach chosen for assessing the impact of the intervention and the approach used to establish whether the observed outcomes were due to intervention.                                                                                                                                                                          |
| <b>Measures</b>                  | Adequately reported the measures chosen for studying the outcomes.<br>Unclear description of the approach to assessment of contextual elements.<br>Did not report on the methods employed for assessing completeness and accuracy of data.                                                                                                                  |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                              |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                           |
| <b>Results</b>                   | Adequately reported the initial steps of the intervention, their evolution over time, the details of the process measures and outcomes, and the observed associations between outcomes and interventions.<br>Did not report on the contextual elements that interacted with the interventions or the unintended consequences and costs of the intervention. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                              |
| <b>Interpretation</b>            | Fully reported                                                                                                                                                                                                                                                                                                                                              |
| <b>Limitations</b>               | Adequately reported on the generalizability of the work and factors that limited the internal validity.<br>Did not report on efforts to minimize and adjust for limitations.                                                                                                                                                                                |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, implications for further practice and suggested next steps.<br>Did not report on sustainability or potential for spread to other contexts.                                                                                                                                                               |
| <b>Funding</b>                   | Reported the funding agency but did not report on role of the funding organization.                                                                                                                                                                                                                                                                         |

| <b>Bernier 2014</b>              |                                                                                                                                                                                                                                                                                                                  |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                   |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing.<br>Adequately summarized key all key information from various sections of the text.                                                                                                                                                             |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                   |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                   |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                              |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                   |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                   |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it.<br>Specifics of the team involved were not applicable for studies where the authors were clearly not involved in implementation.                                                                                             |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                   |
| <b>Measures</b>                  | Adequate description of the measures chosen for studying the process and outcomes.<br>Unclear description of their approach to the assessment of contextual elements and methods employed for assessing completeness and accuracy of the data.                                                                   |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                   |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                |
| <b>Results</b>                   | Unclear description of the initial steps of the intervention and their evolution over time.<br>Adequately reported the details of the process measures, outcomes, observed associations between outcomes and interventions.<br>Unclear description of contextual elements and unintended costs and consequences. |
| <b>Summary</b>                   | Adequately reported key findings.<br>Unclear reporting of the particular strengths of the project.                                                                                                                                                                                                               |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems.<br>Did not report on the reasons for differences between observed and anticipated outcomes or the costs and strategic trade-offs.                                 |
| <b>Limitations</b>               | Adequately reported on the generalizability of the work and factors that limited the internal validity.<br>Did not report on efforts to minimize and adjust for limitations.                                                                                                                                     |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, sustainability, implications for further practice and suggested next steps.<br>Did not report on potential for spread to other contexts.                                                                                                                      |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                              |

| Bou Antoun 2018                  |                                                                                                                                                                                                                                                                                                                                |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                 |
| <b>Abstract</b>                  | Provided adequate information for searching and indexing.<br>Did not summarize all key information from various sections of the text.                                                                                                                                                                                          |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                 |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                 |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                            |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                 |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                 |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it.<br>Missing details on the team involved in the work.                                                                                                                                                                                       |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                 |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                 |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                 |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                 |
| <b>Results</b>                   | Unclear description of the initial steps of the intervention and their evolution over time, contextual elements, and unintended costs and consequences.<br>Adequately reported the details of the process measures and observed associations between outcomes and interventions.<br>Did not report the extent of missing data. |
| <b>Summary</b>                   | Adequately reported key findings.<br>Did not report the particular strengths of the project.                                                                                                                                                                                                                                   |
| <b>Interpretation</b>            | Clearly reported the nature of the association and comparison with findings from other publications.<br>Unclear description of differences between observed and anticipated outcomes and the impact of the project on people and systems.<br>Did not report on the costs and strategic trade-offs.                             |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                 |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, implications for further practice and suggested next steps.<br>Did not report on sustainability and potential for spread to other contexts.                                                                                                                                 |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                 |

| Chahwakilian 2011                |                                                                                                                                                                                                                                                                                                                    |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                     |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                     |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                     |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                     |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                     |
| <b>Context</b>                   | Unclear description of their approach to the assessment of contextual elements.                                                                                                                                                                                                                                    |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it.<br>Specifics of the team involved were not applicable for studies where the authors were clearly not involved in implementation.                                                                                               |
| <b>Study of the Intervention</b> | Did not report the approach chosen for assessing the impact of the intervention or the approach used to establish whether the observed outcome was due to the intervention.                                                                                                                                        |
| <b>Measures</b>                  | Adequately described the measures chosen for studying the outcomes and intervention.<br>Did not describe the approach to the ongoing assessment of context or the methods for assessing the completeness and accuracy of the data.                                                                                 |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                     |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                  |
| <b>Results</b>                   | Unclear description of the initial steps of the intervention and their evolution over time, the context, observed association between outcome and intervention, and unintended consequences.<br>Adequately reported the details of the process measures and outcome.<br>Did not report the extent of missing data. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                     |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes.<br>Did not report on the costs and strategic trade-offs.                                     |
| <b>Limitations</b>               | Did not report on generalizability of the work.<br>Adequately reported the factors that limited internal validity and efforts made to minimize and adjust for limitations.                                                                                                                                         |
| <b>Conclusions</b>               | Unclear description of the usefulness of the work and suggested next steps.<br>Did not report on the sustainability and potential for spread to other contexts.<br>Adequately reported on the implications for practice.                                                                                           |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                |

| <b>Chang 2001</b>                |                                                                                                                                                                                                                                                                                                                      |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                       |
| <b>Abstract</b>                  | Provided adequate information for searching and indexing<br>Did not provide a full summary of key information for the background or local problem.                                                                                                                                                                   |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                       |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                       |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                  |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                       |
| <b>Context</b>                   | Did not describe their approach to the assessment of contextual elements.                                                                                                                                                                                                                                            |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it. Specifics of the team involved were not applicable for studies where the authors were clearly not involved in implementation.                                                                                                    |
| <b>Study of the Intervention</b> | Did not report the approach chosen for assessing the impact of the intervention or the approach used to establish whether the observed outcome was due to the intervention.                                                                                                                                          |
| <b>Measures</b>                  | Unclear description of the measures chosen for studying the outcomes, their approach to the assessment of contextual elements and methods employed for assessing completeness and accuracy of the data. Unclear how many sites were excluded for missing data.                                                       |
| <b>Analysis</b>                  | Unclear description of methods used to draw inferences about the data or for understanding variation within the data.                                                                                                                                                                                                |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                    |
| <b>Results</b>                   | Unclear description of the initial steps of the intervention and their evolution over time, observed association between outcome and intervention, unintended costs and consequences, and the extent of missing data.<br>Adequately reported the details of the process measures, outcomes, and contextual elements. |
| <b>Summary</b>                   | Unclear description of key findings and strengths.                                                                                                                                                                                                                                                                   |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, and impact of the project on people and systems.<br>Unclear description of the reasons for differences between observed and anticipated outcomes.<br>Did not report on the costs and strategic trade-offs.         |
| <b>Limitations</b>               | Did not report on limits to the generalizability of the work, factors that might have limited internal validity, or efforts to minimize and adjust for limitations.                                                                                                                                                  |
| <b>Conclusions</b>               | Unclear description of the usefulness of the work, implications for further practice and suggested next steps.<br>Did not report on sustainability or potential for spread to other contexts.                                                                                                                        |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                  |

| <b>Curry 2006</b>                |                                                                                                                                                                                                                                                                                                                       |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                        |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing.<br>Summary of key information is missing the background and local problem.                                                                                                                                                                           |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                        |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                        |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                   |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                        |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                        |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it. Didn't provide survey or survey questions, did not show calculation of sample size. Did not clearly report the specifics of the team involved in the work.                                                                        |
| <b>Study of the Intervention</b> | Adequately described the approach chosen for assessing the impact of the intervention<br>Unclear description of the approach used to establish whether the observed outcomes were due to the intervention.                                                                                                            |
| <b>Measures</b>                  | Did not fully report the measures chosen for studying the outcomes including the choice of survey questions and validity and reliability.<br>Adequately described the approach to ongoing assessment of context.<br>Did not report on the methods employed for assessing completeness and accuracy of data.           |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                        |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                        |
| <b>Results</b>                   | Unclear description of the initial steps of the intervention and their evolution over time, unintended costs and consequences, and the extent of missing data.<br>Adequately reported the details of the process measures, outcomes, contextual elements and observed associations between outcomes and intervention. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                        |
| <b>Interpretation</b>            | Clearly reported the nature of the association and comparisons with findings from other publications.<br>Unclear descriptions of the impact of the project on people and systems, reasons for differences between observed and anticipated outcomes, and costs and strategic trade-offs.                              |
| <b>Limitations</b>               | Unclear description of the generalizability of the work and efforts made to adjust for limitations.<br>Did not report on the factors that might have limited internal validity.                                                                                                                                       |
| <b>Conclusions</b>               | Unclear description of the usefulness of the work, implications for further practice and suggested next steps.<br>Did not report on sustainability or potential for spread to other contexts.                                                                                                                         |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                   |

| D'Acremont 2011                  |                                                                                                                                                                                                                                                                             |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                              |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing.<br>Adequately summarized key all key information from various sections of the text.                                                                                                                        |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                              |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                              |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                              |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                              |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                              |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it. Does not describe who conducted data collection or who lead sensitization meetings.                                                                                                     |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                              |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                              |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                              |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                              |
| <b>Results</b>                   | Fully reported                                                                                                                                                                                                                                                              |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                              |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes. Did not report on the costs and strategic trade-offs. |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                              |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work and implications for further practice<br>Did not report on the sustainability, potential for spread to other contexts, and suggested next steps.                                                                          |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                              |

| Dommergues 2012                  |                                                                                                                                                                                                                                                                          |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Title does not specify that there is an intervention under evaluation.                                                                                                                                                                                                   |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                           |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                           |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                           |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                      |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                           |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                           |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it.<br>Specifics of the team involved were not applicable for studies where the authors were clearly not involved in implementation.                                                     |
| <b>Study of the Intervention</b> | Clearly report the approach for assessing the impact of the intervention. Unclear whether the evaluation was conducted by the study team or external team.                                                                                                               |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                           |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                           |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                        |
| <b>Results</b>                   | Clearly reported the details of process measures, outcome, contextual elements, and observed associations between outcome and intervention. Unclear description of the initial steps of the intervention, unintended costs and consequences, and extent of missing data. |
| <b>Summary</b>                   | Adequately reported the key findings.<br>Did not report the strengths of the study.                                                                                                                                                                                      |
| <b>Interpretation</b>            | Fully reported                                                                                                                                                                                                                                                           |
| <b>Limitations</b>               | Unclear description of the generalizability of the work and efforts to minimize and adjust for limitations.<br>Adequately reported the factors that might have limited the internal validity.                                                                            |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work and suggested next steps.<br>Unclear description of sustainability, potential for spread to other contexts and implications for practice.                                                                              |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source. Particularly important because funder was a pharmaceutical company.                                                                                                                                  |

| <b>Dowell 2012</b>               |                                                                                                                                                                                                                                                                                                                          |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing; missing key information for background and local problem.                                                                                                                                                                                               |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                      |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Context</b>                   | Did not report on the demographics of the included study sites.                                                                                                                                                                                                                                                          |
| <b>Intervention</b>              | Described the intervention in sufficient detail that others could reproduce it.<br>Did not report the specifics of the team involved in the work.                                                                                                                                                                        |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Results</b>                   | Did not clearly report the initial steps of the intervention and their evolution over time, the unintended costs and consequences, and or extent of missing data.<br>Adequately reported the details of process outcomes and measures, contextual elements, and observed associations between outcomes and intervention. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, and impact of the project on people and systems.<br>Did not clearly report on the costs and strategic trade-offs or reasons for differences between observed and anticipated outcomes.                                 |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Conclusions</b>               | Did not clearly report on the usefulness of the work, sustainability, potential for spread to other contexts, or suggested next steps.<br>Adequately reported the implications for future practice.                                                                                                                      |
| <b>Funding</b>                   | Did not report on the sources of funding or the role of the funding organization. Particularly unclear because authors are CDC but they include a statement that the findings do not necessarily represent the views of CDC.                                                                                             |

| <b>Duval 2007</b>                |                                                                                                                                                                                                                                                                                                                          |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing. Adequately summarized key all key information from various sections of the text.                                                                                                                                                                        |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                      |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Context</b>                   | Did not provide sufficient information on context or how context might affect the effectiveness and generalizability of the intervention.                                                                                                                                                                                |
| <b>Intervention</b>              | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Study of the Intervention</b> | Did not clearly report on the approach chosen for assessing the impact of the intervention or the approach used to establish whether the observed outcomes were due to the intervention.                                                                                                                                 |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                           |
| <b>Results</b>                   | Did not clearly report the initial steps of the intervention and their evolution over time, observed associations between outcomes and interventions, contextual elements and the unintended costs and consequences, and or extent of missing data.<br>Adequately reported the details of process outcomes and measures. |
| <b>Summary</b>                   | Key findings and strengths are not clearly summarized in the discussion.                                                                                                                                                                                                                                                 |
| <b>Interpretation</b>            | Clearly reported the nature of the association, compared their findings with results from other publications and reported reasons for the difference between observed and anticipated outcomes,<br>Did not clearly report on the impact of the project on people and systems, or costs and strategic trade-offs.         |
| <b>Limitations</b>               | Unclear discussion of the generalizability and efforts made to address limitations.<br>Clearly reported the factors that might have limited internal validity.                                                                                                                                                           |
| <b>Conclusions</b>               | Clearly reported on the usefulness of the work, implications for further practice and suggested next steps.<br>Did not report on sustainability and potential for spread to other contexts.                                                                                                                              |
| <b>Funding</b>                   | Did not report on the sources of funding or the role of the funding organization.                                                                                                                                                                                                                                        |

| Ellegard 2018                    |                                                                                                                                                                                                                                                                                                                   |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                    |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing and did not fully summarize all key information from various sections of the text.                                                                                                                                                                |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                    |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention.<br>Did not report on reasons why the P4P intervention was expected to work.                                                                                                                       |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                    |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                    |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it, or the specifics of the team involved.                                                                                                                                                                                        |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                    |
| <b>Measures</b>                  | Did not clearly report the measures chosen for studying the processes and outcomes of the intervention, or methods employed for assessing the completeness and accuracy of the data.<br>Description of the ongoing assessment not applicable given study design.                                                  |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                    |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                    |
| <b>Results</b>                   | Did not clearly report the initial steps of the intervention and their evolution over time, contextual elements, unintended costs and consequences, and extent of missing data.<br>Adequately reported the details of process outcomes and measures and observed associations between outcomes and interventions. |
| <b>Summary</b>                   | Adequately reported the key findings.<br>Did not report on the particular strengths of the study.                                                                                                                                                                                                                 |
| <b>Interpretation</b>            | Clearly reported the nature of the association, compared their findings with results from other publications and reported reasons for the difference between observed and anticipated outcomes.<br>Did not clearly report on the impact of the project on people and systems, or costs and strategic trade-offs.  |
| <b>Limitations</b>               | Did not report on the limits to generalizability.<br>Adequately reported the factors that might have limited internal validity and efforts made to minimize and adjust for limitations.                                                                                                                           |
| <b>Conclusions</b>               | Clearly reported the usefulness of the work.<br>Sustainability, potential for spread to other contexts, implications for further practice, and suggested next steps were not reported.                                                                                                                            |
| <b>Funding</b>                   | Did not report on the sources of funding or the role of the funding organization.                                                                                                                                                                                                                                 |

