

**The management of gonococcal infections and the development and use of
treatment guidelines**

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Synopsis

N. Gonorrhoeae is a major public health concern due to its capacity to develop antibiotic resistance and its potential complications including pelvic inflammatory disease, epididymitis, infertility, and disseminated infection. In order to keep up with resistance trends, the treatment recommendations for gonorrhea have changed frequently. In other areas of medicine, guideline adherence has been shown to be limited, even without frequent guideline changes. In the case of gonorrhea, inappropriate treatment can have serious individual and public health implications, making the quality of and compliance with clinical guidelines critical. This thesis is a three-part mixed methods research project assessing the development and uptake of gonorrhea treatment guidelines. We conducted a systematic review of current gonorrhea treatment guidelines and used the AGREE II tool to assess the quality of guideline development (Chapter 2). We observed that guideline quality varied greatly with many guidelines having weaknesses in their use of existing evidence to develop recommendations, their reporting of potential conflicts of interest and how they were addressed, and their consideration of barriers to the implementation of their recommendations. We then assessed physician adherence to first-line treatment recommendations in Ontario by conducting a segmented time series analysis of Ontario gonorrhea treatment data from iPHIS, the province's reportable disease database (Chapter 3). Following the introduction of new guidelines that recommended substantial changes from current practice, we found very dramatic drops in guidelines adherence that then improved slowly over time. We then explored the use of process mapping as a tool to look at the local management of cases in the City of Ottawa by following them across the various possible treatment pathways (Chapter 4). Here, we noted differences in practice between the management of cases at Ottawa Public Health's Sexual Health Clinic and the management of cases elsewhere in the community.

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Glossary

AGREE: Appraisal of Guidelines for Research and Evaluation
BASHH: the British Association of Sexual Health and HIV
CDC: Centers for Disease Control and Prevention
CI: confidence interval
CMA: Canadian Medical Association
COM-B: Capability, Opportunity, Motivation, and Behaviour model
ER: emergency room
GIN: Guideline International Network
GUIDE-M: Guideline Implementability for Decision Excellence Model
GRADE: Grading of Recommendations Assessment, Development and Evaluation
GUM: genitourinary medicine
HIV: human immunodeficiency virus
IM: intramuscular
iPHIS: Integrated Public Health Information System
ITS: interrupted time series
IUSTI: International Union Against Sexually Transmitted Infections
JAMA: Journal of the American Medical Association
MSM: men who have sex with men
NAAT: nucleic acid amplification test
NICE: National Institute for Health Care Excellence
Ob/Gyn: obstetrics and gynecology
OPH: Ottawa Public Health
PHAC: the Public Health Agency of Canada
PHO: Public Health Ontario
PO: *per os* (i.e., administered orally)
SIGN: Scottish Intercollegiate Guidelines Network
STI: sexually transmitted infection
Tx: treatment
UK: United Kingdom
US: United States

Chapter 1 - Introduction

Gonococcal infections and antimicrobial resistance

Gonorrhea, or gonococcal infection, is caused by *Neisseria Gonorrhoeae*, a gram-negative diplococcal bacteria. Gonorrhea is transmitted sexually and can cause urogenital, anal or oropharyngeal infections.¹ Complications from untreated infection include infertility in both men and women, epididymitis in men, as well as endometrial infection, pelvic inflammatory disease, and increased risk of ectopic pregnancy in women, and the increased risk of transmission of HIV. Systemic gonococcal infections, such as septicemia, arthritis, meningitis, and endocarditis can also occur as rare complications of gonorrhea infection.¹ Gonorrhea can be transmitted vertically to newborns of infected mothers and can cause neonatal sepsis, ocular infections or joint infections.¹

Gonococcal infections are often asymptomatic,¹ leading to higher risk of transmission, as patients would not know to change their behaviours or seek treatment. Anal and oropharyngeal infections in particular are usually asymptomatic^{1, 2} and may be at even greater risk of being either undiagnosed or misdiagnosed if a clinician is not considering the possibility of a sexually transmitted infection (STI). Many gonococcal infections are picked up through screening of asymptomatic patients.^{1, 2}

Gonorrhea is the second most common reportable STI in Canada (after chlamydia), with rates that have been increasing since 1997.³ In Canada, 12,561 cases were reported in 2012 (incidence rate: 36.2 per 100,000 population).³ Incidence rates are highest in young adults (20-24 years old); in 2012, Canadian incidence rates were 153.0 per 100,000 among males aged 20-24 and 148.5 per 100,000 among females aged 20-24.³

Since the introduction of antibiotics as a tool of modern medicine, gonorrhea has shown itself to be highly adaptable and can rapidly develop resistant strains to antibiotics used as treatment.⁴ Over time, *N. Gonorrhoeae* has developed and has maintained resistance (limiting the possibility of reintroducing an old drug) to nearly

every family of antibiotic that has been successfully used to treat it: in the 1970's, penicillin resistance emerged; in the 1980's, spectinomycin resistance emerged; and the 1990's saw the emergence of fluoroquinolone resistance.⁴ In the current decade, we are seeing increasing reports of cases with resistance to the current gonorrhea treatment of choice, third generation cephalosporins.⁵⁻¹¹ Few new drug choices are available for the treatment of gonorrhea and thus it is important to extend the use of third generation cephalosporins for as long as possible.^{2, 4, 12} A recent outbreak of gonorrhea that is highly resistant to azithromycin (currently the recommended first-line treatment for gonorrhea in combination with a third-generation cephalosporin) in the northern UK has led to much concern that a fully drug resistant strain of gonorrhea may be fast approaching.^{13, 14} For the first time since antibiotics were first used to treat STIs in the 1930s, gonorrhea infections are at risk of becoming untreatable.⁴

Clinical guidelines for the treatment of gonococcal infections

The recommended first-line treatment for gonorrhea has changed numerous times in order to try to keep ahead of antimicrobial resistance patterns. Recommended first-line treatment antibiotic doses have, on occasion, been increased to ensure that a sufficient concentration of drug is present to treat a strain of *N. gonorrhoeae* with reduced susceptibility¹⁵ (meaning that the antibiotic will have an effect but that a larger dose is needed). If an ineffective drug or an insufficient dosage is used to treat a gonococcal infection, there is risk of treatment failure.^{4, 12} If the infection is asymptomatic, an individual with treatment failure may be unaware that they are still infected and may not return for further clinical follow-up. Thus, treatment failure comes with the risk of further spread of infection as well as the risk of complications of infection. Treatment failure can be difficult to differentiate from re-infection.

Up to date clinical guidelines are needed to ensure that patients with gonorrhea receive adequate treatment with an appropriate antibiotic. Inadequate antibiotic treatment may select for more resistant strains that are then passed on in subsequent infections.⁴ Thus, clinicians' uptake of clinical guidelines recommending

adequate doses of appropriate antibiotics may slow progression of resistance to the drugs currently used.

In Canada, to address antimicrobial resistance in gonorrhea, the *Canadian Guidelines on Sexually Transmitted Infections'* gonorrhea treatment guidelines were updated twice within four years: first, in early 2008, to remove fluoroquinolones as first-line treatment;¹⁶ and then, in late 2011, to double the recommended dose of third generation cephalosporins, to require intramuscular ceftriaxone for pharyngeal infections as well as for men who have sex with men (MSM) due to reports of more resistant strains within this subpopulation, and to recommend dual treatment with azithromycin in all cases.¹⁵ Less than two years later, Ontario introduced new guidelines recommending intramuscular ceftriaxone plus azithromycin for all cases.¹⁷ Figure 1-1 summarizes the changes in guidelines in Canada and Ontario over time.

In Ontario, local public health units offer STI preventive, diagnostic and treatment care through public health-run sexual health services.¹⁸ However, STIs may also be diagnosed and managed in a variety of clinical settings including, but not limited to, family physicians' offices, walk-in clinics, emergency departments, pediatricians' offices, obstetrics and gynecology clinics, and HIV clinics. Clinical guideline recommendations must therefore reach a diverse range of clinicians.

Challenges to the uptake of clinical treatment guidelines

Studies on other clinical practice guidelines suggest that adherence to guidelines can be low. Studies from both the United States and the Netherlands suggest that 30-40% of patients do not receive care that is consistent with current evidence-based practice and that 20-25% receive unnecessary or potentially harmful treatment.^{19, 20} In the case of gonorrhea treatment guidelines, physician adherence to guidelines may be particularly challenging due to the high frequency at which the recommended treatment has changed. What may be even more confusing to Ontario physicians is that the source of the guidelines that they are expected to follow for the treatment of gonorrhea has changed. While the *Canadian Guidelines for Sexually Transmitted Infections* are still the resource of choice for treating all other STIs,

Ontario clinicians are expected to follow the Ontario *Guidelines for Testing and Treatment of Gonorrhea* for the management of gonorrhea infections. An additional barrier to following the new Ontario guidelines, particularly outside of sexual health clinic settings, is the recommended intramuscular ceftriaxone treatment. Patients may refuse an injection, some clinics may not keep ceftriaxone in stock and require a patient to return at a later time for an injection or to go to another clinic for their treatment, and, as ceftriaxone needs to be reconstituted at the time of injection, providing the treatment is an additional time burden for a busy practice. There is also the possibility of allergies or other medical contraindications to the recommended first-line treatment, requiring that a second-line option be prescribed instead.

The uptake of best practices has been demonstrated to be limited in the management of STIs. Previous evaluations of physician adherence to STI management guidelines have been carried out in different jurisdictions and in a variety of practice settings where STI management may be the majority of the practice, such as in sexual health clinics or genitourinary medicine (GUM) clinics, or a small component of the practice, such as general practices, or emergency room settings.²¹⁻⁶⁴ These evaluations showed mixed results with some components of management being done fairly well while other components were lacking. However, in general, these studies suggested that guidelines were not perfectly followed and/or that some clinicians lacked some knowledge regarding the most up-to-date STI management best practices.²¹⁻⁶⁴

Most of the existing evaluations of STI guideline adherence are not from a Canadian setting and not necessarily generalizable to Ontario physicians. Different guidelines apply for different jurisdictions and dissemination practices and physician familiarity with the local guidelines may differ. In addition, physicians' training on STI management may differ, and physicians in different settings may have different degrees of experience managing STI cases due to the prevalence of STIs and the organization of STI care in their jurisdiction. For example, in the United Kingdom, most gonorrhea cases are diagnosed and treated in GUM clinics. A recent study showed that general practitioners diagnosed between 6-9% of gonorrhea cases in

England and most of these cases were then referred on to a GUM clinic for treatment.⁶⁴ Of the cases treated by general practitioners in this study, 40% received the recommended treatment regimen and it took six years after the guideline change recommending cephalosporins over fluoroquinolones for cefixime (a cephalosporin) to surpass ciprofloxacin (a fluoroquinolone) as the drug most commonly prescribed by general practitioners to treat gonorrhea.⁶⁴ Recent studies of adherence to gonorrhea treatment guidelines in the US suggest that guideline adherence varies by geographic location (e.g., Swails et al. found that adherence was greater in cities or towns with higher rates of gonorrhea,⁵⁶ and both Kerani et al. and Dowell et al. noted variance in guideline adherence between different cities and states^{22, 53}), type of practice (e.g., STI clinics are more likely to adhere to guidelines),^{53, 54, 56, 59} and number of gonorrhea cases treated at a location or by a provider (providers or clinics that treated fewer cases were less likely to adhere to current practice guidelines).^{57, 59}

The small number of Canadian publications on physician adherence to STI guidelines all date from prior to any of the recent guideline changes.^{39, 47, 49, 50, 52} The most recent Canadian publication found was a review of STI management practices in Manitoba published in 2002.³⁹ The Canadian evaluations suggest that, at the time that they were done, clinical management of STIs varied and was often not consistent with current practice guidelines.^{39, 47, 49, 50, 52}

Thesis objectives and work

With the serious implications of further gonorrhea antibiotic resistance, the complexity of guideline development and dissemination, and the particular challenge that the need for frequent new antibiotic recommendations provides for guideline uptake in mind, my thesis looks at:

- Gonorrhea treatment guideline development,
- Gonorrhea treatment guideline uptake at the provincial level, and
- Gonorrhea management at the local level.

My thesis has been designed as a manuscript-based thesis with one manuscript intended for journal publication written for each of my three thesis objectives.

Objective 1: To review the development of existing gonorrhea treatment guidelines.

- To meet this objective, I conducted a systematic review of current guidelines and assessed their reported development processes using the AGREE II instrument. (Chapter 2)

Objective 2: To assess the impact of recent changes in best practices on the treatment of gonorrhea in Ontario.

- To meet this objective, I conducted interrupted time series analyses to assess changes in antibiotics used to treat patients with gonorrhea in Ontario over time. These analyses covered three changes in guideline recommendations. (Chapter 3)

Objective 3: To identify clinical pathways/processes in the management of gonorrhea that could be changed to improve patient care.

- To meet this objective, I used process mapping to describe the possible management pathways for a patient with gonorrhea in Ottawa. I estimated the proportion of patients following each branch with local reportable disease data where such data were available, and flagged branches that did not correspond with treatment guidelines. (Chapter 4)

Authors' contributions

I am first author for all three papers. I came up with the idea for the research project, developed the research protocol, completed the research ethics board applications, conducted the systematic review, acted as one of the AGREE II appraisers, worked with Public Health Ontario and Ottawa Public Health to obtain the data sets, conducted the data analysis and conducted the majority of the write-up for each chapter.

Co-authors for Chapter 2 - *A systematic review of the quality of guidelines for the management of gonococcal infections*:

- Trevor Arnason acted as one of the AGREE II appraisers.
- Gila Metz provided guidance on the planning of this chapter, and provided input on the write-up of the chapter.
- Dara Spatz Friedman provided guidance on the planning of this chapter, and provided input on the write-up of the chapter.
- Tom Wong provided guidance on the planning of this chapter, and provided input on the write-up of the chapter.
- Jeremy Grimshaw provided guidance on the planning of this chapter, recommended the use of the AGREE II tool, and provided input on the write-up of the chapter.

Co-authors for Chapter 3 - *The antibiotic management of gonorrhea in Ontario following multiple changes in guidelines: An interrupted time series analysis*:

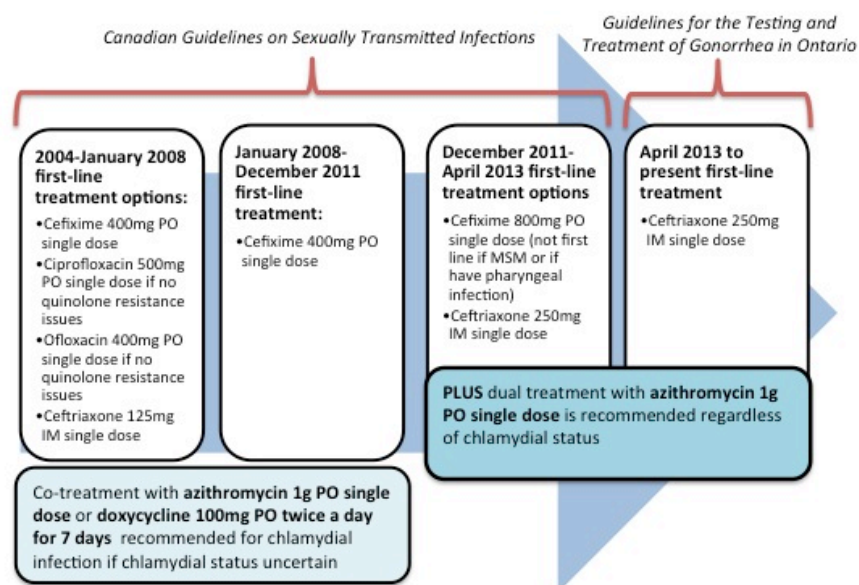
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- Gila Metz provided guidance on the planning of this chapter, and provided input on the write-up of the chapter.

- Dara Spatz Friedman provided guidance on the planning of this chapter, assisted with data access, and provided input on the write-up of the chapter.
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- Jeremy Grimshaw provided guidance on the planning of this chapter, and provided input on the write-up of the chapter.

Figure 1-1: The changes in the first-line treatment of gonorrhea over time.^{15-17, 65}



Chapter 2 - A systematic review of the quality of guidelines for the management of gonococcal infections

Abstract

Objective: To assess the quality of current guidelines for the treatment of gonorrhea.