| Eythorsson 2018                  |                                                                                                                                                                                                                                                                                                                                                       |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Intervention</b>              | Fully reported<br>Specifics of the team involved were not applicable for studies where the authors were clearly not involved in implementation.                                                                                                                                                                                                       |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Measures</b>                  | Did not fully report the measures chosen for studying the outcome, their approach to the ongoing assessment of contextual elements, and the methods employed for assessing completeness of the data.                                                                                                                                                  |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Results</b>                   | Clearly reported the initial steps of the intervention and their evolution over time, and the observed associations between outcomes and intervention.<br>Did not clearly describe the details of the process measures, contextual elements that interacted with the intervention, the unintended costs and consequences, and extent of missing data. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes.<br>Did not report on the costs and strategic trade-offs.                                                                        |
| <b>Limitations</b>               | Did not clearly report on the limits to generalizability or the factors that might have limited internal validity.<br>Adequately described the efforts made to adjust for limitations.                                                                                                                                                                |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work.<br>Did not report on sustainability, implications for further practice, potential for spread to other contexts and suggested next steps.                                                                                                                                                           |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                        |

| Fan 2015                         |                                                                                                                                                                                                                                                                                                                 |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                  |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing or summarize all key information from various sections of the text.                                                                                                                                                                             |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                  |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                  |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                             |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                  |
| <b>Context</b>                   | Did not describe their approach to the assessment of contextual elements.                                                                                                                                                                                                                                       |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                           |
| <b>Study of the Intervention</b> | Did not clearly report on the approach chosen for assessing the impact of the intervention or the approach used to establish whether the observed outcomes were due to the intervention.                                                                                                                        |
| <b>Measures</b>                  | Did not fully report the measures chosen for studying the outcome, their approach to the ongoing assessment of contextual elements, and the methods employed for assessing completeness of the data.                                                                                                            |
| <b>Analysis</b>                  | Did not fully report on the quantitative methods used to draw inferences from the data or the methods used for understanding variation within the data.                                                                                                                                                         |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                               |
| <b>Results</b>                   | Did not clearly report the initial steps of the intervention and their evolution over time, contextual elements, and extent of missing data. Adequately reported the details of process outcomes, unintended costs and consequences, and measures and observed associations between outcomes and interventions. |
| <b>Summary</b>                   | No summary section, key findings not reported.                                                                                                                                                                                                                                                                  |
| <b>Interpretation</b>            | Clearly reported the nature of the association.<br><br>Did not clearly compare with findings from other publications, or report the impact of the project on people and systems, the reasons for differences between observed and anticipated outcomes, or costs and strategic trade-offs.                      |
| <b>Limitations</b>               | Did not report on generalizability, factors that limited internal validity, or efforts made to adjust for limitations.                                                                                                                                                                                          |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work and implications for practice.<br>Did not report on sustainability, potential for spread to other contexts and suggested next steps.                                                                                                                          |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                             |

| Finkelstein 2008                 |                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                  |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                  |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                  |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                  |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                             |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                  |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                  |
| <b>Intervention</b>              | Clearly reported intervention in sufficient detail for replication. Unclear report of the specifics of the team involved in the work.                                                                                                                                                                                           |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                  |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                  |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                  |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                               |
| <b>Results</b>                   | Did not clearly report the initial steps of the intervention and their evolution over time, costs and consequences of the intervention, or extent of the missing data.<br>Clearly reported on the details of the process measures and outcomes, contextual elements, and observed association between outcome and intervention. |
| <b>Summary</b>                   | Clearly report key findings.<br>Did not report the strengths of the project.                                                                                                                                                                                                                                                    |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, and impact of the project on people and systems.<br>Did not report on reasons for differences between observed and anticipated outcomes or costs and strategic trade-offs.                                                    |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                  |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, implications for further practice and suggested next steps.<br>Did not report on sustainability or potential for spread to other contexts.                                                                                                                                   |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                  |

| <b>Formoso 2013</b>              |                                                                                                                                                                                                                                                                                                                                         |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing. Adequately summarized all key information from various sections of the text.                                                                                                                                                                                           |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Context</b>                   | Did not report the contextual elements considered important. Did not detail how the provinces were similar or different from each other.                                                                                                                                                                                                |
| <b>Intervention</b>              | Intervention was described in sufficient detail that others could reproduce it. Did not provide details on the specifics of the team involved in the project.                                                                                                                                                                           |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Results</b>                   | Did not clearly report the initial steps of the intervention and their evolution over time, unintended costs and consequences of the intervention, or extent of the missing data. Clearly reported on the details of the process measures and outcomes, contextual elements, and observed association between outcome and intervention. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Interpretation</b>            | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work and implications for further practice. Unclear description of sustainability, potential for spread to other contexts, and suggested next steps.                                                                                                                                       |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                     |

| <b>Fuertes</b>                   |                                                                                                                                                                                                                                                                                                                                                            |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                             |
| <b>Abstract</b>                  | Reported adequate information for searching and indexing. Did not provide sufficient information on the background or local problem in the abstract.                                                                                                                                                                                                       |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                             |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                             |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                                                                                             |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                             |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                             |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that others could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                     |
| <b>Study of the Intervention</b> | Clearly reported their approach for assessing the impact of the intervention. Unclear whether the authors conducted the evaluation.                                                                                                                                                                                                                        |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                             |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                             |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                          |
| <b>Results</b>                   | Did not clearly report the initial steps of the intervention and their evolution of time, contextual elements that interacted with the intervention, unintended costs and consequences, or the extent of missing data. Adequately reported the details of the process measures and outcomes, and observed associations between outcomes and interventions. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                             |
| <b>Interpretation</b>            | Clearly reported the nature of the association and impact of the project on people and systems. Did not clearly report the comparison with findings from other publications, the reasons for differences between observed and anticipated outcomes or the costs and strategic trade-offs.                                                                  |
| <b>Limitations</b>               | Did not clearly report on generalizability or efforts to minimize and adjust for limitations. Adequately reported the factors that might have limited internal validity.                                                                                                                                                                                   |
| <b>Conclusions</b>               | Did not clearly report on the usefulness of the work, sustainability, potential for spread to other contexts or implications for future practice. Adequately reported the suggested next steps.                                                                                                                                                            |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                             |

| Furst 2015                       |                                                                                                                                                                                                                                                                                                                        |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                         |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                         |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                         |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                         |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                    |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                         |
| <b>Context</b>                   | Did not report the contextual and sociocultural elements considered important.                                                                                                                                                                                                                                         |
| <b>Intervention</b>              | Not applicable for this intervention.                                                                                                                                                                                                                                                                                  |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                         |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                         |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                         |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                      |
| <b>Results</b>                   | Adequately reported the initial steps of the intervention and their evolution over time, the details of the process measures and outcomes, and observed associations between outcomes and intervention.<br>Did not clearly report contextual elements, unintended costs and consequences, and details of missing data. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                         |
| <b>Interpretation</b>            | Fully reported                                                                                                                                                                                                                                                                                                         |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                         |
| <b>Conclusions</b>               | Adequately reported the usefulness of the work.<br>Did not clearly describe the sustainability, potential for spread to other contexts, implications for future practice, or suggested next steps.                                                                                                                     |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                         |

| Gong 2016                        |                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                               |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it.<br>Specifics of the team involved in the work were not clearly described.                                                                                                                                                                                                     |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Measures</b>                  | Clearly reported the measures chosen for studying processes and outcomes, and the description of the approach to ongoing assessment of context.<br>Did not describe the methods used for assessing completeness of data.                                                                                                                                          |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                 |
| <b>Results</b>                   | Did not clearly report the initial steps of the intervention and their evolution of time, unintended costs and consequences, or the extent of missing data.<br>Adequately reported the details of the process measures and outcomes, the contextual elements that interacted with the intervention, and observed associations between outcomes and interventions. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Interpretation</b>            | Clearly reported the nature of the association and comparison with findings from other publications.<br>Unclear description of the impact of the project on people and systems, reasons for differences between observed and anticipated outcomes or the costs and strategic trade-offs.                                                                          |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity.<br>Did not report on generalizability or the efforts to minimize and adjust for limitations.                                                                                                                                                                                               |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work or implications for further practice.<br>Did not report on sustainability, potential for spread to other contexts, or next steps.                                                                                                                                                                               |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                               |

| Gonzales 2005                    |                                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                         |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                         |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                         |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                         |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                                    |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                         |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                         |
| <b>Intervention</b>              | Intervention was reported in sufficient detail that others could reproduce it.<br>Did not clearly describe the specifics of the team involved in the work.                                                                                                                                                                                                             |
| <b>Study of the Intervention</b> | Clearly reported the approach chosen for assessing the impact of the intervention.<br>Did not clearly describe who conducted the analyses.                                                                                                                                                                                                                             |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                         |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                         |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                                         |
| <b>Results</b>                   | Did not clearly report the initial steps of the intervention and their evolution of time, the observed associations between outcome and intervention, the unintended costs and consequences, or the extent of missing data.<br>Adequately reported the details of the process measures and outcomes and the contextual elements that interacted with the intervention. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                         |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, and impact of the project on people and systems.<br>Did not report on the differences between observed and anticipated outcomes or the costs and strategic trade-offs.                                                                                               |
| <b>Limitations</b>               | Adequately reported on the generalizability of the work and factors that limited the internal validity.<br>Did not report on efforts to minimize and adjust for limitations.                                                                                                                                                                                           |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, and implications for further practice.<br>Did not report on sustainability, potential for spread to other contexts, or suggested next steps.                                                                                                                                                                        |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                                    |

| Hallsworth 2016                  |                                                                                                                                                                                                                                                                                 |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing.<br>Adequately summarized all key information from various sections of the text.                                                                                                                                |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Intervention</b>              | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Results</b>                   | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and the costs and strategic trade-offs.<br>Did not report the reasons for differences between observed and anticipated outcomes. |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Conclusions</b>               | Fully reported                                                                                                                                                                                                                                                                  |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                  |

| Hennessy 2002                    |                                                                                                                                                                                                                                                                                                                                                                            |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                             |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing.<br>Missing key information from background and rationale sections.                                                                                                                                                                                                                                        |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                             |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                             |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                                        |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                             |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                             |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it.<br>Did not full describe the specifics of the team involved in the work                                                                                                                                                                                                                |
| <b>Study of the Intervention</b> | Clearly reported the approach chosen for assessing the impact of the intervention.<br>Did not clearly report who conducted the evaluation or the timing of the evaluation.                                                                                                                                                                                                 |
| <b>Measures</b>                  | Missing rationale for choice of measures, missing validity & reliability, operational definitions.<br>Did not clearly describe the approach to the ongoing assessment of contextual elements or methods employed for assessing completeness and accuracy of the data.                                                                                                      |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                             |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                                             |
| <b>Results</b>                   | Did not clearly report the initial steps of the intervention and their evolution of time, and the contextual elements that interacted with the intervention, the unintended costs and consequences, or the extent of missing data.<br>Adequately reported the details of the process measures and outcomes and the observed associations between outcome and intervention. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                             |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems.<br>Did not report the reasons for differences between observed and anticipated outcomes or the costs and strategic trade-offs.                                                                                              |
| <b>Limitations</b>               | Does not clearly report the limitations to generalizability or internal validity.<br>Does not clearly report the efforts made to adjust for limitations.                                                                                                                                                                                                                   |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, implications for further practice and suggested next steps.<br>Did not report on sustainability or potential for spread to other contexts.                                                                                                                                                                              |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                                        |

| Hernandez-Santiago 2015          |                                                                                                                                                                                                                                                                                                                                                         |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                          |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                          |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                          |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                          |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                     |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                          |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                          |
| <b>Intervention</b>              | Fully reported                                                                                                                                                                                                                                                                                                                                          |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                          |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                          |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                          |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                          |
| <b>Results</b>                   | Clearly reported the initial steps of the intervention and their evolution over time, the details of the process measures and outcome, the observed associations between outcomes, and the unintended costs and consequences.<br>Did not clearly describe the contextual elements that interacted with the intervention, or the extent of missing data. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                          |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes.<br>Did not report on the costs and strategic trade-offs.                                                                          |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                                          |
| <b>Conclusions</b>               | Fully reported                                                                                                                                                                                                                                                                                                                                          |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                          |

| Ho 2004                          |                                                                                                                                                                                                                                                                                                                                                       |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                   |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Intervention</b>              | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                        |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                     |
| <b>Results</b>                   | Unclear description of the initial steps of the intervention and their evolution over time, contextual elements that interacted with the intervention, observed associations between outcomes and intervention, unintended costs and consequences, and the extent of missing data. Clearly reported the details of the process measures and outcomes. |
| <b>Summary</b>                   | Does not include a summary section. Did not clearly report key findings and strengths of the project.                                                                                                                                                                                                                                                 |
| <b>Interpretation</b>            | Clear description of the nature of the association between intervention and outcome, and comparison of results with findings from other publications. Did not clearly report the impact on people and systems, reasons for difference between observed and anticipated outcomes, and costs and strategic trade-offs.                                  |
| <b>Limitations</b>               | Did not clearly report on limits to the generalizability of the work, the factors that might have limited internal validity, or the efforts made to minimize and adjust for limitations.                                                                                                                                                              |
| <b>Conclusions</b>               | Did not clearly report on the usefulness of the work, potential for spread to other contexts, implications for further practice and suggested next steps. Adequately reported on sustainability.                                                                                                                                                      |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                   |

| Kelly 2017                       |                                                                                                                                                                                                                                                                                                                |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Not clearly reported, not clear that this is an evaluation rather than just a list of efforts.                                                                                                                                                                                                                 |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing. Adequately summarized all key information from various sections of the text.                                                                                                                                                                  |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                 |
| <b>Available Knowledge</b>       | Did not clearly describe what is currently known about the intervention including any reference to the effectiveness of AM.                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                            |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                 |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                 |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or describe the specifics of the team involved in the work.                                                                                                                                                                 |
| <b>Study of the Intervention</b> | Clearly described the approach chosen for assessing the impact of the interventions. Did not clearly describe the approach for establishing whether the observed outcomes were due to the interventions.                                                                                                       |
| <b>Measures</b>                  | Did not clearly describe the measures chosen for studying processes and outcomes, the approach to the ongoing assessment of contextual elements, or the methods employed for assessing completeness of data.                                                                                                   |
| <b>Analysis</b>                  | Clearly described the methods used to draw inferences from the data. Did not clearly describe the methods for understanding variation within the data.                                                                                                                                                         |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                 |
| <b>Results</b>                   | Did not clearly describe the initial steps of the intervention and their evolution over time, the details of the process measures and outcomes, contextual elements that interacted with the intervention, the observed associations between outcomes and interventions, or unintended costs and consequences. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                 |
| <b>Interpretation</b>            | Clearly reported the nature of the association and compared with findings from other publications. Did not report on the impact of the project on people and systems, reasons for differences between observed and anticipated outcomes, or the costs and strategic trade-offs.                                |
| <b>Limitations</b>               | Did not clearly describe the limits to the generalizability of the work, or the efforts made to minimize and adjust for limitations. Clearly reported the factors that might have limited internal validity.                                                                                                   |
| <b>Conclusions</b>               | Clearly described the usefulness of the work. Did not describe sustainability, potential for spread to other contexts, implications for practice, or suggested next steps.                                                                                                                                     |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                 |

| Klieman 2016                     |                                                                                                                                                                                                                                                                             |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                              |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing. Adequately summarized all key information from various sections of the text.                                                                                                                               |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                              |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                              |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                         |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                              |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                              |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                       |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                              |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                              |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                              |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                              |
| <b>Results</b>                   | Fully reported                                                                                                                                                                                                                                                              |
| <b>Summary</b>                   | Did not report on the strengths of the study. Clearly reported the key findings.                                                                                                                                                                                            |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes. Did not report on the costs and strategic trade-offs. |
| <b>Limitations</b>               | Did not report on generalizability or efforts to minimize and adjust for limitations. Adequately reported on sustainability.                                                                                                                                                |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, implications for further practice and suggested next steps. Did not report on sustainability or potential for spread to other contexts.                                                                                  |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                              |

| Kurt 2010                        |                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                               |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Context</b>                   | Did not report on the contextual elements considered important.                                                                                                                                                                                                                                                                                                   |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                             |
| <b>Study of the Intervention</b> | Did not clearly describe the approach chosen for assessing the impact of the intervention or the approach used to establish whether the observed outcomes were due to the interventions.                                                                                                                                                                          |
| <b>Measures</b>                  | Clearly reported the measures chosen for studying processes and outcomes.<br>Description of the approach to ongoing assessment was not applicable given the intervention implementation.<br>Did not report on the methods employed for assessing completeness and accuracy of data.                                                                               |
| <b>Analysis</b>                  | Did not clearly report the details of the methods used to draw inferences or understand variation within the data.                                                                                                                                                                                                                                                |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                 |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, or the extent of missing data.<br>Clearly described the details of the process measures and outcome, the observed associations between outcomes and interventions, and the unintended costs and consequences. |
| <b>Summary</b>                   | Did not include a summary, did not describe the strengths of the project. Clearly described the key findings.                                                                                                                                                                                                                                                     |
| <b>Interpretation</b>            | Clearly reported the comparison with findings from other publications. Did not clearly report the nature of the association, the impact on people and systems, the reasons for differences between observed and anticipated outcomes, and the costs and strategic trade-offs.                                                                                     |
| <b>Limitations</b>               | Did not report on generalizability, factors that limited internal validity, or efforts made to adjust for limitations.                                                                                                                                                                                                                                            |
| <b>Conclusions</b>               | Clearly reported on the usefulness of the work.<br>Did not clearly describe sustainability, potential for spread to other contexts, implications for practice, or suggested next steps.                                                                                                                                                                           |
| <b>Funding</b>                   | Did not report on the sources of funding or the role of the funding organization.                                                                                                                                                                                                                                                                                 |

| Lambert 2007                     |                                                                                                                                                                                                                                                                                                                              |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                               |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                               |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                               |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                               |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                                                               |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                               |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                               |
| <b>Intervention</b>              | Did not clearly describe the intervention in sufficient detail that others could reproduce it, or the specifics of the team involved in the work.                                                                                                                                                                            |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                               |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                               |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                               |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                            |
| <b>Results</b>                   | Clearly reported the initial steps of the intervention and their evolution over time, the details of the process measures and outcomes, contextual elements that interacted with the intervention, and the observed associations between outcomes and interventions.<br>Did not report the unintended costs or consequences. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                               |
| <b>Interpretation</b>            | Fully reported                                                                                                                                                                                                                                                                                                               |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                               |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, sustainability, and suggested next steps.<br>Did not report on potential for spread to other contexts and implications for further practice.                                                                                                                              |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                               |

| Lambert 2015                     |                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing.<br>Adequately summarized all key information from various sections of the text.                                                                                                                                                                                                                |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                           |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Measures</b>                  | Clearly reported the measures chosen for studying processes and outcomes.<br>Did not report on the approach to the ongoing assessment of contextual elements, or the methods employed for assessing completeness and accuracy of data.                                                                                                                          |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                               |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, the unintended costs and consequences or the extent of missing data.<br>Clearly described the details of the process measures and outcome and the observed associations between outcomes and interventions. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, and impact of the project on people and systems.<br>Did not clearly report on the costs and strategic trade-offs or the reasons for differences between observed and anticipated outcomes.                                                                    |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work and implications for further practice.<br>Did not report on sustainability, potential for spread to other contexts, or suggested next steps.                                                                                                                                                                  |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                             |

|                                  |                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Lee 2014</b>                  |                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                               |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Context</b>                   | Did not report on the contextual elements considered important.                                                                                                                                                                                                                                                                                                   |
| <b>Intervention</b>              | Clearly reported the intervention in sufficient detail that others could reproduce it.<br>Did not describe the specifics of the team involved in the work.                                                                                                                                                                                                        |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Measures</b>                  | Clearly described the measures chosen for studying the processes and outcomes.<br>Description of the approach to ongoing assessment was not applicable given the intervention implementation.<br>Did not report on the methods employed for assessing completeness and accuracy of data.                                                                          |
| <b>Analysis</b>                  | Clearly reported the methods used to draw inferences from the data.<br>Did not clearly report the methods for understanding variation within the data.                                                                                                                                                                                                            |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                 |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the details of the process measures and outcome, the observed associations between outcomes and interventions, and the unintended costs and consequences, or the extent of missing data.<br>Clearly described the contextual elements that interacted with the intervention, |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, and impact of the project on people and systems.<br>Did not report on reasons for differences between observed and anticipated outcomes or the costs and strategic trade-offs.                                                                                  |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, and implications for further practice.<br>Did not report on sustainability, potential for spread to other contexts or suggested next steps.                                                                                                                                                                    |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                               |

|                                  |                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Long 2017</b>                 |                                                                                                                                                                                                                                                                                                                                                               |
| <b>Title</b>                     | Not clear that the study reports on an intervention.                                                                                                                                                                                                                                                                                                          |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing.<br>Adequately summarized all key information from various sections of the text.                                                                                                                                                                                                              |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                           |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                         |
| <b>Study of the Intervention</b> | Did not clearly describe the approach chosen for assessing the impact of the intervention or to establish whether the observed outcomes were due to the interventions.                                                                                                                                                                                        |
| <b>Measures</b>                  | Did not report on the measures chosen for studying processes and outcomes, the approach to the ongoing assessment of contextual elements, or the methods employed for assessing completeness and accuracy of data.                                                                                                                                            |
| <b>Analysis</b>                  | Clearly described the methods used to draw inferences from the data.<br>Did not clearly describe the methods for understanding variation within the data.                                                                                                                                                                                                     |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                             |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, details of the process measures and outcomes, the observed associations between outcomes and interventions, and the unintended costs and consequences or the extent of missing data.<br>Clearly described the contextual elements that interacted with the intervention. |
| <b>Summary</b>                   | Clearly reported the key findings.<br>Did not report the strengths of the study.                                                                                                                                                                                                                                                                              |
| <b>Interpretation</b>            | Clearly reported the nature of the association, and comparison with findings from other publications.<br>Did not report on the impact of the project on people and systems, the reasons for differences between observed and anticipated outcomes or the costs and strategic trade-offs.                                                                      |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity.<br>Did not report on generalizability of the work or efforts to minimize and adjust for limitations.                                                                                                                                                                                   |
| <b>Conclusions</b>               | Did not clearly report on usefulness of the work or implications for future practice.<br>Did not report the sustainability, potential for spread to other contexts, or suggested next steps.                                                                                                                                                                  |
| <b>Funding</b>                   | Did not report on the sources of funding or the role of the funding organization. Particularly important because they are government employees, but the paper includes a statement that the views expressed do not necessarily represent the opinions of the agencies involved.                                                                               |

|                                  |                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Ma 2016</b>                   |                                                                                                                                                                                                                                                                                                                                                               |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                           |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it. Did not report how the data was collected.                                                                                                                                                                                                                                |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Measures</b>                  | Clearly reported the measures chosen for studying processes and outcomes, and the measures for assessing completeness of the data. Did not report on the context or ongoing assessment.                                                                                                                                                                       |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, the unintended costs and consequences or the extent of missing data. Clearly described the details of the process measures and outcome, and the observed associations between outcomes and interventions. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes. Did not report on the costs and strategic trade-offs.                                                                                   |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity. Did not report on generalizability or efforts to minimize and adjust for limitations.                                                                                                                                                                                                  |
| <b>Conclusions</b>               | Clearly reported on the usefulness of the work. Did not adequately report on sustainability, potential for spread to other contexts, implications for practice, or suggested next steps.                                                                                                                                                                      |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                           |

|                                  |                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>MacCara 2011</b>              |                                                                                                                                                                                                                                                                                                                                                               |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                           |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Context</b>                   | Did not report on the contextual elements considered important.                                                                                                                                                                                                                                                                                               |
| <b>Intervention</b>              | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Measures</b>                  | Clearly reported on the measures chosen for studying processes and outcomes. Did not report on the approach to the ongoing assessment of contextual elements, or the methods employed for assessing completeness and accuracy of data.                                                                                                                        |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                             |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, the unintended costs and consequences or the extent of missing data. Clearly described the details of the process measures and outcome, and the observed associations between outcomes and interventions. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Interpretation</b>            | Clearly reported the nature of the association, costs and strategic trade-offs, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes. Did not compare intervention effectiveness with findings from other publications.                                                                         |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity. Did not report on generalizability or efforts to minimize and adjust for limitations.                                                                                                                                                                                                  |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work. Did not report on sustainability, implications for further practice, potential for spread to other contexts and suggested next steps.                                                                                                                                                                      |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                |

| <b>Mamdani 2007</b>              |                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing.<br>Adequately summarized all key information from various sections of the text.                                                                                                                                                                                                          |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Context</b>                   | Did not report on the contextual elements considered important.                                                                                                                                                                                                                                                                                           |
| <b>Intervention</b>              | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Measures</b>                  | Clearly reported on the measures chosen for studying processes and outcomes.<br>Did not report on the approach to the ongoing assessment of contextual elements, or the methods employed for assessing completeness and accuracy of data.                                                                                                                 |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Results</b>                   | Clearly described the steps of the intervention and their evolution over time, details of the process measures and outcome, the observed associations between outcomes and interventions.<br>Did not clearly describe the contextual elements that interacted with the intervention, the unintended costs and consequences or the extent of missing data. |
| <b>Summary</b>                   | Clearly reported key findings.<br>Did not report the strengths of the project.                                                                                                                                                                                                                                                                            |
| <b>Interpretation</b>            | Clearly reported the nature of the association, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes.<br>Did not report on comparison with findings from other publications, or the costs and strategic trade-offs.                                                                         |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, sustainability, and suggested next steps.<br>Did not report on implications for further practice or potential for spread to other contexts.                                                                                                                                                            |
| <b>Funding</b>                   | Did not report on the sources of funding or the role of the funding organization.                                                                                                                                                                                                                                                                         |

| <b>Manns 2012</b>                |                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                               |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Intervention</b>              | Not applicable based on intervention implementation.                                                                                                                                                                                                                                                                                                              |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Measures</b>                  | Clearly reported on the measures chosen for studying processes and outcomes.<br>Did not report on the approach to the ongoing assessment of contextual elements, or the methods employed for assessing completeness and accuracy of data.                                                                                                                         |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                 |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, the observed associations between outcomes and interventions, or the extent of missing data.<br>Clearly described the details of the process measures and outcome, and the unintended costs and consequences. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Interpretation</b>            | Clearly reported the nature of the association, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes.<br>Did not report on comparison with findings from other publications, or the costs and strategic trade-offs.                                                                                 |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity and the efforts to minimize and adjust for limitations.<br>Did not report on generalizability.                                                                                                                                                                                              |
| <b>Conclusions</b>               | Adequately reported on the implications for further practice.<br>Did not report on usefulness of the work, sustainability, potential for spread to other contexts, or suggested next steps.                                                                                                                                                                       |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |

|                                  |                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Marra 2005</b>                |                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Context</b>                   | Did not report on the contextual elements considered important.                                                                                                                                                                                                                                                                                                                               |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work. Unclear which patients were eligible.                                                                                                                                                                                                                   |
| <b>Study of the Intervention</b> | Did not clearly describe the approach chosen for assessing the impact of the intervention or to establish whether the observed outcomes were due to the interventions.                                                                                                                                                                                                                        |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                                             |
| <b>Results</b>                   | Clearly described the steps of the intervention and their evolution over time, the details of the process measures and outcome, and the observed associations between outcomes and intervention.<br>Did not clearly describe the contextual elements that interacted with the intervention or the unintended costs and consequences.<br>Missing data was not applicable based on data source. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, and impact of the project on people and systems.<br>Did not report on the reasons for differences between observed and anticipated outcomes or costs and strategic trade-offs.                                                                                                              |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity.<br>Did not report on generalizability or the efforts to minimize and adjust for limitations.                                                                                                                                                                                                                           |
| <b>Conclusions</b>               | Did not clearly report on the usefulness of the work, sustainability, potential for spread to other contexts, or suggested next steps.<br>Clearly reported on the implications for practice.                                                                                                                                                                                                  |
| <b>Funding</b>                   | Did not report on the sources of funding or the role of the funding organization.                                                                                                                                                                                                                                                                                                             |

|                                  |                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Marshall 2006</b>             |                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Abstract</b>                  | Did not adequately provide information on the background or local problem.<br>Provided sufficient information for searching and indexing.                                                                                                                                                                                                                        |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Intervention</b>              | Intervention was described in sufficient detail for replication.<br>Did not report the specifics of the team involved.                                                                                                                                                                                                                                           |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Measures</b>                  | Clearly reported on the measures chosen for studying processes and outcomes.<br>Did not report on the approach to the ongoing assessment of contextual elements, or the methods employed for assessing completeness and accuracy of data.                                                                                                                        |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                |
| <b>Results</b>                   | Clearly described the steps of the intervention or their evolution over time, the details of the process measures and outcome, and the observed associations between outcomes and intervention.<br>Did not clearly describe the contextual elements that interacted with the intervention, the unintended costs and consequences, or the extent of missing data. |
| <b>Summary</b>                   | Did not include a summary, did not describe the strengths of the study.<br>Clearly reported the key findings.                                                                                                                                                                                                                                                    |
| <b>Interpretation</b>            | Clearly reported the nature of the association, and reasons for differences between observed and anticipated outcomes.<br>Did not report on a comparison with findings from other publications, impact of the project on people and systems, or the costs and strategic trade-offs                                                                               |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity.<br>Did not report on the generalizability of the work or efforts to minimize and adjust for limitations.                                                                                                                                                                                  |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, and implications for further practice.<br>Did not report on sustainability, potential for spread to other contexts, or suggested next steps.                                                                                                                                                                  |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.<br>Important because the funder was a pharmaceutical company.                                                                                                                                                                                                                                |

| McKay 2011                       |                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Context</b>                   | Did not report on the contextual elements considered important or how they would impact the intervention.                                                                                                                                                                                                                                                     |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                         |
| <b>Study of the Intervention</b> | Clearly reported the approach chosen to assess the impact of the intervention.<br>Did not report who conducted the analyses.                                                                                                                                                                                                                                  |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, the unintended costs and consequences or the extent of missing data. Clearly described the details of the process measures and outcome, and the observed associations between outcomes and interventions. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Interpretation</b>            | Clearly reported the nature of the association, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes.<br>Did not report on comparison with findings from other publications, or the costs and strategic trade-offs.                                                                             |
| <b>Limitations</b>               | Adequately reported on the generalizability of the work and factors that limited the internal validity.<br>Did not report on efforts to minimize and adjust for limitations.                                                                                                                                                                                  |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work.<br>Did not report on sustainability, implications for further practice, potential for spread to other contexts or suggested next steps.                                                                                                                                                                    |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                           |