Methods: Original and current gonorrhea treatment guidelines were identified using multiple databases and selected using pre-determined criteria. Two appraisers assessed the guidelines independently using the AGREE II tool and their scores were combined as per the AGREE II users' manual.

Results: We identified 10 guidelines meeting the inclusion criteria. Quality of the guidelines varied. Most scored poorly on *Rigour of Development*; information on the evidence review process and methods for formulating recommendations was often missing. Conflicts of interest were often not addressed. Most guidelines did not address the implementation and applicability of recommendations.

Discussion: Clinical guidelines for the management of gonorrhea may slow the progression of antimicrobial resistance. By identifying limitations in current guidelines, this study can help developers improve the quality of future clinical guidelines. As many guidelines recommended a change from oral cefixime to intramuscular ceftriaxone, advice on how to adopt this practice may help practitioners provide the recommended care and prevent cases of treatment failure.

Background

Clinical guidelines are a tool for ensuring that medical care is consistent between providers and in line with current evidence.¹ However, these guidelines are only as good as their development process. Guideline quality, or “the confidence that the biases linked to the rigour of development, presentation and applicability of a guideline had been minimized during the development process”⁶⁶ is important to ensure that optimal recommendations are made.

Gonorrhea is a bacterial infection caused by the organism *Neisseria gonorrhoeae*. *N. gonorrhoeae* has developed and maintained resistance to nearly every antibiotic that has been used to treat it⁶⁷⁻⁶⁹, presenting a particular challenge for guideline developers. In order to delay the development of resistance to current treatment options and to prevent the sequelae of undertreated infections, clinicians need up to date treatment guidelines based on current evidence, including local epidemiology of resistance patterns.

Numerous gonorrhea treatment guidelines exist across different jurisdictions to guide appropriate antibiotic and dosage selection. In addition to improving individual patient outcomes, actions to ensure high quality gonorrhea treatment guidelines would improve public health outcomes. Appropriate treatment of gonorrhea will prevent treatment failure and subsequent re-infections and potentially help delay further progression of antimicrobial resistance.

In this study, we conducted a systematic review of current clinical guidelines for the treatment of gonococcal infections and reviewed the quality of the guidelines using the AGREE II, a critical appraisal tool designed to assess the quality of clinical guidelines.⁷⁰

Methods

Guideline selection

We developed a search strategy with the assistance of a medical librarian. Relevant guidelines were identified using multiple databases: Medline, Pubmed, Embase, National Guideline Clearinghouse, Guideline International Network (GIN),

Canadian Medical Association (CMA) Infobase: Clinical Practice Guidelines Database, Trip Database, National Institute for Health Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), Australian Government National Health and Medical Research Council Clinical Practice Guidelines Portal, Google (limited to the first 5 pages), and Google Scholar (limited to the first 5 pages). In addition, individual guideline documents were reviewed to determine if they referenced other relevant guidelines. Search terms included: gonorrhea, neisseria gonorrhoeae, gonorrh*, gonococc*, guidelines, guideline, practice guidelines, practice guideline, health planning guidelines, clinical protocols, clinical pathways, health care planning, gonorrhea treatment guidelines. A detailed description of each search is found in Table 2-1 of the Supplementary Appendix.

One author (CD) conducted the searches between August 11 and 18, 2014 and selected the guidelines for inclusion in the review using the following pre-determined inclusion criteria:

- English language,
- Guidelines for the treatment of gonococcal infection in the general adult population,
- Guidelines include recommendations on the treatment of uncomplicated gonococcal infections (i.e., urogenital, rectal, and pharyngeal infections without complications such as pelvic inflammatory disease or epididymitis) – including antibiotic name and dose,
- Guidelines geared towards an audience of health professionals,
- Original guideline document (i.e., not recommendations based on another guideline),
- Most recent version of the guideline available at the time.

We identified accompanying documents, such as methods papers, through the systematic review and through scanning the guidelines for any reference to such documents. Guideline-accompanying documents, if available, were reviewed along with each guideline.

When the guidelines covered multiple infections, the appraisers reviewed the full documents but focused on the sections and recommendations for gonococcal infections.

In December 2014, CD verified that there were no updates to any of the selected guidelines in order to ascertain that the two appraisers reviewed the same version of each guideline. If a guideline had been updated or replaced with a new guideline, both appraisers reviewed the newer version. We replaced one guideline with a more recently published update.

Data extraction

One appraiser (CD) reviewed each guideline to document: the guideline development agency, publication year, country or jurisdiction that guideline applied to, and the recommended treatment for uncomplicated gonococcal infection.

Guideline appraisal

Two appraisers (CD and TA) assessed each of the selected guidelines independently using the Appraisal of Guidelines, Research and Evaluation (AGREE) II instrument.⁷⁰ AGREE II is a critical appraisal tool that appraises a guideline's development process and the reporting of the process. The instrument assesses 23 items in 6 domains (*Scope and Purpose, Stakeholder Involvement, Rigour of Development, Clarity of Presentation, Applicability, and Editorial Independence*). Each item is scored using a scale of 1 (strongly disagree) to 7 (strongly agree). In addition, appraisers are asked to rate the overall quality of the guideline (1 to 7).⁷⁰

Prior to reviewing the guidelines, both appraisers reviewed the AGREE II user's manual.⁷¹ In addition, CD completed the online training module on the AGREE II instrument available on the AGREE Enterprise website.⁷² The two appraisers also used the instrument to review an unrelated guideline (*Guidelines for the Prevention and Control of Measles Outbreaks in Canada*)⁷³ together to verify that they had a common understanding of the AGREE II items and domains.

The two appraisers discussed any criterion that had a scoring discrepancy of 3 points or more out of 7. If, following the discussion, an appraiser changed their

mind, they were permitted to change their score but the appraisers did not need to reach consensus.

Calculating Domain Scores

We combined the appraisers' scores according to the instructions in the AGREE II users' manual. A separate quality score was calculated for each domain by summing up the scores from the appraisers for all the items in the domain and expressing it as a percentage of the maximum possible score to give a scaled domain score as follows:⁷⁰

$$\text{Scaled domain score} = \frac{\text{obtained score} - \text{minimum possible score}}{\text{maximum possible score} - \text{minimum possible score}}$$

Inter-rater reliability

We measured inter-rater reliability using Cohen's weighted kappa.⁷⁴ We selected this measure because our study is a fully crossed design with two observers (i.e., the same two appraisers reviewed all the guidelines), which Cohen's weighted kappa is designed to handle. Cohen's weighted kappa is frequently used for categorical measures with an ordinal scale (such as AGREE II's 1 to 7 scales) because the weighting allows for a greater penalty to values that are further apart.⁷⁵ We calculated inter-rater reliability for each of the six domain scores as well as for overall guideline quality. We used the guidelines from Landis and Koch to interpret kappa values: 0.0 to 0.2 indicate slight agreement, 0.21 to 0.40 indicate fair agreement, 0.41 to 0.60 indicate moderate agreement, 0.61 to 0.80 indicate substantial agreement, and 0.81 to 1.0 indicate almost perfect or perfect agreement.⁷⁶ Inter-rater reliabilities were assessed before and after the appraisers discussed the scores with discrepancies and potentially changed their scores.

Statistical software

Domain scores were calculated using Microsoft Excel. Inter-rater reliability was determined using SAS 9.4.

Results

Ten guidelines from North America, Europe and Australasia met our inclusion criteria (Table 2-1). Most of the guidelines recommend a combination of intramuscular ceftriaxone (the North American and Singapore guidelines recommend 250mg^{17,77-79} and the UK, European and Australian guidelines recommend 500mg⁸⁰⁻⁸⁵) plus 1g of oral azithromycin (although the European guidelines⁸⁰ recommend 2g, and the US CDC includes oral doxycycline twice a day for a week as an alternative to azithromycin^{77,78}). The 2013 gonorrhea chapter from the *Canadian Guidelines on Sexually Transmitted Infections*⁷⁹ and Singapore's 2009 *Management of Genital Ulcers and Discharges*⁷⁷ document allow oral cefixime as an alternative to intramuscular ceftriaxone.