| Molstad 1999                     |                                                                                                                                                                                                                                                                                                                                                              |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                               |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing or summarize all key information from the text.                                                                                                                                                                                                                                              |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                               |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                               |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem or develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                          |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                               |
| <b>Context</b>                   | Did not report on the contextual elements considered important.                                                                                                                                                                                                                                                                                              |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                        |
| <b>Study of the Intervention</b> | Did not clearly report the approach chosen for assessing the impact of the interventions, or the approach used to establish whether the observed outcomes were due to the intervention.                                                                                                                                                                      |
| <b>Measures</b>                  | Clearly reported on the measures chosen for studying processes and outcomes.<br>Did not report on the approach to the ongoing assessment of contextual elements, or the methods employed for assessing completeness and accuracy of data.                                                                                                                    |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                               |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required                                                                                                                                                                                                                                                                                             |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, the unintended costs and consequences or the extent of missing data. Clearly described the details of the process measures and outcome, and the observed associations between outcomes and intervention. |
| <b>Summary</b>                   | Did not include a summary, did not clearly summarize key findings or the strengths of the project.                                                                                                                                                                                                                                                           |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, and impact of the project on people and systems.<br>Did not report on the costs and strategic trade-offs or reasons for differences between observed and anticipated outcomes.                                                                             |
| <b>Limitations</b>               | Did not report on generalizability, factors that limited the internal validity, or efforts to minimize and adjust for limitations.                                                                                                                                                                                                                           |
| <b>Conclusions</b>               | Did not adequately report on the usefulness of the work, sustainability, implications for further practice, potential for spread to other contexts or suggested next steps.                                                                                                                                                                                  |
| <b>Funding</b>                   | Did not report on the sources of funding or the role of the funding organization.                                                                                                                                                                                                                                                                            |

|                                  |                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Moura 2015</b>                |                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing, no keywords provided.<br>Adequately summarized all key information from various sections of the text.                                                                                                                                                                                          |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                             |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                           |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the unintended costs and consequences or the extent of missing data.<br>Clearly described the contextual elements that interacted with the intervention, the details of the process measures and outcome and the observed associations between outcomes and interventions. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes. Did not report on the costs and strategic trade-offs.                                                                                     |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity. Did not report on the generalizability of the work or efforts to minimize and adjust for limitations.                                                                                                                                                                                    |
| <b>Conclusions</b>               | Did not adequately report on the usefulness of the work, sustainability, implications for further practice, potential for spread to other contexts or suggested next steps.                                                                                                                                                                                     |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                             |

|                                  |                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Ouldali 2017</b>              |                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                               |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it.<br>Specifics of the team involved were not applicable for studies where the authors were clearly not involved in implementation.                                                                                                                                              |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Measures</b>                  | Clearly reported on the measures chosen for studying processes and outcomes.<br>Did not report on the approach to the ongoing assessment of contextual elements, or the methods employed for assessing completeness and accuracy of data.                                                                                                                         |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, or the extent of missing data.<br>Clearly described the details of the process measures and outcome, the contextual elements that interacted with the intervention, the observed associations between outcomes and interventions, and the unintended costs and consequences. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes. Did not report on the costs and strategic trade-offs.                                                                                       |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Conclusions</b>               | Clearly reported on the usefulness of the work.<br>Did not adequately report sustainability, implications for further practice, potential for spread to other contexts or suggested next steps.                                                                                                                                                                   |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |

| Park 2005                        |                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Context</b>                   | Did not describe their approach to the assessment of contextual elements or give details on the population.                                                                                                                                                                                                                                                      |
| <b>Intervention</b>              | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, the observed associations between outcomes and interventions or the extent of missing data.<br>Clearly described the details of the process measures and outcome, and the unintended costs and consequences. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, or impact of the project on people and systems.<br>Did not report on the reasons for differences between observed and anticipated outcomes or costs and strategic trade-offs.                                                                                  |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work and potential for spread to other contexts<br>Did not report on sustainability, implications for further practice and suggested next steps.                                                                                                                                                                    |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                              |

| Perz 2002                        |                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing.<br>Adequately summarized all key information from various sections of the text.                                                                                                                                                                                                                 |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                              |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Intervention</b>              | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Measures</b>                  | Clearly reported on the measures chosen for studying processes and outcomes, and the approach to the ongoing assessment of contextual elements.<br>Did not report on the methods employed for assessing completeness and accuracy of data.                                                                                                                       |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the unintended costs and consequences, or the extent of missing data.<br>Clearly described the details of the process measures and outcome, the contextual elements that interacted with the intervention, or the observed associations between outcomes and interventions. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes.<br>Did not report on the costs and strategic trade-offs.                                                                                   |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity and efforts to minimize and adjust for limitations.<br>Did not report on generalizability.                                                                                                                                                                                                 |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, potential for spread to other contexts, or implications for further practice.<br>Did not report on sustainability or suggested next steps.                                                                                                                                                                    |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                              |

| Sabuncu 2009                     |                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing. Adequately summarized all key information from various sections of the text.                                                                                                                                                                                                             |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                       |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it. Specifics of the team involved were not applicable for studies where the authors were clearly not involved in implementation.                                                                                                                                         |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                         |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, unintended costs and consequences or the extent of missing data. Clearly described the details of the process measures and outcome, and the observed associations between outcomes and interventions. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes. Did not report on the costs and strategic trade-offs.                                                                               |
| <b>Limitations</b>               | Adequately reported on the generalizability of the work and factors that limited the internal validity. Did not report on efforts to minimize and adjust for limitations.                                                                                                                                                                                 |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, potential for spread to other contexts and implications for further practice. Did not report on sustainability or suggested next steps.                                                                                                                                                                |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                            |

| Santa Ana Tellez 2013            |                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing. Adequately summarized all key information from various sections of the text.                                                                                                                                                                                                             |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                     |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                         |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, unintended costs and consequences or the extent of missing data. Clearly described the details of the process measures and outcome, and the observed associations between outcomes and interventions. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                            |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes. Did not report on the costs and strategic trade-offs.                                                                               |
| <b>Limitations</b>               | Adequately reported on factors that limited the internal validity and efforts to minimize and adjust for limitations. Did not report on the generalizability of the work.                                                                                                                                                                                 |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, and implications for further practice. Did not report on sustainability, potential for spread to other contexts or suggested next steps.                                                                                                                                                               |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                            |

| Santa Ana Tellez 2015            |                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing. Adequately summarized all key information from various sections of the text.                                                                                                                                                                                                                    |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                              |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it. Specifics of the team involved were not applicable for studies where the authors were clearly not involved in implementation.                                                                                                                                                |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                |
| <b>Results</b>                   | Clearly described the steps of the intervention or their evolution over time, the details of the process measures and outcome, and the observed associations between outcomes and interventions.<br>Did not clearly describe the contextual elements that interacted with the intervention, the unintended costs and consequences or the extent of missing data. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes. Did not report on the costs and strategic trade-offs.                                                                                      |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, implications for further practice and suggested next steps.<br>Did not report on sustainability or potential for spread to other contexts.                                                                                                                                                                    |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                   |

| Shin 2014                        |                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Title does not mention an intervention and sounds like it could have been surveillance.                                                                                                                                                                                                                                                                          |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Available Knowledge</b>       | Did not clearly summarize what is known about the problem, and minimal details on over prescribing and no details on why fluoroquinolones should be used cautiously in kids.                                                                                                                                                                                     |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                              |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                            |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Results</b>                   | Clearly described the steps of the intervention or their evolution over time, the details of the process measures and outcome and the observed associations between outcomes and interventions.<br>Did not clearly describe the contextual elements that interacted with the intervention, the unintended costs and consequences, or the extent of missing data. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Interpretation</b>            | Clearly reported the nature of the association, and comparison with findings from other publications.<br>Did not report on the impact of the project on people and systems, reasons for differences between observed and anticipated outcomes, and the costs and strategic trade-offs.                                                                           |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, sustainability, implications for further practice and suggested next steps.<br>Did not report on potential for spread to other contexts.                                                                                                                                                                      |
| <b>Funding</b>                   | Did not report on the sources of funding or the role of the funding organization.                                                                                                                                                                                                                                                                                |

| Song 2017                        |                                                                                                                                                                                                                                                                                                                                         |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing. Adequately summarized all key information from various sections of the text.                                                                                                                                                                                           |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                     |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                   |
| <b>Study of the Intervention</b> | Did not clearly describe the approach chosen for assessing the impact of the intervention.                                                                                                                                                                                                                                              |
| <b>Measures</b>                  | Did not clearly report on the measures chosen for studying processes and outcomes, the approach to the ongoing assessment of contextual elements, or the methods employed for assessing completeness and accuracy of data.                                                                                                              |
| <b>Analysis</b>                  | Clearly reported the methods used to draw inferences from the data. Did not describe the methods used for understanding variation within the data.                                                                                                                                                                                      |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the details of the process measures and outcome, the contextual elements that interacted with the intervention, the observed associations between outcomes and interventions, the unintended costs and consequences or the extent of missing data. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                          |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes. Did not report on the costs and strategic trade-offs.                                                             |
| <b>Limitations</b>               | Adequately reported on the generalizability of the work and factors that limited the internal validity. Did not clearly report on efforts to minimize and adjust for limitations.                                                                                                                                                       |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work and potential for spread to other contexts. Did not report on sustainability, implications for further practice or suggested next steps                                                                                                                                               |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                          |

| Steffensen 1997                  |                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Abstract</b>                  | Provided sufficient information for searching and indexing. Did not clearly report on the background and local problem section of the abstract.                                                                                                                                                                                                               |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                           |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Context</b>                   | Did not report on the contextual elements considered important or how they would affect the intervention.                                                                                                                                                                                                                                                     |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                         |
| <b>Study of the Intervention</b> | Did not clearly report the approach chosen for assessing the impact of the interventions or the approach used to establish whether the observed outcomes were due to the intervention.                                                                                                                                                                        |
| <b>Measures</b>                  | Clearly reported on the measures chosen for studying processes and outcomes. Did not report on the approach to the ongoing assessment of contextual elements, or the methods employed for assessing completeness and accuracy of data.                                                                                                                        |
| <b>Analysis</b>                  | Did not describe the methods used to draw inferences from the data, or the methods understanding variation within the data. Conducted analyses that were not described in the methods section.                                                                                                                                                                |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                             |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, the unintended costs and consequences, or the extent of missing data. Clearly described the details of the process measures and outcome and the observed associations between outcomes and interventions. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, and impact of the project on people and systems. Did not report on the reasons for differences between observed and anticipated outcomes or costs and strategic trade-offs.                                                                                 |
| <b>Limitations</b>               | Adequately reported on the generalizability of the work. Did not report on factors that limited the internal validity or efforts to minimize and adjust for limitations                                                                                                                                                                                       |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, implications for further practice and suggested next steps. Did not report on sustainability or potential for spread to other contexts.                                                                                                                                                                    |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                           |

|                                  |                                                                                                                                                                                                                                                                                                                                                              |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Sun 2015</b>                  |                                                                                                                                                                                                                                                                                                                                                              |
| <b>Title</b>                     | Title does not mention an intervention, sounds like it could have been surveillance.                                                                                                                                                                                                                                                                         |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                               |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                               |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                               |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                          |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                               |
| <b>Context</b>                   | Did not report on the contextual elements considered important. Their reasons for choosing hospitals was not well explained.                                                                                                                                                                                                                                 |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                        |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                               |
| <b>Measures</b>                  | Clearly reported on the measures chosen for studying processes and outcomes.<br>Did not report on the approach to the ongoing assessment of contextual elements, or the methods employed for assessing completeness and accuracy of data.                                                                                                                    |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                               |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                               |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, the unintended costs and consequences or the extent of missing data. Clearly described the details of the process measures and outcome and the observed associations between outcomes and interventions. |
| <b>Summary</b>                   | Clearly described the key findings.<br>Did not report the strengths of the study.                                                                                                                                                                                                                                                                            |
| <b>Interpretation</b>            | Clearly reported the nature of the association.<br>Did not report a comparison with findings from other publications, the impact of the project on people and systems, reasons for differences between observed and anticipated outcomes or the costs and strategic trade-offs.                                                                              |
| <b>Limitations</b>               | Adequately reported on the generalizability of the work and factors that limited the internal validity.<br>Did not report on efforts to minimize and adjust for limitations.                                                                                                                                                                                 |
| <b>Conclusions</b>               | Did not adequately report on the usefulness of the work, sustainability, implications for further practice, potential for spread to other contexts or suggested next steps.                                                                                                                                                                                  |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                               |

|                                  |                                                                                                                                                                                                                                                                                                   |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Tang 2018</b>                 |                                                                                                                                                                                                                                                                                                   |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                    |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                    |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                    |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                               |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                    |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                    |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                             |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                    |
| <b>Measures</b>                  | Did not clearly report the measures chosen for studying processes and outcomes, the approach to the ongoing assessment of contextual elements, or the methods employed for assessing the completeness and accuracy of the data.                                                                   |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                    |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                    |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the details of the process measures and outcome, the observed associations between outcomes and interventions, the contextual elements that interacted with the intervention, or the extent of missing data. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                    |
| <b>Interpretation</b>            | Clearly reported the nature of the association, and comparison with findings from other publications.<br>Did not report on the impact of the project on people and systems, the reasons for differences between observed and anticipated outcomes, or costs and strategic trade-offs.             |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity.<br>Did not report on generalizability or efforts to minimize and adjust for limitations                                                                                                                                    |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work.<br>Did not report on sustainability, implications for further practice, potential for spread to other contexts, or suggested next steps.                                                                                                       |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                    |

| Tao 2013                         |                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Title does not mention an intervention, sounds like it could have been a policy paper.                                                                                                                                                                                                                                                                            |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                               |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Context</b>                   | Did not report on the contextual elements considered important.                                                                                                                                                                                                                                                                                                   |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                             |
| <b>Study of the Intervention</b> | Did not clearly describe the approach chosen for assessing the impact of the intervention or the approach used to establish whether the observed outcomes were due to the intervention.                                                                                                                                                                           |
| <b>Measures</b>                  | Clearly reported on the measures chosen for studying processes and outcomes. The approach to the ongoing assessment of contextual elements was not applicable based on intervention implementation. Did not report on the methods employed for assessing completeness and accuracy of data.                                                                       |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                 |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, or the extent of missing data.<br>Clearly described the details of the process measures and outcome, the observed associations between outcomes and interventions, and the unintended costs and consequences. |
| <b>Summary</b>                   | Clearly described the key findings.<br>Did not describe the strengths of the study.                                                                                                                                                                                                                                                                               |
| <b>Interpretation</b>            | Clearly reported the nature of the association, and reasons for differences between observed and anticipated outcomes.<br>Did not report a comparison with findings from other publications, the impact of the project on people and systems, or the costs and strategic trade-offs.                                                                              |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity. Did not report on generalizability of the work or efforts to minimize and adjust for limitations.                                                                                                                                                                                          |
| <b>Conclusions</b>               | Did not adequately report on the usefulness of the work, sustainability, implications for further practice, potential for spread to other contexts or suggested next steps.                                                                                                                                                                                       |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |

| Thornhill 2011                   |                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing. Adequately summarized all key information from various sections of the text.                                                                                                                                                                                                                    |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                              |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Context</b>                   | Did not report on the contextual elements considered important including the patient population.                                                                                                                                                                                                                                                                 |
| <b>Intervention</b>              | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Study of the Intervention</b> | Did not clearly describe the approach chosen for assessing the impact of the intervention or the approach used to establish whether the observed outcomes were due to the intervention.                                                                                                                                                                          |
| <b>Measures</b>                  | Clearly reported on the measures chosen for studying processes and outcomes. The approach to the ongoing assessment of contextual elements was not applicable based on intervention implementation. Did not report on the methods employed for assessing completeness and accuracy of data.                                                                      |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Results</b>                   | Clearly described the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, or the observed associations between outcomes and interventions.<br>Did not clearly describe the details of the process measures and outcome, the unintended costs and consequences, or the extent of missing data. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Interpretation</b>            | Clearly reported the nature of the association, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes.<br>Did not report on comparison with findings from other publications or the costs and strategic trade-offs.                                                                                 |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, implications for further practice and suggested next steps.<br>Did not report on sustainability or potential for spread to other contexts.                                                                                                                                                                    |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                   |

|                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Walker 2019</b>               |                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing. Adequately summarized all key information from various sections of the text.                                                                                                                                                                                                                                                                                   |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                                                                                             |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                                                                                           |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Measures</b>                  | Clearly reported the methods employed for assessing completeness and accuracy of data.<br>Did not report on the measures chosen for studying processes and outcomes or the approach to the ongoing assessment of contextual elements.                                                                                                                                                                                           |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                                                                               |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, the observed associations between outcomes and interventions, or the unintended costs and consequences. The authors clarify in discussion that assessing the extent of missing data was not possible.<br>Clearly described the details of the process measures and outcome. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Interpretation</b>            | Clearly reported the nature of the association, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes.<br>Did not report a comparison with findings from other publications, or the costs and strategic trade-offs.                                                                                                                                                |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work.<br>Did not report on sustainability, implications for further practice, potential for spread to other contexts, or suggested next steps.                                                                                                                                                                                                                                     |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                                                                                  |

|                                  |                                                                                                                                                                                                                                                                                   |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Wei 2017</b>                  |                                                                                                                                                                                                                                                                                   |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                    |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                    |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                    |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                               |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                    |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                    |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it. Specifics of the team were not applicable because they did not implement.                                                                                                                     |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                    |
| <b>Measures</b>                  | Clearly reported the measures chosen for studying the process.<br>Did not report the approach to assessment of context or the approach to assessing the completeness and accuracy of the data.                                                                                    |
| <b>Analysis</b>                  | Clearly reported the methods used to draw inferences from the data.<br>Did not clearly report the methods for assessing variation within the data.                                                                                                                                |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                    |
| <b>Results</b>                   | The initial steps of the intervention were clearly reported in a table. The details of the measures, outcomes and context were unclear as the interpretation of results was confusing based on the data available in tables. Unintended costs and consequences were not reported. |
| <b>Summary</b>                   | Clearly described the key findings.<br>Did not describe the strengths of the study.                                                                                                                                                                                               |
| <b>Interpretation</b>            | Did not clearly report the nature of the association, the reasons for differences between observed and anticipated outcomes, or the costs and strategic trade-offs.<br>Clearly reported the impact on people and systems and comparison with findings from other publications.    |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                    |
| <b>Conclusions</b>               | Clearly reported the usefulness of the work.<br>Did not clearly report on sustainability, potential for spread to other contexts, implications for practice, or suggested next steps.                                                                                             |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                    |

| Weiss 2011                       |                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing. Adequately summarized all key information from various sections of the text.                                                                                                                                                                                                                     |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                               |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Context</b>                   | Did not report on the contextual elements considered important.                                                                                                                                                                                                                                                                                                   |
| <b>Intervention</b>              | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                 |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, or the contextual elements that interacted with the intervention.<br>Clearly described the details of the process measures and outcome, the observed associations between outcomes and interventions, the unintended costs and consequences, and the extent of missing data. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, and impact of the project on people and systems.<br>Did not report on the reasons for differences between observed and anticipated outcomes or the costs and strategic trade-offs.                                                                              |
| <b>Limitations</b>               | Adequately reported on the generalizability of the work and factors that limited the internal validity.<br>Did not report on efforts to minimize and adjust for limitations.                                                                                                                                                                                      |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, and implications for further practice.<br>Did not report on sustainability, the potential for spread to other contexts, and suggested next steps.                                                                                                                                                              |
| <b>Funding</b>                   | Did not report on the sources of funding or the role of the funding organization.                                                                                                                                                                                                                                                                                 |

| Wirtz 2013                       |                                                                                                                                                                                                                                                                                |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Context</b>                   | Did not report on the contextual elements considered important.                                                                                                                                                                                                                |
| <b>Intervention</b>              | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                              |
| <b>Results</b>                   | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes.<br>Did not report on the costs and strategic trade-offs. |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                 |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work.<br>Did not report on sustainability, potential for spread to other contexts, implications for further practice and suggested next steps.                                                                                    |
| <b>Funding</b>                   | Did not report on the sources of funding or the role of the funding organization.                                                                                                                                                                                              |

|                                  |                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Wu 2018</b>                   |                                                                                                                                                                                                                                                                                                                                                               |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                           |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                         |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Results</b>                   | Clearly described the steps of the intervention or their evolution over time, and the observed associations between outcomes and interventions. Did not clearly describe the details of the process measures and outcome, the contextual elements that interacted with the intervention, the unintended costs and consequences or the extent of missing data. |
| <b>Summary</b>                   | Clearly described the key findings.<br>Did not report on the strengths of the project.                                                                                                                                                                                                                                                                        |
| <b>Interpretation</b>            | Clearly reported the nature of the association, and comparison with findings from other publications.<br>Did not report on the impact of the project on people and systems, reasons for differences between observed and anticipated outcomes, or costs and strategic trade-offs.                                                                             |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                                                |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work.<br>Did not report on sustainability, potential for spread to other contexts, implications for further practice and suggested next steps.                                                                                                                                                                   |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                |

|                                  |                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Wutzke 2007</b>               |                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Abstract</b>                  | Did not clearly describe the methods in the abstract.<br>Provided adequate information for searching and indexing.                                                                                                                                                                                                                                                |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                               |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Intervention</b>              | The intervention was reported in sufficient detail that others could reproduce it.<br>The specifics of the team involved in creating intervention materials were not clearly described.                                                                                                                                                                           |
| <b>Study of the Intervention</b> | Clearly reported the approach chosen for assessing the impact of the intervention.<br>Did not clearly describe who conducted the analyses.                                                                                                                                                                                                                        |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                 |
| <b>Results</b>                   | Clearly reported the initial steps of the intervention and their evolution over time, the details of the process measures and outcomes, and observed associations between outcomes and interventions.<br>Did not clearly report the contextual elements that interacted with the interventions, unintended costs and consequences, or the extent of missing data. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Interpretation</b>            | Clearly reported the nature of the association, and comparison with findings from other publications.<br>Did not clearly report on the impact of the project on people and systems, reasons for differences between observed and anticipated outcomes, and costs and strategic trade-offs.                                                                        |
| <b>Limitations</b>               | Adequately reported on the factors that limited internal validity.<br>Did not report on the generalizability of the work or efforts to minimize and adjust for limitations.                                                                                                                                                                                       |
| <b>Conclusions</b>               | Adequately reported on suggested next steps.<br>Did not clearly report the usefulness of the work, sustainability, implications for further practice or on potential for spread to other contexts.                                                                                                                                                                |
| <b>Funding</b>                   | Did not clearly report on the source of funding. Probably internally funded by NPS.                                                                                                                                                                                                                                                                               |

|                                  |                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Xiao 2016</b>                 |                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Abstract</b>                  | Provided adequate information for searching and indexing.<br>Did not clearly summarize the background or local problem in the abstract.                                                                                                                                                                                                                          |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                              |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Context</b>                   | Did not report on the contextual elements considered important; not enough details on the socioeconomic status of the regions that were selected.                                                                                                                                                                                                                |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it or the specifics of the team involved in the work.                                                                                                                                                                                                                            |
| <b>Study of the Intervention</b> | Clearly reported the approach chosen for assessing the impact of the intervention.<br>Did not fully report on the approach used to establish whether the outcomes were due to the intervention.                                                                                                                                                                  |
| <b>Measures</b>                  | Clearly reported on the measures chosen for studying processes and outcomes and the approach to the ongoing assessment of contextual elements.<br>Not clear from their description which methods were employed for assessing completeness and accuracy of data.                                                                                                  |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, the observed associations between outcomes and interventions or the extent of missing data.<br>Clearly described the details of the process measures and outcome, and the unintended costs and consequences. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                   |
| <b>Interpretation</b>            | Did not clearly reported the nature of the association, comparison with findings from other publications, impact of the project on people and systems, the reasons for differences between observed and anticipated outcomes or the costs and strategic trade-offs.                                                                                              |
| <b>Limitations</b>               | Did not report on the generalizability of the work, factors that limited the internal validity or on efforts to minimize and adjust for limitations.                                                                                                                                                                                                             |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work and suggested next steps.<br>Did not report on potential for spread to other contexts, sustainability, or implications for further practice.                                                                                                                                                                   |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                              |

|                                  |                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Yang 2013</b>                 |                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                               |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Intervention</b>              | Described the intervention in sufficient detail that others could reproduce it.<br>Did not report the specifics of the team involved in implementation.                                                                                                                                                                                                           |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Measures</b>                  | Clearly reported on the measures chosen for studying processes and outcomes and the approach to the ongoing assessment of contextual elements.<br>Did not report on the methods employed for assessing completeness and accuracy of data.                                                                                                                         |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                 |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the observed associations between outcomes and interventions, or the extent of missing data.<br>Clearly described the details of the process measures and outcome, the contextual elements that interacted with the intervention, and the unintended costs and consequences. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Interpretation</b>            | Clearly reported the nature of the association, and comparison with findings from other publications.<br>Did not report on the impact of the project on people and systems, reasons for differences between observed and anticipated outcomes and costs and strategic trade-offs.                                                                                 |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity.<br>Did not report on generalizability of the work or efforts to minimize and adjust for limitations                                                                                                                                                                                        |
| <b>Conclusions</b>               | Adequately reported on the implications for further practice.<br>Did not report on potential for spread to other contexts, usefulness of the work, sustainability, and suggested next steps.                                                                                                                                                                      |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                               |

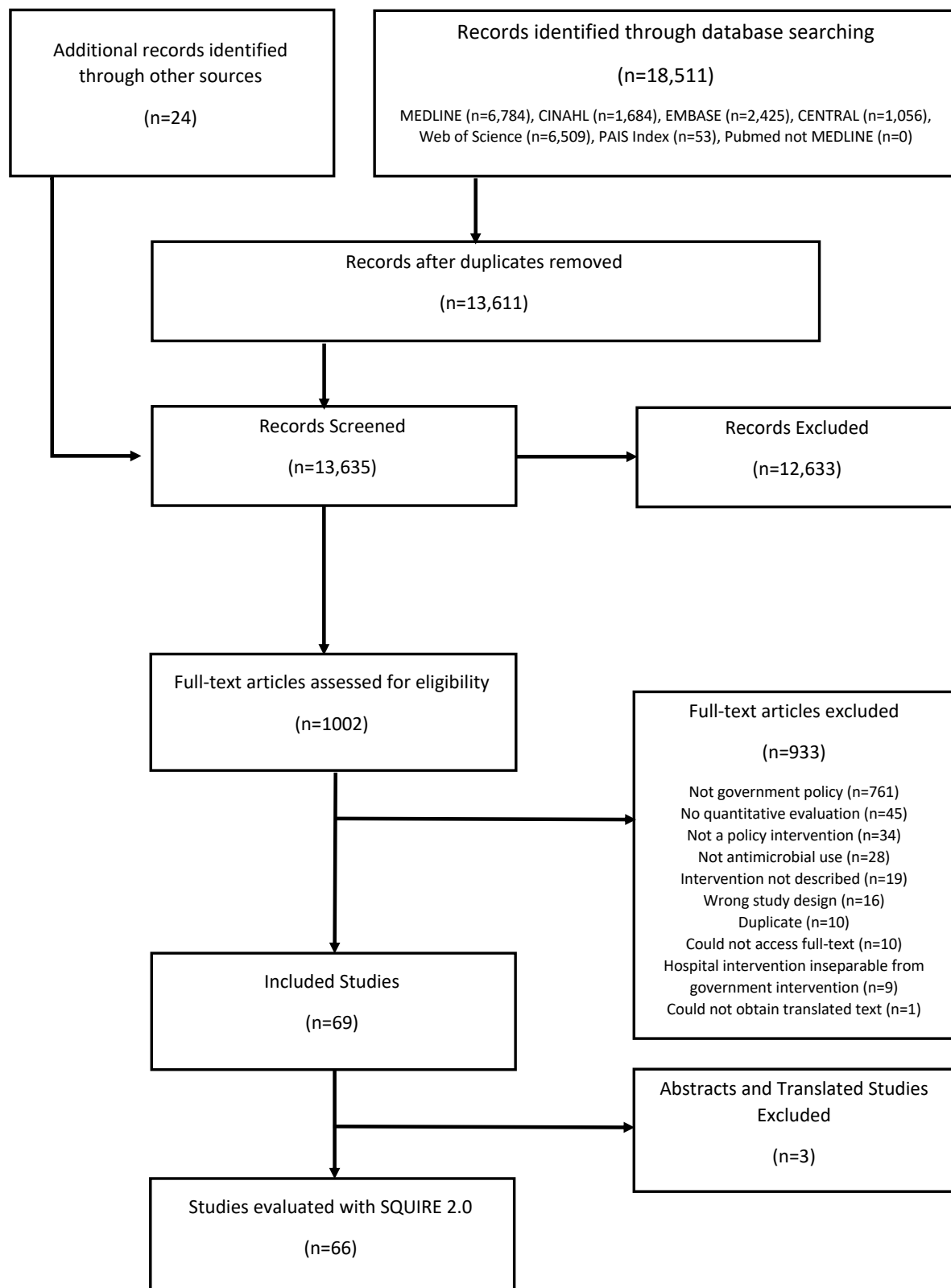
| Yip 2014                         |                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Abstract</b>                  | Did not provide adequate information for searching and indexing. Adequately summarized all key information from various sections of the text.                                                                                                                                                                                                                     |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                               |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Intervention</b>              | Clearly reported the intervention in sufficient detail that others could reproduce it.<br>Did not clearly report the specifics of the team involved in the work, including who conducted the data abstraction.                                                                                                                                                    |
| <b>Study of the Intervention</b> | Clearly reported the approach chosen for assessing the impact of the intervention.<br>Did not clearly describe the approach used to establish whether the observed outcomes were due to the intervention, including who conducted the analyses.                                                                                                                   |
| <b>Measures</b>                  | Clearly reported on the measures chosen for studying processes and outcomes and the approach to the ongoing assessment of contextual elements.<br>Did not report on the methods employed for assessing completeness and accuracy of data.                                                                                                                         |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, or the extend of missing data.<br>Clearly described the details of the process measures and outcome, the contextual elements that interacted with the intervention, the observed associations between outcomes and interventions, and the unintended costs and consequences. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Interpretation</b>            | Clearly reported the nature of the association, impact of the project on people and systems, and reasons for differences between observed and anticipated outcomes.<br>Did not clearly report on the comparison with findings from other publications or costs and strategic trade-offs.                                                                          |
| <b>Limitations</b>               | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, potential for spread to other contexts and implications for further practice.<br>Did not report on sustainability or suggested next steps.                                                                                                                                                                     |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |

| Zhang 2008                       |                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Abstract</b>                  | Provided adequate information for searching and indexing.<br>Did not clearly summarize the background or local problem in the abstract.                                                                                                                                                                                                                           |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                               |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Intervention</b>              | Reported the intervention in sufficient detail that other could reproduce it.<br>Did not report on the specifics of the team involved in the work.                                                                                                                                                                                                                |
| <b>Study of the Intervention</b> | Did not clearly report the approach chosen for assessing the impact of the intervention or the approach used to establish whether the observed outcomes were due to the intervention.                                                                                                                                                                             |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                                 |
| <b>Results</b>                   | Did not clearly describe the steps of the intervention or their evolution over time, the contextual elements that interacted with the intervention, the observed associations between outcomes and interventions, or the extent of missing data.<br>Clearly described the details of the process measures and outcome, and the unintended costs and consequences. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                    |
| <b>Interpretation</b>            | Clearly reported the nature of the association, comparison with findings from other publications, and reasons for differences between observed and anticipated outcomes.<br>Did not report on the impact of the project on people and systems, or costs and strategic trade-offs.                                                                                 |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity.<br>Did not report on generalizability of the work or efforts to minimize and adjust for limitations.                                                                                                                                                                                       |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work and suggested next steps.<br>Did not report on potential for spread to other contexts, sustainability, or implications for further practice.                                                                                                                                                                    |
| <b>Funding</b>                   | Reported the funding source but not the role of the funding source.                                                                                                                                                                                                                                                                                               |

|                                  |                                                                                                                                                                                                                                                                                                                                                        |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Zhen 2018</b>                 |                                                                                                                                                                                                                                                                                                                                                        |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                         |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                         |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                         |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                         |
| <b>Rationale</b>                 | Fully reported                                                                                                                                                                                                                                                                                                                                         |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                         |
| <b>Context</b>                   | Did not report on the contextual elements considered important.                                                                                                                                                                                                                                                                                        |
| <b>Intervention</b>              | Reported the intervention in sufficient detail that others could reproduce it.<br>Did not clearly report the specifics of the team involved in the work.                                                                                                                                                                                               |
| <b>Study of the Intervention</b> | Fully reported                                                                                                                                                                                                                                                                                                                                         |
| <b>Measures</b>                  | Clearly reported on.<br>Did not report on the measures chosen for studying processes and outcomes, the approach to the ongoing assessment of contextual elements, or the methods employed for assessing completeness and accuracy of data.                                                                                                             |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                         |
| <b>Ethical Considerations</b>    | Fully reported                                                                                                                                                                                                                                                                                                                                         |
| <b>Results</b>                   | Did not clearly describe the contextual elements that interacted with the intervention, the observed associations between outcomes and interventions, the unintended costs and consequences or the extent of missing data. details of the process measures and outcome, Clearly described the steps of the intervention and their evolution over time. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                         |
| <b>Interpretation</b>            | Clearly reported the nature of the association and the impact of the project on people and systems.<br>Did not report on a comparison with findings from other publications, the reasons for differences between observed and anticipated outcomes, and the costs and strategic trade-offs.                                                            |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity. Did not report on generalizability of the work or efforts to minimize and adjust for limitations.                                                                                                                                                                               |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work.<br>Did not report on potential for spread to other contexts, sustainability, suggested next steps or implications for further practice.                                                                                                                                                             |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                         |

|                                  |                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Zou 2014</b>                  |                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Title</b>                     | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Abstract</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Problem Description</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Available Knowledge</b>       | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Rationale</b>                 | Did not report on either formal or informal frameworks used to explain the problem on develop the intervention; did not report on reasons why the intervention as expected to work.                                                                                                                                                                             |
| <b>Specific Aims</b>             | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Context</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Intervention</b>              | Did not report the intervention in sufficient detail that other could reproduce it.<br>Specifics of the team involved were not applicable for studies where the authors were clearly not involved in implementation.                                                                                                                                            |
| <b>Study of the Intervention</b> | Clearly reported the approach chosen for assessing the impact of the intervention.<br>Did not clearly describe the approach used to establish whether the observed outcomes were due to the intervention, including who conducted the analyses.                                                                                                                 |
| <b>Measures</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Analysis</b>                  | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Ethical Considerations</b>    | Did not report on whether ethics review was received or required.                                                                                                                                                                                                                                                                                               |
| <b>Results</b>                   | Clearly reported the steps of the intervention and their evolution over time, the details of the process measures and outcomes, the observed associations between outcomes and intervention, and the unintended costs and consequences.<br>Did not clearly report the contextual elements that interacted with the intervention, or the extent of missing data. |
| <b>Summary</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                  |
| <b>Interpretation</b>            | Clearly reported the nature of the association and reasons for differences between observed and anticipated outcomes.<br>Did not report a comparison with findings from other publications, impact of the project on people and systems, or the costs and strategic trade-offs.                                                                                 |
| <b>Limitations</b>               | Adequately reported on the factors that limited the internal validity. Did not report on generalizability of the work or efforts to minimize and adjust for limitations.                                                                                                                                                                                        |
| <b>Conclusions</b>               | Adequately reported on the usefulness of the work, implications for further practice and suggested next steps.<br>Did not report on sustainability or the potential for spread to other contexts.                                                                                                                                                               |
| <b>Funding</b>                   | Fully reported                                                                                                                                                                                                                                                                                                                                                  |

### A4-3. PRISMA flow diagram



## Supplemental information – Chapter 5

### A5-1. Detailed results and study characteristics for each of the 18 included studies

| Study                                                                     | Country                  | Policy Approach | Policy Level | Enacting Government                           | Intervention Summary                                                                                                                                         | Methods                                                                                         | Outcome                                                                      | Study Population/Setting                                                   | Results                                                                                                                                                                                                                                                                                                                                                                                                                               | Secondary Findings                                                                                                                                                                                                                                                            |
|---------------------------------------------------------------------------|--------------------------|-----------------|--------------|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Finkelstein JA, et al. Pediatrics. 2008;121(1):e15-23.                    | United States of America | Communication   | Regional     | Massachusetts Department of Public Health     | Annual public and provider education campaign "REACH Mass" during cold and influenza season.                                                                 | Cluster RCT using health insurance claims data.                                                 | Number of oral antibiotics dispensed per person-year of observation          | 16 towns in Massachusetts                                                  | Intervention impact:<br>Age 3 to <24 mo.:<br>–0.5% (p=0.69)<br><br>Age 24 to <48 mo.:<br>–4.2% (p<0.01)<br><br>Age 48 to <72 mo.:<br>–6.7% (p<0.0001)<br><b>2000-2001</b> adjusted for influenza like illness:<br>–6.5% (p<0.05)<br><b>2001-2001</b> adjusted for influenza like illness:<br>–3.4% (p>0.05)                                                                                                                           | The intervention effect was greater among Medicaid insured children compared with commercially insured children.                                                                                                                                                              |
| Bauraind I, et al. JAMA. 2004;292(20):2468-70.                            | Belgium                  | Communication   | National     | Belgian Scientific Institute of Public Health | Two public campaigns using booklets, handouts, posters and television to promote rational use of antibiotics and reduce overuse and misuse in the community. | Interrupted time-series analysis using IMS Health data.                                         | Antibiotic sales in DDD                                                      | Population of Belgium                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                       | None                                                                                                                                                                                                                                                                          |
| Bernier A, et al. Antimicrobial Agents and Chemotherapy. 2014;58(1):71-7. | France                   | Communication   | National     | French National Health Insurance              | National public health campaign "Antibiotics Are Not Automatic!" repeated every winter.                                                                      | Interrupted time-series analysis using data from the French National Health Insurance Database. | Weekly Outpatient antibiotics prescribed and reimbursed per 1000 inhabitants | All outpatients, private-practice patients and pharmacy patients in France | Relative to baseline:<br>–11% (p<0.001) 1 <sup>st</sup> campaign period<br>–14% (p<0.001) 2 <sup>nd</sup> campaign period<br>–19% (p<0.001) 3 <sup>rd</sup> campaign period<br>–25% (p<0.001) 4 <sup>th</sup> campaign period<br>–30% (p<0.001) 5 <sup>th</sup> campaign period<br>–27% (p<0.001) 6 <sup>th</sup> campaign period<br>–25% (p<0.001) 7 <sup>th</sup> campaign period<br>–26% (p<0.001) 8 <sup>th</sup> campaign period | Trends differed according to therapeutic class with lower use of all antibiotics except quinolones.<br><br>The largest intervention impact was on children <15 years old.<br><br>Antibiotic use in seniors >60 antibiotic decreased until 2006-2007 and increased thereafter. |
| Wu J, et al. The Journal of international medical                         | Australia                | Communication   | National     | NPS Medicinewise Australia                    | NPS Medicinewise: a series of nationwide educational and advertising interventions for general                                                               | Bayesian structural time series model using prescriber level                                    | Total number of dispensed scripts                                            | 17,000 GPs in Australia                                                    | Average reduction in dispensing of 126,536 prescriptions per                                                                                                                                                                                                                                                                                                                                                                          | None                                                                                                                                                                                                                                                                          |

research.  
2018;46(4):1326-38.

practitioners and consumers.

data from PBS and the Medicare Benefit Schedule.

month (Bayesian CI95 = 71,580 to 181,490)

Overall 14% reduction in dispensed scripts between 2009 and 2015.

Township Health Centers:  
– 6.6 percentage points (p<0.05) (adjusted risk ratio of 15%)

Village Posts  
–6.0 percentage points (p<0.05) (adjusted risk ratio 16%)

Change in Level: – 14.65 items per 1000 RTI consultations (p=0.0022)

Change in Slope: 0.0018 items per 1000 RTI consultations (p=0.9950)

Absolute change 12 months post intervention = – 14.62

Absolute change 24 months post intervention = – 14.60

Relative change 12 months post intervention = –3%

Relative change 24 months post intervention = –3%

The intervention had no effect on total expenditure or the expenditure for drugs alone at the township level.

Concurrent 2% relative reduction in the rate of broad-spectrum antibiotic prescribing.

Yip W, et al. Health affairs. 2014;33(3):502-10.

China

Fiscal Measures

Regional

Government of Ningxia

Pilot program changing fee-for-services to pay-for-performance in rural healthcare settings.

Cluster RCT using data from health centre information system, a household survey, a village clinic survey and a township health centre survey.

Prescription Rate

28 towns and 266 villages in Ningxia province

Bou-Antoun S, et al. Journal of Antimicrobial Chemotherapy. 2018;73(10):2883-92.

England

Fiscal Measures

National

NHS England

NHS England Quality Premium: Financial incentives for Clinical Commissioning Groups to reduce antibiotic prescribing in primary care

Interrupted time series analysis using data from the Clinical Practice Research Datalink.

Antibiotic items per 1000 RTI consultations

2,198,602 primary care patients (6,480,900 consultations for respiratory tract infections)

Hallsworth M, et al. Lancet. 2016;387(10029):1743-52.

England

Guidelines

National

Department of Health – Chief Medical Officer

Feedback letter from England's Chief Medical Officer informing high using practitioners that

A 2x2 factorial RCT using national prescribing data.

Prescriptions per 1000 STAR-PU

1581 GP Practices in England

Feedback intervention:

Estimated public sector cost savings associated with

|                                                                                          |                          |            |          |                                                 |                                                                                                                                                                                                  |                                                                                                                        |                                                              |                                                                                             |                                                                                                                                                                                                                      |                                                                                                                                                                                                                                |
|------------------------------------------------------------------------------------------|--------------------------|------------|----------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                          |                          |            |          |                                                 | they were prescribing antibiotics at a higher rate than 80% of practices in their region; and provider education materials                                                                       |                                                                                                                        |                                                              |                                                                                             | IRR= 0.967 (95%CI= 0.957 to 0.977)                                                                                                                                                                                   | the intervention: £92,356                                                                                                                                                                                                      |
|                                                                                          |                          |            |          |                                                 |                                                                                                                                                                                                  |                                                                                                                        |                                                              |                                                                                             | Patient Education Intervention: IRR=1.007 (95% CI: 0.998 to 1.016)                                                                                                                                                   |                                                                                                                                                                                                                                |
|                                                                                          |                          |            |          |                                                 |                                                                                                                                                                                                  |                                                                                                                        |                                                              |                                                                                             | Both interventions -2.89 (95% CI:-3.95 to 0.61)                                                                                                                                                                      |                                                                                                                                                                                                                                |
| Dowell D, et al. American Journal of Public Health. 2012;102(1):148-55.                  | United States of America | Guidelines | Regional | Centers for Disease Control and Prevention      | Publication and circulation of revised CDC guidelines for the treatment of gonorrhea through MMWR, state and local health departments, a dear colleague letter, and a national press conference. | Interrupted time-series using data from a national network of health departments conducting enhanced STD surveillance. | Percentage of Infections treated with antibiotic             | 5 Health Departments participating a national network conducting enhanced STD surveillance  | Absolute change in fluoroquinolones prescribed two weeks post intervention: -21.5% (95%CI = -37.2% to -15.9%)                                                                                                        | Prescribing at STD clinics was consistent with an abrupt, permanent change. Prescribing in primary care and emergency departments was most consistent with a gradual permanent change.                                         |
| Hernandez-Santiago V, et al. Journal of Antimicrobial Chemotherapy. 2015;70(8):2397-404. | Scotland                 | Guidelines | Regional | National Health Service Tayside                 | National policy changes including guidelines, educational interventions and feedback for practices, and information leaflets to explain prescribing changes to individuals.                      | Interrupted time-series analysis using administrative data.                                                            | Quarterly rate of 4C antibiotics dispensed per 1000 patients | ~400,000 residents of Tayside region of Scotland registered with a GP                       | Change in slope: -0.70 change per quarter in patients per 1000 4C dispensed (95%CI= -0.49 to -0.91)                                                                                                                  | Significant increases in prescribing of antimicrobials recommended by local and national guidelines for respiratory tract and urinary tract infections: doxycycline (123.9% at 12 months), nitrofurantoin (20.9% at 12 months) |
| Ouldali N, et al. Clinical infectious diseases. 2017;65(9):1469-76.                      | France                   | Guidelines | National | French Agency for the safety of Health Products | Introduction of national guidelines (2011) on antibiotic prescriptions for acute respiratory tract infection in pediatric emergency departments.                                                 | Interrupted time series analysis using routinely collected hospital data.                                              | Antibiotic prescription rate for ARI per 1000 PED visits     | 242,534 patients aged <18 years with an ARTI diagnosis in 7 pediatric emergency departments | Significant and sustained decrease in 4C antimicrobial prescribing by -33.5% (95%CI= -26.1% to -40.9%), -42.2% (95%CI -34.2 to -50.2), and -55.5% (95%CI= -45.9 to -65.1%) at 6, 12 and 24 months post intervention. | Antibiotic prescriptions for viral ARTI also decreased significantly (-40.8%, 95% CI: -79.1 to -2.5)                                                                                                                           |