The domain and overall scores for each guideline are summarized in Table 2-2 and individual scores by item for each guideline are summarized in Table 2-2 of the Supplementary Appendix. Inter-rater reliability scores are summarized in Table 2-3. Following discussion between appraisers, inter-rater reliability increased for each domain score and overall inter-rater reliability improved from 0.51 (moderate agreement as per Landis and Koch)⁷⁶ to 0.70 (substantial agreement).⁷⁶

Domain 1: Scope and Purpose

This domain considers the clarity of the guideline's overall objectives, the specific clinical questions addressed by the guideline, and the population to whom the guideline is meant to apply. Scores for this domain ranged from 38.9% (Queensland) to 88.9% (Ontario, UK, and US CDC). Most of the guidelines scored high in this domain. Only one guideline scored below 50%.

Domain 2: Stakeholder Involvement

This domain considers whether all relevant professional groups were represented on the guideline development group, whether patients in the target group were consulted regarding their options or preferences, and whether the target users of the guideline are clearly identified. Scores ranged from 22.2% (Melbourne)

to 69.4% (UK). Seven out of ten guidelines scored above 50%. Guidelines scored particularly poorly on the item “The views and preferences of the target population (patients, public, etc.) have been sought”; all but one gave no indication of having consulted the target population. The one that mentioned having consulted the target population gave no description of who was consulted or how.

Domain 3: Rigour of Development

This domain relates to the process used for collecting, reviewing, and synthesizing existing evidence and using it to develop guideline recommendations as well as the process for updating the guideline. Scores ranged from 5.2% (Melbourne) to 89.6% (UK). Six out of ten guidelines scored below 50%. Information was frequently lacking for the following items: “A procedure for updating the guideline is provided”, “Systematic methods were used to search for evidence”, “The criteria for selecting the evidence are clearly described”, “The guideline has been externally reviewed by experts prior to its publication”, “The methods for formulating the recommendations are clearly described”, and “The strengths and limitations of the body of evidence are clearly described”.

Domain 4: Clarity of Presentation

This domain considers the clarity of the wording of the recommendations, the clarity of the presentation of different management options, and how easily identifiable key recommendations are. Scores for this domain ranged from 47.2% (Queensland) to 91.7% (*Australian STI Management Guidelines for Use in Primary Care*). All but one guideline scored above 50% for this domain.

Domain 5: Applicability

This domain considers whether or not: facilitators and barriers to implementing the recommendations are addressed, recommendations or tools to assist in implementing the recommendations are provided, the resource implications of the guideline’s recommendations are considered, and the guideline provides monitoring and/or auditing criteria. Scores ranged from 4.2% (Melbourne) to 66.7%

(*Australian STI Management Guidelines for Use in Primary Care*). All but three guidelines scored below 50% for this domain. Most guidelines did not provide auditing or monitoring criteria, and did not address potential resource implications of applying the guideline's recommendations (such as the need to provide intramuscular antibiotics).

Domain 6: Editorial Independence

This domain considers the influence of the funding body on the guideline's content and whether or not the potential conflicts of interest of individuals involved in the development of the guidelines have been recorded and addressed. Scores for this domain ranged from 0% (Melbourne, Queensland, and *Western Australia Silver Book*) to 91.7% (*Australian STI Management Guidelines for Use in Primary Care*). Only three guidelines scored above 50% for this domain. Several guidelines did not address how conflicts of interest of developers were recorded and addressed. Guidelines also often did not state whether or not the funding body's views influenced the guideline's content.

Overall quality

Overall quality scores from the appraisers ranged from 2 (Queensland) to 6 (UK and US CDC) out of 7. As *Rigour of Development* ultimately affects the scientific basis of the recommendations made, it can be considered as the most important domain when assessing the quality of a guideline. The *2012 European Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults*, the US CDC's *Sexually Transmitted Diseases Guidelines*, and the *UK National Guideline for the Management of Gonorrhoea in Adults* deserve recognition as the only guidelines to score above 50% in *Rigour of Development*. Over the 5-year time frame during which the reviewed guidelines were released, we did not see a trend towards improvement in quality between guidelines over time. However, in Australia, the most recent *Australian STI Management Guidelines for Use in Primary Care* did score better than earlier state guidelines.

Discussion

Using the AGREE II tool to assess the quality of current clinical guidelines for the treatment of gonococcal infections, we determined that quality varied considerably between guidelines. The guidelines generally scored high on *Scope and Purpose*, and *Clarity of Presentation*. *Stakeholder Involvement*, *Rigour of Development*, *Applicability*, and *Editorial Independence* scores varied. Key guideline development information, such as the evidence review process, methods used for formulating recommendations, and potential conflicts of interest were often missing. Most guidelines did not include suggestions as to how the guideline could be put into practice nor did they address potential resource implications of most guidelines' recent change in recommended treatment from an oral to an intramuscular antibiotic.

This is the first systematic review of guideline quality that we could find in the literature reviewing treatment guidelines for a sexually transmitted infection. Our review used a large number of databases in order to identify guidelines that were published in peer-review journals as well as in the grey literature. The use of the AGREE II tool is an additional strength as it was developed by a large group of experts in the area of clinical guidelines and has been validated;^{70, 86, 87} it has also been applied to clinical guidelines in a range of medical areas.⁸⁸⁻⁹¹

Limitations of our study include the restriction of our analysis to English language guidelines, which excluded one additional guideline found in our search.⁹² In addition, we only assessed publicly available information in order to assess the information that is reported transparently to the medical community; this method can be considered as a limitation in that it does not allow us to differentiate between items that were addressed but not reported from items that were not addressed by guideline developers. Although we attempted to identify all publicly available material on each guideline through searching multiple databases and within each guideline and its website, it is possible that we missed some material. However, we have likely identified the material that a general guideline user is likely to access and work with.

Our results were similar to other reviews of guidelines in other clinical areas.⁸⁸⁻⁹¹ In general, other reviews found that guidelines often did well in *Scope and Purpose*, and *Clarity of Presentation* but had mixed results in *Rigour of Development*, *Applicability*, and *Editorial Independence*.

In light of ongoing concerns regarding the impact of antibiotic selection on resistance patterns as well as treatment failure, high quality up to date clinical treatment recommendations for gonococcal infections are important to prevent further drug resistance. Some of the guidelines that we reviewed are “parent” guidelines that have been used by other jurisdictions to create “daughter” guidelines based on the original guideline; this broad use of existing guidelines to guide clinical care in other jurisdictions underlines the importance of well-developed and transparent guidelines. The results of our systematic review, using the AGREE II to assess guideline quality, can help guideline developers understand limitations in current clinical guidelines and identify ways to improve on guideline quality in future versions. Most of the reviewed guidelines could be improved by focusing on *Rigour of Development* and reporting the details of their development process, addressing and recommending solutions for potential issues with implementation (such as the introduction of intramuscular antibiotics), and addressing editorial independence and conflicts of interest. In addition, guideline developers may wish to use the AGREE II to guide their guideline development and reporting process and identify information to report on in guideline documents.

Conclusion

Clinical guidelines for the management of gonorrhea may help to slow further spread of antimicrobial resistance as well as prevent transmission of infection and disease sequelae due to treatment failure. By considering the AGREE II criteria during guideline development and disclosing further details on the guidelines development process, guideline developers can improve users' confidence that their recommendations are evidence-informed.

Table 2-1. Summary of selected guidelines.