|                                                                                                 |         |            |                    |                                 |                                                                                                                                                                                                                           |                                                                                                                |                                         |                                                                      |  |                                                                                                            |                                                                                                                                                                                                                                                |
|-------------------------------------------------------------------------------------------------|---------|------------|--------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------|----------------------------------------------------------------------|--|------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                 |         |            |                    |                                 |                                                                                                                                                                                                                           |                                                                                                                |                                         |                                                                      |  | Change in slope:<br>–0.4% per 15-day<br>period (95% CI= –<br>0.8 to –0.0)                                  | No significant<br>change in<br>number of ARTI<br>diagnoses, UTI<br>diagnoses, or<br>percentage of<br>15-day<br>readmission.                                                                                                                    |
| Walker AJ,<br>Curtis HJ,<br>Goldacre B.<br>Journal of<br>Antimicrobial<br>Chemotherapy<br>2019. | England | Guidelines | National           | NHS England                     | Five-year antimicrobial<br>stewardship strategy and a<br>suite of actions taken by<br>the Chief Medical Officer                                                                                                           | Interrupted time<br>series analysis<br>using the<br>Prescription Cost<br>Analysis Dataset<br>from NHS Digital. | Prescriptions<br>per 1000<br>STAR-PU    | Primary care<br>patients in<br>England                               |  | Change in level:<br>50.6 prescriptions<br>per 1000 STAR PU<br>(95% CI = –42.2 to<br>143.4)                 |                                                                                                                                                                                                                                                |
|                                                                                                 |         |            |                    |                                 |                                                                                                                                                                                                                           |                                                                                                                |                                         |                                                                      |  | Change in slope: –<br>46.4 prescriptions<br>per 1000 STAR PU<br>per month<br>(95% CI = –61.4 to<br>–31.3); | None                                                                                                                                                                                                                                           |
|                                                                                                 |         |            |                    |                                 |                                                                                                                                                                                                                           |                                                                                                                |                                         |                                                                      |  | Annual prescribing<br>rate decreased by<br>–14.1% between<br>2013 and 2017                                 |                                                                                                                                                                                                                                                |
|                                                                                                 |         |            |                    |                                 |                                                                                                                                                                                                                           |                                                                                                                |                                         |                                                                      |  | Estimated 9.7<br>million<br>prescriptions<br>prevented.                                                    |                                                                                                                                                                                                                                                |
| Zhen L, Jin C,<br>Xu H-N. BMC<br>health services<br>research.<br>2018;18(1):777.                | China   | Guidelines | National           | Huangdao<br>Bureau of<br>Health | Rural Clinics Prescription<br>Commitment: creation of<br>antibiotic guidelines with<br>audit and feedback to rural<br>prescribers.                                                                                        | Interrupted time<br>series analysis<br>using data from<br>electronic medical<br>records.                       | Total number<br>of dispensed<br>scripts | Population of<br>Huangdao District<br>of Qingdao                     |  | Change in level:<br>– 6.15% (p=0.089)                                                                      | None                                                                                                                                                                                                                                           |
|                                                                                                 |         |            |                    |                                 |                                                                                                                                                                                                                           |                                                                                                                |                                         |                                                                      |  | Change in slope:<br>– 1.12% per month<br>P=0.034                                                           |                                                                                                                                                                                                                                                |
| Manns B, et al.<br>BMC Health<br>Services<br>Research.<br>2012;12:290.                          | Canada  | Regulation | State/<br>Province | Alberta Health<br>and Wellness  | Regulation requiring<br>physicians to submit<br>additional paperwork in<br>order for patients to have<br>their quinolone<br>prescription reimbursed<br>unless they registered as a<br>designated quinolone<br>prescriber. | Interrupted time-<br>series analysis<br>using<br>administrative<br>drug claims data.                           | Prescription<br>Rate                    | All residents over<br>the age of 65 in<br>the province of<br>Alberta |  | Change in level:<br>–3.5 (95% CI= –5.5<br>to 1.4)<br>prescriptions per<br>1000 index visits                | No change in 30<br>day mortality<br>(p=0.54)<br>No change in<br>hospitalization<br>for one of the<br>four infections<br>of interest (1.4%<br>vs 1.4%, p=0.2)<br>Small increase<br>in proportion of<br>patients<br>requiring<br>hospitalization |
|                                                                                                 |         |            |                    |                                 |                                                                                                                                                                                                                           |                                                                                                                |                                         |                                                                      |  | Change in slope:<br>No change in slope<br>(p=0.95)                                                         |                                                                                                                                                                                                                                                |

|                                                                             |        |            |                |                             |                                                                                                                                                                                                                                                         |                                                                                                                    |                                     |                                                                                                                   |                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------------------------------------------------------|--------|------------|----------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                             |        |            |                |                             |                                                                                                                                                                                                                                                         |                                                                                                                    |                                     |                                                                                                                   |                                                                                                                                                                                                                                                                                                                                             | (all cause) (4.9% vs 5.2%, P=0.0001)                                                                                                                                                                                                                                                                                                                        |
| Marra F, et al. Journal of Antimicrobial Chemotherapy. 2005;55(1):95-101.   | Canada | Regulation | State/Province | British Columbia Government | Formulary change delisting clarithromycin                                                                                                                                                                                                               | Interrupted time series using BC PharmaNet data.                                                                   | DDDs per 1000 population/day        | Population of British Columbia                                                                                    | Change in Level: -0.2929 (SEM=0.1409, p=0.038) DDD/1000 population /day<br>Change in Slope: -0.0037 (SEM=0.0152, p=0036) DDD/1000 population/day                                                                                                                                                                                            | Significant increase in erythromycin prescriptions corresponding to delisting of clarithromycin 0.3449 DDD/1000 population/day (p=0.036)                                                                                                                                                                                                                    |
| Sun J, et al. Journal of Global Antimicrobial Resistance. 2015;3(2):95-102. | China  | Regulation | National       | Ministry of Health China    | Multifaceted national intervention to promote rational use of antibiotics including target setting, monitoring, prescribing restrictions, training and revoking prescribing rights for prescribers who continuously do not meet the hospital's targets. | Interrupted time-series using data from the National Antimicrobial Clinical Use and Resistance Monitoring Network. | Prescription Rate                   | 15 tertiary care hospitals belonging to the National Antimicrobial Clinical Use and Resistance Monitoring Network | Change in Level: -4.7% (SE=2.0)<br>Change in Slope: -0.4% (SE=0.5)                                                                                                                                                                                                                                                                          | 8.6% Decline in proportion of patients given antibiotic prophylaxis for >24h                                                                                                                                                                                                                                                                                |
| Tang YQ, et al. Cost Effectiveness and Resource Allocation. 2018;16.        | China  | Regulation | National       | Government of China         | Chinese government issued administrative rules for the clinical use of antibiotics which included the creation of restricted groups of antibiotics and penalties for violating the administrative rules.                                                | Controlled ITS with a difference-in-difference approach                                                            | Volume of procured medicines in DDD | Population of the province of Hubei                                                                               | Restricted Oral Antibiotics: Change in Level: -0.33 million DDD (95% CI: -2.08 to 1.42) Change in Slope=0.055 million DDD per month (95%CI: -0.18 to 0.29)<br>Restricted Parenteral Antibiotics: Change in Level: -0.18 million DDD (95% CI: -0.44 to 0.086) Change in Slope=-0.035 million DDD per month (95%CI: -0.069 to 0.001, p=0.043) | All antibiotics: Change in Level: -0.32 million DDD (95% CI: -3.92 to 3.27) Change in Slope= -0.51 million DDD per month(95%CI: -0.97 to -0.05) decline in the secular trend of costs for non-restricted oral antibiotics (-0.36 million Yuan per month, p = 0.029) compared to the control 27.84% reduction in the cost of non-restricted oral antibiotics |

|                                                                                                  |                                                   |            |                      |                                                        |                                                                                                                                                                            |                                                                   |                                        |                                                                                                                                                |                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                        |
|--------------------------------------------------------------------------------------------------|---------------------------------------------------|------------|----------------------|--------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Santa-Ana-Tellez Y, et al<br>PloS one.<br>2013;8(10):e755<br>50.                                 | Mexico<br>and Brazil                              | Regulation | National             | Governments of<br>Mexico and<br>Brazil                 | Restriction on the sale of<br>antibiotics without a<br>prescription in pharmacies,<br>and introduction of a fine<br>on the owners of<br>pharmacies for non-<br>compliance. | Interrupted time-<br>series analysis<br>using IMS Health<br>data. | DDD per<br>1000<br>inhabitants/d<br>ay | Populations of<br>Brazil and Mexico<br>purchasing<br>antibiotics in the<br>private sector                                                      | MEXICO:<br>Change in Level: –<br>1.172 (p=0.001)<br>Change in Slope:<br>0.026 (p=0.663)<br><br>BRAZIL:<br>Change in Level: –<br>1.348 (p=0.005)<br>Change in Slope: –<br>0.018 (p=0.798)                                                                                           | Brazil: Decrease<br>in level of<br>penicillin,<br>sulfonamide and<br>macrolide<br>consumption.<br><br>Mexico:<br>Decrease in level<br>of penicillin and<br>sulfonamide<br>consumption. |
| Wirtz VJ, et al.<br>Tropical<br>Medicine &<br>International<br>Health.<br>2013;18(6):665-<br>73. | Chile,<br>Columbia,<br>Mexico<br>and<br>Venezuela | Regulation | Multiple<br>Policies | Governments of<br>Chile,<br>Colombia, and<br>Venezuela | Banning over-the-counter<br>antibiotics sales and<br>requiring retention of<br>prescriptions and<br>inspections of pharmacies.                                             | Interrupted time-<br>series using IMS<br>Health data.             | DDD per<br>1000<br>inhabitants/d<br>ay | Populations of<br>Chile, Venezuela,<br>and the national<br>capital region of<br>Colombia<br>purchasing<br>antibiotics in the<br>private sector | CHILE<br>Change in Level: –<br>5.56 (p<0.05)<br>Change in Slope: –<br>1.31 (p>0.05)<br><br>COLUMBIA<br>Change in Level: –<br>1.00 (p<0.001)<br>Change in Slope: –<br>1.31 (p>0.05)<br><br>VENEZUELA<br>Change in Level:<br>0.0123 (p>0.05)<br>Change in Slope: –<br>0.074 (p>0.05) | None                                                                                                                                                                                   |

## A5-2. The PRISMA for Abstracts Checklist

| TITLE                                     | CHECKLIST ITEM                                                                                                                                                                                       | REPORTED ON PAGE # |
|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| 1. Title:                                 | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                  | 69                 |
| <b>BACKGROUND</b>                         |                                                                                                                                                                                                      |                    |
| 2. Objectives:                            | The research question including components such as participants, interventions, comparators, and outcomes.                                                                                           | 71                 |
| <b>METHODS</b>                            |                                                                                                                                                                                                      |                    |
| 3. Eligibility criteria:                  | Study and report characteristics used as criteria for inclusion.                                                                                                                                     | 71                 |
| 4. Information sources:                   | Key databases searched and search dates.                                                                                                                                                             |                    |
| 5. Risk of bias:                          | Methods of assessing risk of bias.                                                                                                                                                                   |                    |
| <b>RESULTS</b>                            |                                                                                                                                                                                                      |                    |
| 6. Included studies:                      | Number and type of included studies and participants and relevant characteristics of studies.                                                                                                        | 71                 |
| 7. Synthesis of results:                  | Results for main outcomes (benefits and harms), preferably indicating the number of studies and participants for each. If meta-analysis was done, include summary measures and confidence intervals. |                    |
| 8. Description of the effect:             | Direction of the effect (i.e. which group is favoured) and size of the effect in terms meaningful to clinicians and patients.                                                                        |                    |
| <b>DISCUSSION</b>                         |                                                                                                                                                                                                      |                    |
| 9. Strengths and Limitations of evidence: | Brief summary of strengths and limitations of evidence (e.g. inconsistency, imprecision, indirectness, or risk of bias, other supporting or conflicting evidence)                                    | 71-72              |
| 10. Interpretation:                       | General interpretation of the results and important implications                                                                                                                                     |                    |
| <b>OTHER</b>                              |                                                                                                                                                                                                      |                    |
| 11. Funding:                              | Primary source of funding for the review.                                                                                                                                                            | 72                 |
| 12. Registration:                         | Registration number and registry name.                                                                                                                                                               |                    |

### A5-3. The PRISMA Checklist

| Section/topic             | #  | Checklist item                                                                                                                                                                                                                                                                                              | Reported in section                  |
|---------------------------|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|
| <b>TITLE</b>              |    |                                                                                                                                                                                                                                                                                                             |                                      |
| Title                     | 1  | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                                                                                                                         | Title page                           |
| <b>ABSTRACT</b>           |    |                                                                                                                                                                                                                                                                                                             |                                      |
| Structured summary        | 2  | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | Abstract                             |
| <b>INTRODUCTION</b>       |    |                                                                                                                                                                                                                                                                                                             |                                      |
| Rationale                 | 3  | Describe the rationale for the review in the context of what is already known.                                                                                                                                                                                                                              | Background                           |
| Objectives                | 4  | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                                                                                                                  | Background                           |
| <b>METHODS</b>            |    |                                                                                                                                                                                                                                                                                                             |                                      |
| Protocol and registration | 5  | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                                                                                                               | Methods: Protocol and registration   |
| Eligibility criteria      | 6  | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                                                                                      | Methods: Eligibility criteria        |
| Information sources       | 7  | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                                                                                                                  | Methods: Search strategy & selection |
| Search                    | 8  | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                                                                                                               | Protocol                             |
| Study selection           | 9  | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                                                                                                                   | Methods: Search strategy & selection |
| Data collection process   | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                                                                                                  | Methods: Search strategy & selection |

|                                    |    |                                                                                                                                                                                                                        |                           |
|------------------------------------|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| Data items                         | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                                  | Protocol                  |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | Data analysis             |
| Summary measures                   | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                          | N/A                       |
| Synthesis of results               | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.                                                              | N/A                       |
| Risk of bias across studies        | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).                                                                           | N/A                       |
| Additional analyses                | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.                                                                       | N/A                       |
| <b>RESULTS</b>                     |    |                                                                                                                                                                                                                        |                           |
| Study selection                    | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                                        | Figure 5-1                |
| Study characteristics              | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                                           | Table 5-1                 |
| Risk of bias within studies        | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                              | Figure 5-2                |
| Results of individual studies      | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.               | Table A-1                 |
| Synthesis of results               | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                                | N/A                       |
| Risk of bias across studies        | 22 | Present results of any assessment of risk of bias across studies (see Item 15).                                                                                                                                        | Quality of incl. studies  |
| Additional analysis                | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).                                                                                                  | N/A                       |
| <b>DISCUSSION</b>                  |    |                                                                                                                                                                                                                        |                           |
| Summary of evidence                | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                                   | Principal findings        |
| Limitations                        | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                                                          | Strengths and limitations |
| Conclusions                        | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                                | Conclusions               |
| <b>FUNDING</b>                     |    |                                                                                                                                                                                                                        |                           |

|         |    |                                                                                                                                            |              |
|---------|----|--------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | Declarations |
|---------|----|--------------------------------------------------------------------------------------------------------------------------------------------|--------------|