Guideline	Country or jurisdiction	Author organization	Publication year	First-line treatment for uncomplicated infection
<i>Australian STI Management Guidelines for Use in Primary Care</i> ⁸²	Australia	Australasian Sexual Health Alliance	2014	Ceftriaxone 500mg IM once PLUS Azithromycin 1g PO once
<i>Canadian Guidelines on Sexually Transmitted Infections</i> ⁷⁹	Canada	Public Health Agency of Canada (PHAC)	2013	Ceftriaxone 250mg IM once OR Cefixime 800mg PO once PLUS Azithromycin 1g PO once
<i>Guidelines for the Testing and Treatment of Gonorrhea in Ontario</i> ¹⁷	Canada (Ontario)	Public Health Ontario (PHO)	2013	Ceftriaxone 250 mg IM once PLUS Azithromycin 1 g PO once
<i>Melbourne Sexual Health Centre Treatment Guidelines</i> ⁸⁴	Australia (Melbourne)	Melbourne Sexual Health Centre	2012	Ceftriaxone 500mg IM once PLUS Azithromycin 1g PO once
<i>2012 European Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults</i> ⁸⁰	Europe	International Union Against Sexually Transmitted Infections (IUSTI)	2012	Ceftriaxone 500mg IM once PLUS Azithromycin 2g PO once
<i>Queensland Sexual Health Clinical Management Guidelines</i> ⁸⁵	Australia (Queensland)	Queensland Health	2010 (updated 2012)	Ceftriaxone 500mg IM once PLUS Azithromycin 1g PO once “in some parts of Australia due to the development of antimicrobial resistance.”
<i>Sexually Transmitted Diseases Treatment Guidelines</i> ⁷⁸	United States	Centers for Disease Prevention and Control (CDC)	2010 (updated 2012)	Ceftriaxone 250 mg IM once PLUS either Azithromycin 1 g PO once OR doxycycline 100 mg PO twice a day for 7 days
<i>UK National Guideline for the Management of Gonorrhoea in Adults</i> ⁸¹	United Kingdom	British Association for Sexual Health and HIV (BASHH)	2011	Ceftriaxone 500mg IM once PLUS Azithromycin 1g PO once
<i>Silver Book. Guidelines for Managing Sexually Transmitted Infections (4th edition)</i> ⁸³	Australia (Western Australia)	Government of Western Australia Department of Health	2010	Ceftriaxone 500mg IM once PLUS Azithromycin 1g PO once
<i>Management of Genital Ulcers and Discharges</i> ⁷⁷	Singapore	Singapore Ministry of Health	2009	Ceftriaxone 250 mg IM OR cefixime 400 mg PO once PLUS all patients should be given concurrent treatment for chlamydia*

*doxycycline 100mg PO twice a day for 7 days OR azithromycin 1g PO once OR erythromycin 500mg PO four times a day for 7 days or 500mg PO twice a day for 14 days OR ofloxacin 200mg PO twice a day or 400 mg PO daily for 7 days

Table 2-2: Summary table of scaled domain scores by guideline.

Guideline	Domain - with scaled domain score given as a %						Overall (1-7)
	Scope & Purpose	Stakeholder Involvement	Rigour of Development	Clarity of Presentation	Applicability	Editorial Independence	
<i>Australian STI Management Guidelines for Use in Primary Care</i> ⁸²	83.3%	52.7%	9.4%	91.7%	66.7%	91.7%	4.5
<i>Canadian Guidelines on Sexually Transmitted Infections</i> ⁷⁹	80.6%	63.9%	46.9%	77.8%	29.2%	4.2%	4.5
<i>Guidelines for the Testing and Treatment of Gonorrhea in Ontario</i> ¹⁷	88.9%	55.6%	26.0%	80.6%	29.2%	33.3%	4
<i>Melbourne Sexual Health Centre Treatment Guidelines</i> ⁸⁴	66.7%	22.2%	5.2%	63.9%	4.2%	0	2.5
<i>2012 European Guideline on the Diagnosis and Treatment of Gonorrhoea in Adults</i> ⁸⁰	55.6%	36.1%	62.5%	66.7%	14.6%	58.3%	4
<i>Queensland Sexual Health Clinical Management Guidelines</i> ⁸⁵	38.9%	36.1%	14.6%	47.2%	6.3%	0	2
<i>Sexually Transmitted Diseases Treatment Guidelines (US CDC)</i> ⁷⁸	88.9%	61.1%	85.4%	66.7%	41.7%	8.3%	6
<i>UK National Guideline for the Management of Gonorrhoea in Adults</i> ⁸¹	88.9%	69.4%	89.6%	88.9%	64.6%	83.3%	6
<i>Silver Book. Guidelines for Managing Sexually Transmitted Infections (4th edition)</i> ⁸³	80.6%	66.7%	15.6%	86.1%	33.3%	0	4
<i>Management of Genital Ulcers and Discharges (Singapore)</i> ⁷⁷	80.6%	61.1%	28.1%	72.2%	58.9%	8.3%	3.5

Table 2-3: Inter-rater reliability before and following appraisers' discussions of scores with discrepancies.

Domain	Initial Cohen's weighted kappa (95% CI)	Cohen's weighted kappa (95% CI) following appraisers' discussion
Scope & Purpose	0.33 (0.10-0.55)	0.37 (0.14-0.59)
Stakeholder Involvement	0.49 (0.27-0.70)	0.62 (0.46-0.78)
Rigour of Development	0.52 (0.39-0.65)	0.72 (0.65-0.80)
Clarity of Presentation	0.18 (-0.01-0.37)	0.47 (0.25-0.70)
Applicability	0.55 (0.38-0.72)	0.72 (0.60-0.83)
Editorial Independence	0.29 (0.04-0.54)	0.73 (0.54-0.91)
Overall score	0.51 (0.44-0.58)	0.70 (0.65-0.74)

Supplementary Appendix for Chapter 2

Table S2-1: Summary of database searches

Source	Search terms	Number of hits	Number of guidelines found	Number meeting inclusion criteria	Number of duplicates from a previously used source	Number of new guidelines meeting inclusion criteria
Medline	Gonorrhea/ or Neisseria gonorrhoeae/ or gonorrh*.tw. or gonococc*.tw. or (neisseria adj2 gonorrh*).tw. and exp guideline/ or Practice Guidelines as Topic/ or Guidelines as Topic/ or Health Planning Guidelines/ or Clinical Protocols/ or Critical Pathways/ or (best adj2 practice*).tw. or (clinical adj2 pathway*).tw. or (practice adj2 pathway*).tw. or guideline*.tw.	435	48	2	2	0
Pubmed	((("Gonorrhea"[Mesh]) OR "Neisseria gonorrhoeae"[Mesh]) AND ("Guideline" [Publication Type] OR "Practice Guideline" [Publication Type] OR "Health Planning Guidelines"[Mesh])	36	27	3	3	0
Embase	gonorrhea/ or Neisseria gonorrhoeae/ or gonorrh*.tw. or gonococc*.tw. or (neisseria adj2 gonorrh*).tw. and practice guideline/ or health care planning/or clinical protocol/ or clinical pathway/ or guideline*.tw.	1104	85	2	1	1
National Guideline Clearinghouse	gono*	62	62	2	2	0

Source	Search terms	Number of hits	Number of guidelines found	Number meeting inclusion criteria	Number of duplicates from a previously used source	Number of new guidelines meeting inclusion criteria
GIN	gono*	11	11	3	2	1
CMA Infobase	gonorrhea	6	6	3	1	2
Trip Database	gono*	3,357	357	4 (plus 2 that could not access/assess)	1	3
NICE	Browsed through list of guidelines under "Infections", "Sexually transmitted infections", "Antibiotic Use", "Gynecological conditions" and "Urological conditions".	0	0	0	0	0
SIGN	Browsed through list of guidelines under "Sexually transmitted infections", "Obstetrics and gynecology", and "Other"	0	0	0	0	0
Australian Government National Health and Medical Research Council Clinical Practice Guidelines Portal	Browsed under "Infection", "Sexually Transmitted Disease"	15	15	2	1	1
Google (first 5 pages)	Gonorrhea treatment guidelines	790,000 (viewed first 5 pages – 50 results)	15	8	6	2
Google Scholar (first 5 pages)	Gonorrhea treatment guidelines	21,900 (viewed first 5 pages – 50 results)	7	1	1	0
Referenced in other guidelines		-	-	1	-	1

Table S2-2: Average of appraisers' scores for each guideline by item.

	Australia Primary Care ⁸²	Canada ⁷⁹	Ontario ¹⁷	Melbourne ⁸⁴	Europe ⁸⁰	Queensland ⁸⁵	US ⁷⁸	UK ⁸¹	Western Australia ⁸³	Singapore ⁷⁷
Domain 1: Scope & Purpose										
The overall objective(s) of the guideline is (are) specifically described.	6	6	6.5	5	3.5	3.5	6.5	7	6.5	6.5
The health question(s) covered by the guideline is (are) specifically described.	5.5	4.5	7	4.5	4	2	6	5.5	5	5.5
The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	6.5	7	5.5	5.5	5.5	4.5	6.5	6.5	6	5.5
Domain 2: Stakeholder Involvement										
The guideline development group includes individuals from all relevant professional groups.	5	7	5.5	2	3.5	3	5	4	6.5	5.5
The views and preferences of the target population (patients, public, etc.) have been sought.	1	1.5	1.5	1	1	1	3	5	1.5	1.5
The target users of the guideline are clearly defined.	6.5	6	6	4	5	5.5	6	6.5	7	7
Domain 3: Rigour of Development										
Systematic methods were used to search for evidence.	1.5	1	1.5	1	6.5	1	7	7	1	1.5
The criteria for selecting the evidence are clearly described.	1	1	1	1.5	6	1	6.	6	1	1
The strengths and limitations of the body of evidence are clearly described.	1	5.5	5	1	5.5	1	5	6.5	1	5.5
The methods for formulating the recommendations are clearly described.	2	1.5	1	1	1.5	1	6	7	1	2
The health benefits, side effects, and risks have been considered in formulating the recommendations.	3.5	4.5	3.5	2.5	4.5	4.5	6	5	2.5	2
There is an explicit link between the recommendations and the supporting evidence.	1.5	5.5	5.5	1.5	6	2.5	6	5.5	1.5	4.5
The guideline has been externally reviewed by experts prior to its publication.	1	7	2	1	5	1	5.5	7	5	1
A procedure for updating the guideline is provided.	1	4.5	1	1	3	3	7	7	2.5	4
Domain 4: Clarity of Presentation										
The recommendations are specific and unambiguous.	7	5.5	5.5	4.5	6	4	4.5	7	6.5	6
The different options for management of the condition or health issue are clearly presented.	5.5	5.5	5	5	6.5	5	6.5	6.5	6.5	4.5
Key recommendations are easily identifiable.	7	6	7	5	2.5	2.5	4	5.5	5.5	5.5
Domain 5: Applicability										
The guideline describes facilitators and barriers to its	5.5	4	3.5	1	3.5	2	4	4	3	5.5

	Australia Primary Care ⁸²	Canada ⁷⁹	Ontario ¹⁷	Melbourne ⁸⁴	Europe ⁸⁰	Queensland ⁸⁵	US ⁷⁸	UK ⁸¹	Western Australia ⁸³	Singapore ⁷⁷
application.										
The guideline provides advice and/or tools on how the recommendations can be put into practice.	6.5	4.5	5	2	2	1.5	6.5	3	6	4
The potential resource implications of applying the recommendations have been considered.	2	1	1.5	1	1	1	2.5	5.5	2	3.5
The guideline presents monitoring and/or auditing criteria.	6	1.5	1	1	1	1	1	7	1	5
Domain 6: Editorial Independence										
The views of the funding body have not influenced the content of the guideline.	7	1	5	1	3	1	1.5	6.5	1	1.5
Competing interests of guideline development group members have been recorded and addressed.	6	1.5	1	1	6	1	1.5	5.5	1	1.5

Chapter 3 - The antibiotic management of gonorrhea in Ontario following multiple changes in guidelines: An interrupted time series analysis

Abstract

Background: Due to antibiotic resistance, the *Canadian Guidelines for Sexually Transmitted Infections* updated their gonorrhea treatment recommendations in 2008, 2011 and 2013. In 2013, for the first time, Ontario introduced their own recommendations: *Guidelines for the Testing and Treatment of Gonorrhea in Ontario*, which Ontario physicians are expected to follow in lieu of the Canadian ones. For both the Canadian and Ontario guidelines to date, dissemination has consisted largely of passive strategies to promote awareness of the guidelines. This study assesses adherence to gonorrhea treatment guidelines in Ontario in relation to changes in guidelines.

Methods: We analyzed treatment data for all gonorrhea cases reported in Ontario between January 2006 and May 2014. We conducted interrupted times series analyses of the use of first-line treatment according to the guidelines in place at the time and the use of specific antibiotics over time, using the introduction of the new Canadian recommendations in 2008 and 2011, and the Ontario Guidelines in 2013 as interruptions.

Results: Following the release of the 2011 recommendations, adherence dropped substantially by 61% to less than 30%. Adherence slowly recovered but did not return to baseline before the 2013 guidelines were released when adherence dropped by 12.5%. Adherence is slowly recovering but by May 2014, had only reached approximately 60%.

Discussion: Due to antibiotic resistance concerns, gonorrhea treatment guidelines need to be regularly updated. Our study showed slow uptake following dissemination of updated guidelines, particularly those with major changes in recommendations. Over a year after the new Ontario guidelines were released, 40%

of cases are not receiving recommended treatment, putting them at risk of treatment failure and potentially promoting further development of drug resistance. Greater attention should be devoted to dissemination and implementation of guidelines with significant recommendation changes.

Background

With current trends in gonorrhea antimicrobial resistance, we may soon face untreatable multidrug resistant infections.^{68, 69} The World Health Organization highlights “effective prevention and control of gonococcal infections” including “appropriate treatment regimens” as key in slowing the progression of antimicrobial resistance.⁹³ Clinical guidelines assist clinicians in selecting appropriate treatment regimens. Due to rapidly evolving resistance patterns, gonorrhea treatment recommendations have changed frequently. In Canada, within four years, the *Canadian Guidelines on Sexually Transmitted Infections*’ first-line gonorrhea treatment changed twice: first with the removal of fluoroquinolones in 2008,^{16, 94} then in 2011 with the doubling of recommended doses of cefixime and ceftriaxone, the first-line recommendation that ceftriaxone be used to treat men who have sex with men (MSM) as well as pharyngeal infections, and the addition of combination gonorrhea therapy with azithromycin for all cases.^{15, 79} In Ontario, the 2013 *Guidelines for the Treatment and Management of Gonococcal Infections in Ontario* introduced a third change, making intramuscular ceftriaxone plus azithromycin the only first-line treatment.¹⁷ Table 3-1 summarizes the recommended treatments in each new guideline.

In Ontario, gonorrhea patients are seen and managed in a variety of settings: from sexual health and sexually transmitted infection (STI) clinics to community primary care settings that infrequently manage STIs. With frequently changing recommendations, uptake of new guidelines is a concern, especially among clinicians who rarely treat gonorrhea. Past research has shown that best practice uptake in gonorrhea management is limited.^{21, 22, 53, 54, 56-60, 63, 64} Few studies have looked at STI guideline adherence in Canada and none are recent.^{39, 47, 49, 50}

The interrupted time series (ITS) design is a powerful quasi-experimental approach that can be used to evaluate the impact of an intervention such as a policy change or a new clinical guideline in real world settings. In this design, outcomes are measured repeatedly over a period of time, both before and after the intervention is introduced. A major strength of the ITS design is that it can account for underlying

secular trends in order to measure the incremental effect of an intervention.⁹⁵ Segmented regression analysis is typically used to analyze ITS data. The regression model is specified to compare change between pre- and post-intervention, and can be used to assess both immediate changes (a sudden change in level at the time of the intervention) and gradual changes (a change in slope).^{95, 96}

The purpose of this study was to use interrupted time series analysis to describe and assess changes in first-line gonorrhea treatment guideline adherence in Ontario. Our main hypotheses were that practice would lag behind guideline changes and that changes in adherence would vary with guideline releases, based on the scope of the guideline changes. For example, in 2008, only clinicians prescribing fluoroquinolones would need to change their behaviour; however, in 2011, all clinicians would need to double prescribed doses of cephalosporins and prescribe azithromycin combination therapy, and in 2013, clinicians who have not already done so would need to begin prescribing ceftriaxone for all gonorrhea cases.

Methods

Dataset

We analyzed data from Ontario's Integrated Public Health Information System (iPHIS). Local Ontario public health units use iPHIS to submit information on reportable diseases to the Ministry of Health and Long Term Care. In Ontario, physicians and laboratories are mandated by law to report all diagnosed cases of gonorrhea to their local public health unit. Our dataset consisted of all reported gonorrhea cases in Ontario between January 1, 2006 and May 31, 2014 and included sex, infection site(s), treatment, date public health was notified, and whether the patient self-identified as having sex with members of the same sex.

We excluded cases without gonorrhea treatment data and those with either a disseminated or conjunctival infection as the treatment recommendations for these infections differ from those for uncomplicated infections in other sites.⁷⁹

We classified the prescribed antibiotics into drug families as summarized in Table 3-2.

For each patient, we defined a dichotomous indicator for whether or not the patient had received first-line treatment according to the clinical guidelines of the time, considering the provincial guidelines, when they exist, to be the guidelines of the time. Box S3-1 in the supplementary appendix summarizes the criteria used to define adherence to first-line treatment recommendations. Reporting dates were classified into biweekly time intervals. For each interval, we calculated the aggregate percentage of cases receiving first-line treatment and specific antibiotics. We considered a guideline to be in effect as of the first biweekly interval in the month following the guideline's release.