## Supplemental information – Chapter 6

### A6-1. Published and grey literature sources

| Title                                                                                                                   | Organization                              | Year    | Type                          | URL / Identifying information                                                                                                                                                                                                                                                                                                                               |
|-------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|---------|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antimicrobial Resistance and Stewardship                                                                                | Canadian Federation of Medical Students   | 2015    | Policy Statement              | <a href="https://www.cfms.org/files/position-papers/2015%20CFMS%20Antimicrobial%20Resistance%20and%20Stewardship.pdf">https://www.cfms.org/files/position-papers/2015%20CFMS%20Antimicrobial%20Resistance%20and%20Stewardship.pdf</a>                                                                                                                       |
| Progress Report on 2015 Federal Action Plan                                                                             | Public Health Agency of Canada            | 2018    | Government Report             | ISBN: 978-0-660-25744-0                                                                                                                                                                                                                                                                                                                                     |
| Statement of Concern                                                                                                    | Canadian Public Health Association        | 2014    | Policy Statement              | None                                                                                                                                                                                                                                                                                                                                                        |
| Public Consultation on Proposed Amendments to the Food and Drug Regulations Veterinary Drugs - Antimicrobial Resistance | Canadian Public Health Association        | 2016    | Brief                         | None                                                                                                                                                                                                                                                                                                                                                        |
| Multi-stakeholder antimicrobial stewardship expert forum                                                                | Canadian Institutes of Health Research    | 2016    | Workshop Report               | ISBN: 978-0-660-08348-3                                                                                                                                                                                                                                                                                                                                     |
| A Matters Approach to Clinician Engagement                                                                              | Health PEI                                | Undated | Slide Deck                    | Pyke & Boswell                                                                                                                                                                                                                                                                                                                                              |
| ASPIRES at Vancouver Coastal Health                                                                                     | Vancouver Coastal Health                  | Undated | Poster                        | Grant, Lau et al. Poster Presentation.                                                                                                                                                                                                                                                                                                                      |
| Building Canada's Antimicrobial Stewardship Action Plan                                                                 | HealthCare CAN                            | 2016    | Report                        | Rowan & Thompson 2016                                                                                                                                                                                                                                                                                                                                       |
| Brief to HESA on Antimicrobial Resistance                                                                               | Canadian Veterinary Medical Association   | 2017    | Brief                         | Submitted by Dr. Duane Landals to the House of Commons Standing Committee on Health                                                                                                                                                                                                                                                                         |
| Brief to HESA on Antimicrobial Resistance                                                                               | Canadian Nurses                           |         | Brief                         | <a href="https://www.cna-aiic.ca/~media/cna/page-content/pdf-en/antimicrobial-resistance-in-canada-brief-for-the-standing-committee-on-health.pdf?la=en">https://www.cna-aiic.ca/~media/cna/page-content/pdf-en/antimicrobial-resistance-in-canada-brief-for-the-standing-committee-on-health.pdf?la=en</a>                                                 |
| Brief to HESA on Antimicrobial Resistance                                                                               | Canadian Patient Safety Institute         | 2017    | Brief                         | Submitted by Chris Power to the House of Commons Standing Committee on Health                                                                                                                                                                                                                                                                               |
| Canada Communicable Disease Report: Special Issue on AMR                                                                | Public Health Agency of Canada            | 2016    | Academic Journal              | CCDR 42(11):223-238                                                                                                                                                                                                                                                                                                                                         |
| Brief to HESA on Antimicrobial Resistance                                                                               | Chicken Farmers of Canada                 | Undated | Brief                         | None                                                                                                                                                                                                                                                                                                                                                        |
| Brief to HESA on Antimicrobial Resistance                                                                               | Choosing Wisely Canada                    | Undated | Brief                         | Tackling the Drivers of Antibiotic Overuse in Medicine: A Brief from Choosing Wisely Canada; Submitted by Wendy Levinson to the House of Commons Standing Committee on Health                                                                                                                                                                               |
| Antimicrobial Stewardship Annual Report                                                                                 | Fraser Health                             | 2017    | Report                        | <a href="http://medicalstaff.fraserhealth.ca/getattachment/Clinical-Resources/Strips/Clinical-Services/Antimicrobial-Stewardship/Reports/FH-ASP-Annual-Report-2016-17.pdf.aspx/">http://medicalstaff.fraserhealth.ca/getattachment/Clinical-Resources/Strips/Clinical-Services/Antimicrobial-Stewardship/Reports/FH-ASP-Annual-Report-2016-17.pdf.aspx/</a> |
| Brief to HESA on Antimicrobial Resistance                                                                               | FIND                                      | 2017    | Brief                         | Diagnostics: a critical component in addressing the AMR emergency; Submission to the House of Commons Health Committee (HESA)                                                                                                                                                                                                                               |
| Brief to HESA on Antimicrobial Resistance                                                                               | Gerard Wright (McMaster)                  | 2017    | Brief                         | Submitted by Gerard Wright to the House of Commons Standing Committee on Health                                                                                                                                                                                                                                                                             |
| Health Portfolio Actions on Antimicrobial Resistance                                                                    | Government of Canada                      | 2015    | Website                       | <a href="https://www.canada.ca/en/news/archive/2015/04/health-portfolio-actions-antimicrobial-resistance.html">https://www.canada.ca/en/news/archive/2015/04/health-portfolio-actions-antimicrobial-resistance.html</a>                                                                                                                                     |
| Antimicrobial Stewardship in Canada                                                                                     | HealthCare CAN                            | 2017    | Brief                         | <a href="https://ipac-canada.org/photos/custom/pdf/HealthcareCan_Brief.PDF">https://ipac-canada.org/photos/custom/pdf/HealthcareCan_Brief.PDF</a>                                                                                                                                                                                                           |
| Brief to HESA on Antimicrobial Resistance                                                                               | Infection Prevention and Control Canada   | Undated | Brief                         | None                                                                                                                                                                                                                                                                                                                                                        |
| Landscape of antimicrobial stewardship programs in Ontario: a survey of hospitals                                       | Leung et al.                              | 2018    | Academic article              | CMAJ Open 2018. DOI:10.9778/cmajo.20170111                                                                                                                                                                                                                                                                                                                  |
| Antimicrobial Stewardship in Ontario: What's your role                                                                  | Leung and Langford, Public Health Ontario | 2017    | Professional magazine article | PHARMACY CONNECTION. SPRING 2017: 25-27.                                                                                                                                                                                                                                                                                                                    |

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|-------------------------------------------------------------------------------------|---------------------------------------------------------------------|---------|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Radio ad transcript: MRSA Testing #1                                                | University of Manitoba / Saskatchewan's Aboriginal Radio Network    | Undated | Radio Advertisement | None                                                                                                                                                                                                                                                                                                                                                                                       |
| Radio ad transcript: MRSA Testing #2                                                | University of Manitoba / Saskatchewan's Aboriginal Radio Network    | Undated | Radio Advertisement | None                                                                                                                                                                                                                                                                                                                                                                                       |
| Radio ad transcript: MRSA Testing #3                                                | University of Manitoba / Saskatchewan's Aboriginal Radio Network    | Undated | Radio Advertisement | None                                                                                                                                                                                                                                                                                                                                                                                       |
| Education Resources                                                                 | Northern Antibiotic Resistance Partnership                          | 2007    | Website             | Website no longer exists                                                                                                                                                                                                                                                                                                                                                                   |
| Meeting Report: Canadian Roundtable on Antimicrobial Stewardship                    | HealthCare CAN                                                      | 2016    | Workshop Report     | Project No. 272; <a href="https://nccid.ca/publications/canadian-roundtable-antimicrobial-stewardship-meeting-report/?hlite=%27Canadian%27%2C%27Roundtable%27%2C%27Antimicrobial%27%2C%27Stewardship%27">https://nccid.ca/publications/canadian-roundtable-antimicrobial-stewardship-meeting-report/?hlite=%27Canadian%27%2C%27Roundtable%27%2C%27Antimicrobial%27%2C%27Stewardship%27</a> |
| A provincial antimicrobial stewardship program: successes and challenges in Alberta | NCCID                                                               | Undated | Report              | <a href="https://nccid.ca/publications/provincial-antimicrobial-stewardship-program-successes-challenges-alberta/">https://nccid.ca/publications/provincial-antimicrobial-stewardship-program-successes-challenges-alberta/</a>                                                                                                                                                            |
| Putting the Pieces Together                                                         | HealthCare CAN and NCCID                                            | 2016    | Action Plan         | NCCID Project number 279; <a href="https://nccid.ca/publications/putting-pieces-together-national-action-plan-antimicrobial-stewardship/?hlite=%27Putting%27">https://nccid.ca/publications/putting-pieces-together-national-action-plan-antimicrobial-stewardship/?hlite=%27Putting%27</a>                                                                                                |
| Presentation to HESA on Antimicrobial Resistance                                    | National Farmed Animal Health and Welfare Council                   | 2017    | Presentation        | Submitted by Rob McNabb to the House of Commons Standing Committee on Health March 27, 2008;                                                                                                                                                                                                                                                                                               |
| Wash your hands and finish your prescriptions                                       | Nunatsiq News                                                       | 2008    | Newspaper           | <a href="http://old.nunatsiaq.com/stories/article/Wash_your_hands_and_finish_your_prescriptions_health_officials_say/">http://old.nunatsiaq.com/stories/article/Wash_your_hands_and_finish_your_prescriptions_health_officials_say/</a>                                                                                                                                                    |
| When Antibiotics Stop Working                                                       | Ontario Medical Association                                         | 2013    | Policy Statement    | None                                                                                                                                                                                                                                                                                                                                                                                       |
| Ontario Antimicrobial Stewardship Project                                           | Institute for Safe Medication Practices Canada                      | 2010    | Website             | <a href="https://www.ismp-canada.org/abx/">https://www.ismp-canada.org/abx/</a>                                                                                                                                                                                                                                                                                                            |
| Surveillance intégrée de la résistance aux antibiotiques                            | INSPQ                                                               | 2014    | Report              | ISBN : 978-2-550-71519-1                                                                                                                                                                                                                                                                                                                                                                   |
| Campagne québécoise des soins sécuritaires                                          | INSPQ                                                               | 2018    | Website             | <a href="https://www.inspq.qc.ca/expertises/maladies-infectieuses/infections-nosocomiales-et-risques-infectieux-en-milieu-de-soins/les-infections-nosocomiales/campagne-soins-securitaires">https://www.inspq.qc.ca/expertises/maladies-infectieuses/infections-nosocomiales-et-risques-infectieux-en-milieu-de-soins/les-infections-nosocomiales/campagne-soins-securitaires</a>          |
| Tuberculosis: The Heart of the Global Antimicrobial Resistance Crisis               | RESULTS Canada                                                      | 2017    | Brief               | Submitted by Shelley Garnham to the House of Commons Standing Committee on Health                                                                                                                                                                                                                                                                                                          |
| Brief to HESA on Antimicrobial Resistance                                           | Ontario Veterinary College                                          | 2017    | Brief               | Submitted by Scott McEwen to the House of Commons Standing Committee on Health                                                                                                                                                                                                                                                                                                             |
| Surgical Safety Checklist                                                           | Canadian Patient Safety Institute                                   | 2009    | Tool                | Surgical Safety Checklist: Canada; Version 1, January 9, 2009                                                                                                                                                                                                                                                                                                                              |
| Solving the AMR Crisis Starts with Addressing Drug Resistant Tuberculosis           | TB Alliance                                                         | 2017    | Brief               | Submitted by Willo Brock to the House of Commons Standing Committee on Health                                                                                                                                                                                                                                                                                                              |
| Presentation to HESA on Antimicrobial Resistance                                    | PHAC: Howard Njoo                                                   | 2017    | Presentation        | HESA Number 061; June 13, 2017                                                                                                                                                                                                                                                                                                                                                             |
| Presentation to HESA on Antimicrobial Resistance                                    | CIHR III: Marc Ouellette                                            | 2017    | Presentation        | HESA Number 061; June 13, 2017                                                                                                                                                                                                                                                                                                                                                             |
| Presentation to HESA on Antimicrobial Resistance                                    | Health Canada: Mary-Jane Ireland                                    | 2017    | Presentation        | HESA Number 061; June 13, 2017                                                                                                                                                                                                                                                                                                                                                             |
| Presentation to HESA on Antimicrobial Resistance                                    | CFIA: Aline Dimitri                                                 | 2017    | Presentation        | HESA Number 061; June 13, 2017                                                                                                                                                                                                                                                                                                                                                             |
| Presentation to HESA on Antimicrobial Resistance                                    | AMMI: Andrew Morris                                                 | 2017    | Presentation        | HESA Number 062; June 15, 2017                                                                                                                                                                                                                                                                                                                                                             |
| Presentation to HESA on Antimicrobial Resistance                                    | Canadian Nurses Association: Karey Shuhendler and Yoshiko Nakamachi | 2017    | Presentation        | HESA Number 062; June 15, 2017                                                                                                                                                                                                                                                                                                                                                             |
| Presentation to HESA on Antimicrobial Resistance                                    | Canadian Pharmacist Association: Shelita Dattani                    | 2017    | Presentation        | HESA Number 062; June 15, 2017                                                                                                                                                                                                                                                                                                                                                             |
| Presentation to HESA on Antimicrobial Resistance                                    | Royal College of Physicians and Surgeons: Michael Routledge         | 2017    | Presentation        | HESA Number 062; June 15, 2017                                                                                                                                                                                                                                                                                                                                                             |

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| Presentation to HESA on Antimicrobial Resistance                                             | Choosing Wisely Canada: Wendy Levinson                                           | 2017        | Presentation    | HESA Number 076; November 2, 2017                                                                                                                                                                                                                                                                       |
| Presentation to HESA on Antimicrobial Resistance                                             | Sinai Health System: Andrew Morris                                               | 2017        | Presentation    | HESA Number 076; November 2, 2017                                                                                                                                                                                                                                                                       |
| Presentation to HESA on Antimicrobial Resistance                                             | Infection Prevention and Control Canada: Suzanne Rhodenizer Rose, Jennifer Happe | 2017        | Presentation    | HESA Number 076; November 2, 2017                                                                                                                                                                                                                                                                       |
| Presentation to HESA on Antimicrobial Resistance                                             | NCCID: Yoav Keynan                                                               | 2017        | Presentation    | HESA Number 076; November 2, 2017                                                                                                                                                                                                                                                                       |
| Presentation to HESA on Antimicrobial Resistance                                             | Halton Healthcare: Neil Rau                                                      | 2017        | Presentation    | HESA Number 077; November 7, 2017                                                                                                                                                                                                                                                                       |
| Presentation to HESA on Antimicrobial Resistance                                             | Canadian Patient Safety Institute: Saudi Kossey and Kim Neudorf                  | 2017        | Presentation    | HESA Number 077; November 7, 2017                                                                                                                                                                                                                                                                       |
| Presentation to HESA on Antimicrobial Resistance                                             | University of Saskatchewan: Yvonne Shevchuk                                      | 2017        | Presentation    | HESA Number 077; November 7, 2017                                                                                                                                                                                                                                                                       |
| Building on the Federal Framework for Action                                                 | Public Health Agency of Canada                                                   | 2015        | Action Plan     | ISBN: 978-1-100-25929-1                                                                                                                                                                                                                                                                                 |
| Antimicrobial Resistance and Use in Canada: A Federal Framework for Action                   | Public Health Agency of Canada                                                   | 2014        | Action Plan     | ISBN: 978-1-100-25126-4                                                                                                                                                                                                                                                                                 |
| Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action | Public Health Agency of Canada                                                   | 2017        | Action Plan     | ISBN: 978-0-660-08168-7                                                                                                                                                                                                                                                                                 |
| A Canada-UK Workshop: Beating the Bugs                                                       | CIHR Institute of Infection and Immunity                                         | 2008        | Workshop Report | ISBN: 978-0-662-48492-9                                                                                                                                                                                                                                                                                 |
| Notice - Antimicrobials Product Labelling                                                    | Health Canada                                                                    | 2015        | Website         | <a href="https://www.canada.ca/en/health-canada/services/drugs-health-products...-products/announcements/notice-antimicrobials-product-labelling.html">https://www.canada.ca/en/health-canada/services/drugs-health-products...-products/announcements/notice-antimicrobials-product-labelling.html</a> |
| About CIHR's Antimicrobial Resistance Initiatives                                            | Canadian Institutes of Health Research                                           | 2017        | Website         | <a href="http://www.cihr-irsc.gc.ca/e/40485.html">http://www.cihr-irsc.gc.ca/e/40485.html</a>                                                                                                                                                                                                           |
| Antimicrobial stewardship in daily practice: Managing an important resource                  | Canadian Paediatric Society                                                      | 2014 / 2017 | Report          | Paediatr Child Health 2014;19(4):261-65                                                                                                                                                                                                                                                                 |