Interrupted time series analyses

We used a segmented autoregressive linear regression model to analyze changes in the percentage of cases receiving first-line treatment over time following the 2008, 2011 and 2013 guideline updates. As secondary analyses, we conducted separate interrupted times series analyses for cefixime, ceftriaxone, and each drug family that had been a first-line gonorrhea treatment in the past ten years. We conducted the analysis using the autoreg procedure in SAS 9.4. We tested each model for stationarity using the Engle-Granger cointegration test.

In a segmented regression analysis, it is important to allow for autocorrelation, i.e., correlation between successive outcome measurements.⁹⁵ Failure to account for autocorrelation can lead to spurious conclusions about the effect of the intervention. We tested for autocorrelation using the Durbin-Watson test. Where autocorrelation was detected, we included the autoregressive parameters in the model. For simplicity and interpretability, all analyses were conducted on the percentage scale with changes expressed as absolute differences in percentage. We examined the fit of the models using log-likelihood ratio tests, histograms of residuals, normal probability plots, and partial autocorrelation function plots. To account for potential non-linear trends over time and/or deviations from the normal assumption, we repeated the analyses on the log-odds (logit) scale, with changes expressed as relative differences.

Results

Overall, 34,287 gonorrhea cases were reported between January 1, 2006 and May 31, 2014. Treatment data was available for 32,312 (94.2%) cases. Our analysis included 32,272 (94.1%) cases without either a conjunctival or disseminated infection. The monthly number of cases increased gradually over time (biweekly range: 64 to 229 cases). Figure S3-1 in the supplementary appendix shows the monthly distribution of cases.

Adherence to first-line treatment recommendations

Figure 3-1 shows the observed and model-based adherence rates. The results of the segmented regression analysis are presented in Table 3-3. Initially, approximately 90% of cases received guideline-recommended first-line treatment; this level remained relatively stable until 2008. No statistically significant changes were observed after the introduction of new recommendations in 2008 although a gradual reduction in adherence was evident between 2008 and 2011 prior to the 2011 guideline update, where the use of first-line treatment was 82.3%. After the 2011 update to the Canadian recommendations, there was a sudden absolute decline in first-line treatment to 29.1% (a 61.4% greater absolute decrease than otherwise expected, 95% CI: 56.3 to 66.5, $p < 0.0001$) followed by a gradual increase in uptake over time ($p < 0.0001$), reaching 58.3% just prior to the release of the Ontario guidelines. Following the introduction of the new 2013 Ontario guidelines, use of first-line treatment dropped to 42.2% (a 12.5% greater absolute decrease than otherwise expected, 95% CI: 6.6 to 18.4, $p < 0.0001$) and then increased over time, albeit at a slower rate than before ($p = 0.0042$). By the end of the study, adherence to first-line recommended treatment had reached 59.1%, substantially lower than at the beginning of the observation period.

Specific antibiotic use

Figure 3-2 presents the observed and model-based cefixime and ceftriaxone prescription patterns. The results of the segmented regression analyses are

presented in Table S3-1 of the supplementary appendix. Until 2011, the relative frequencies of cefixime and ceftriaxone use remained around 85% and below 5% respectively. After the 2011 guideline change, cefixime use dropped from 85.3% to 79.0% (a 5.8% greater absolute decrease than otherwise expected, 95% CI: 1.4 to 10.3, $p=0.002$) while ceftriaxone use increased from 8.9% to 14.5% (a 4.9% greater absolute increase than otherwise expected, 95% CI: 1.4 to 8.4, $p=0.007$). Following these recommendations, the relative frequency of cefixime use decreased ($p<0.0001$) and the relative frequency of ceftriaxone use increased over time ($p<0.0001$). With the introduction of the 2013 Ontario recommendations, an immediate drop in cefixime use from 61.1% to 39.1% (a 21.5% greater absolute decrease than otherwise expected, 95% CI: 17.0 to 26.0, $p<0.0001$) and a corresponding increase in ceftriaxone use from 36.3% to 58.9% (a 22.1% greater absolute increase than otherwise expected, 95% CI: 17.8 to 26.4, $p<0.0001$) were observed. Following the new recommendations, ceftriaxone use continued to increase and cefixime use continued to decrease at levels not different than those following the introduction of the 2011 Canadian recommendations. By May 2014, 71.6% of cases were treated with ceftriaxone and 26.3% of cases were treated with cefixime, suggesting that most patients receiving non-first-line treatment were treated with cefixime.

In early 2011, when a decrease in first-line treatment not related to a new guideline was noted, a small decline in cefixime use and corresponding rise in ceftriaxone use were observed.

Use of main antibiotic families

Figure 3-3 shows the observed and model-based use of antibiotic families over time, while Table S3-2 shows the results of the segmented regression analyses. Initial cephalosporin (including cefixime and ceftriaxone) use was 87.5% and increased gradually with no changes in trend corresponding to any guideline change. The rate of fluoroquinolone use (not a first-line option since 2008) started at 12.4% and gradually decreased with a small number of cases (2.4%) still receiving fluoroquinolones in 2014.

Initial use of macrolides (including azithromycin) was 74.6%, likely because treatment for chlamydia is recommended unless a negative test result is available. Following the release of the 2011 update that recommended combination therapy with azithromycin for all cases, a sudden increase in macrolide use from 69.7% to 76.2% (a 6.2% greater absolute increase than otherwise expected, 95% CI: 3.4 to 9.0, $p < 0.0001$) was observed followed by increased uptake over time. Following the introduction of the 2013 Ontario guidelines, another sudden increase in uptake from 86.2% to 90.5% (a 4.3% greater increase than otherwise expected, 95% CI: 0.7 to 8.0, $p = 0.022$) was noted followed by a continued rise.

Interpretation

This study showed that adherence to first-line treatment recommendations for gonorrhea in Ontario dropped following guideline changes. A small change (e.g., in 2008, infrequently used fluoroquinolones were removed as first-line treatment) had minimal effect on adherence. After major changes (e.g., in 2011 when recommended doses were doubled and combination therapy was introduced and intramuscular ceftriaxone was made the only first-line treatment option for MSM and pharyngeal infections, or in 2013 when Ontario removed cefixime as first-line treatment), substantial reductions in adherence were noted. These reductions were both statistically and clinically significant; after each major change, fewer than 50% of cases received recommended treatment. Following these changes, adherence gradually increased but, by May 2014, guideline adherence remained well below the rates prior to 2011. It appears that most cases not treated according to current Ontario guidelines receive cefixime; however, fluoroquinolones are still used. Non-adherence to the Ontario guidelines' first-line treatment recommendations may be due to continued use of the Canadian guidelines, challenges in providing intramuscular antibiotics in some settings, patient drug allergy, medical contraindications to azithromycin, or patients refusing injections.

To examine other factors coinciding with guideline changes that might influence physician behaviour, we searched Pubmed and Canadian Newstand,

looking for articles in major medical journals and news stories on gonorrhea in the three months before and after each recommendation was released. Publications found in both medical journals and national or Ontario-based newspapers highlighted antimicrobial resistance trends and likely would have, if anything, promoted current guideline use^{5, 8, 9, 69, 80, 81, 97-107} (the publications are summarized in Box S3-2). We similarly investigated a decline in guideline adherence and an increase in ceftriaxone use in early 2011 that was not related to a guideline change. We searched the same databases for publications between November 1, 2010 and June 30, 2011. Case reports of treatment failure with cephalosporins in Europe and Japan^{6, 7, 10, 108} were published during this time. In addition, cases of cefixime treatment failure in Toronto were reported in early 2011.⁵ Some clinicians may have been aware of these cases and preemptively changed their prescribing behaviour.

Our study was unique in its longitudinal analysis of clinician behaviour across multiple changes in gonorrhea treatment guidelines. Other studies have undertaken cross-sectional analysis of adherence to guideline first-line treatment recommendations,^{21, 54, 56-58, 60} examined changes in trend of guideline adherence,⁵³ or compared behaviour before and after a single guideline change.^{22, 59, 63} Two studies used interrupted time series analyses to look at fluoroquinolone use before and after the US guidelines stopped recommending its use.^{22, 63} Studies that assessed variation of adherence patterns between practitioners found that guideline adherence varied by geographic location^{22, 53, 56}, type of practice (e.g., specialized STI or genitourinary medicine clinics are more likely to adhere to guidelines),^{53, 54, 56, 59, 64} and number of gonorrhea cases treated at a location or by a provider.^{57, 59} US studies on ceftriaxone use found higher guideline adherence than our study.^{53, 56, 57, 59}

Our study has several limitations. The iPHIS database was designed for administrative purposes and only includes information reported to public health. Treatment information may be incomplete if a patient is re-treated without notifying public health. Data are collected and entered locally, and methods may differ between health units. A second limitation is that we did not consider treatment dates when determining whether a case had received first-line treatment. Some cases received multiple courses of treatment and were considered as having received the

first-line treatment if they received the appropriate dose(s) of antibiotics at any point. The proportions of cases receiving first-line treatment would have been lower if we had only considered those who initially received the recommended treatment or who received both combination therapy drugs at the same time as having received first-line treatment. Thirdly, we did not conduct subanalyses by geographic region, clinical setting, or physician's level of experience in managing STIs. As other studies have demonstrated differences in prescribing behaviours according to these factors,^{22, 53, 54, 56, 57, 59, 64} this would be of interest to consider in future studies. Finally, for simplicity of interpretation, we conducted analyses using an additive model and assuming a linear trend over time. Inspection of histograms of residuals and normal probability plots revealed no major departures from the modeling assumptions, and sensitivity analyses conducted on the log-odds scale (not presented) did not change the substantive conclusions of our analyses.

To date, Canadian and Ontario STI guidelines have largely been disseminated through passive strategies, such as journal write-ups, webinars, conference presentations, web materials, and mobile applications. The slow uptake of new treatment recommendations seen in this study suggests the potential need for active dissemination and implementation strategies, such as audit and feedback, outreach to clinicians who do not follow current guidelines, or reminders on current recommendations through electronic medical records.¹⁰⁹ Ineffective gonorrhea treatment has broad public health implications, through permitting transmission of infection, promoting drug resistance, and putting individuals at risk of complications of infection. As treatment recommendations will change further in response to antimicrobial resistance patterns, guideline developers and public health systems should consider ways to enhance uptake. This could also be informative to developers of guidelines for other infections with similarly rapidly evolving resistance patterns. As STIs are managed in a variety of settings, future research could define characteristics of clinicians more likely to provide optimal care following the introduction of new guidelines in order to identify targets for enhanced dissemination efforts.

Table 3-1: A summary of changes in recommendations on the treatment of gonorrhea in Canada and Ontario from 2004 to the present

Year	Jurisdiction	First-line treatment	Second line treatment
2004 (a new version of the guidelines was released in 2006 but the treatment recommendations remained the same) ^{65, 94}	Canada	Cefixime 400 mg PO, once OR Ciprofloxacin 500 mg PO, once* OR Ofloxacin 400 mg PO, once* OR Ceftriaxone 125 mg IM, once	Azithromycin 2 g PO, once OR Spectinomycin 2 g IM, once
January 2008 – chapter was updated in January 2010 but recommendations in summary table remained the same ¹⁶	Canada	Cefixime 400mg PO, once	Ceftriaxone 125 mg IM, once OR Azithromycin 2 g PO, once OR Spectinomycin 2 g IM, once OR Ciprofloxacin 500 mg PO, once OR Ofloxacin 400 mg PO, once
December 2011 ⁷⁹	Canada - update	Ceftriaxone 250mg IM, once** + Azithromycin 1 g PO, once OR Cefixime 800mg PO, once + Azithromycin 1 g PO, once	Cefixime 800mg PO, once*** + Azithromycin 1 g PO, once OR Azithromycin 2 g PO, once OR Spectinomycin 2 g IM, once + Azithromycin 1 g PO, once
April 2013 ¹⁷	Ontario	Ceftriaxone 250 mg IM, one dose + Azithromycin 1 g PO, one dose	Cefixime 400 mg PO, once + Azithromycin 1 g PO, once OR Spectinomycin 2 g IM, once + Azithromycin 1 g PO, once OR Azithromycin 2 g PO, once

* if quinolones not contraindicated due to resistance

** if patient is a man who has sex with men (MSM), or the infection is pharyngeal, this is the only first-line option

*** if patient is an MSM, or the infection is pharyngeal

Table 3-2: Classification of antibiotics entered in iPHIS for the treatment of gonorrhea into antibiotic families.

Antibiotic family	Drugs included (as entered in IPHIS)
Cephalosporins	Cephalexin, Cefuroxime, Cefoxitin, Cefixime, Ceftriaxone, Cefotaxime
Macrolides	Azithromycin, Clarithromycin, Erythromycin
Fluoroquinolones	Ciprofloxacin, Fluoroquinolones, Gatifloxacin, Levofloxacin, Moxifloxacin, Ofloxacin

Figure 3-1: Percentage of gonorrhea patients in Ontario receiving first-line treatment according to the current treatment guideline over time from January 1, 2006 to May 31, 2014

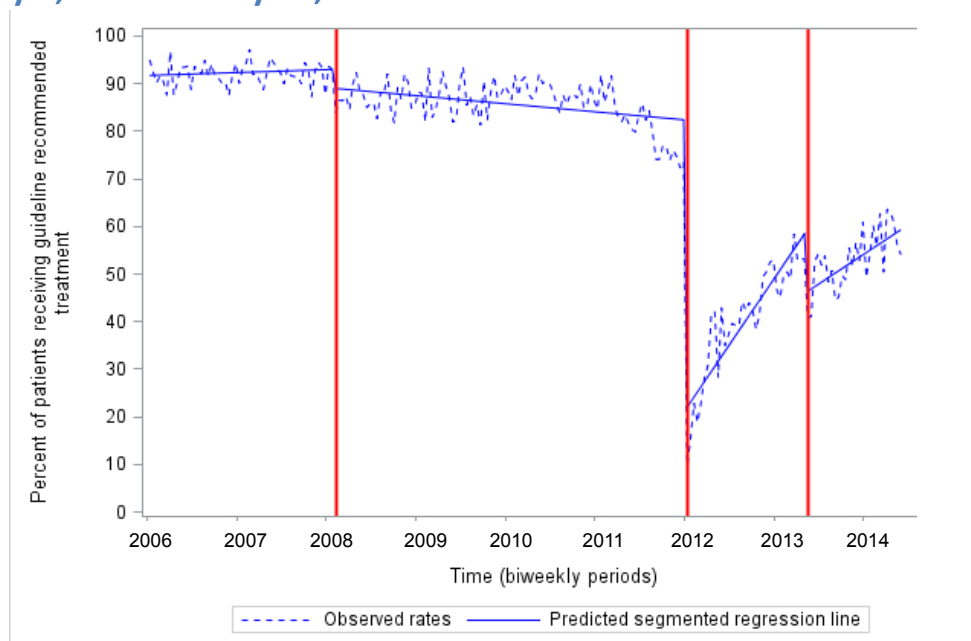


Table 3-3: Segmented regression analysis of percent adherence to current guidelines, showing regression coefficient estimates, standard errors and p-values.

	Regression coefficient	Standard error	p-value
2004 Canadian Guidelines on Sexually Transmitted Infections update (measured as of January 1, 2006)			
Intercept	91.5	2.02	<0.0001
Baseline trend	0.02	0.06	0.703
2008 Canadian Guidelines on Sexually Transmitted Infections update (January 2008)			
Level change after 2008 guideline change	-3.92	2.26	0.085
Trend change after 2008 guideline change	-0.09	0.07	0.199
2011 Canadian Guidelines on Sexually Transmitted Infections update (December 2011)			
Level change after 2011 guideline change	-61.4	2.59	<0.0001
Trend change after 2011 guideline change	1.13	0.12	<0.0001
2013 Guidelines for Testing and Treatment of Gonorrhea in Ontario (April 2013)			
Level change after 2013 guideline change	-12.5	3.03	<0.0001
Trend change after 2013 guideline change	-0.59	0.20	0.004

Figure 3-2: Percent of gonorrhea patients in Ontario receiving cefixime and ceftriaxone over time from January 1, 2006 to May 31, 2014.

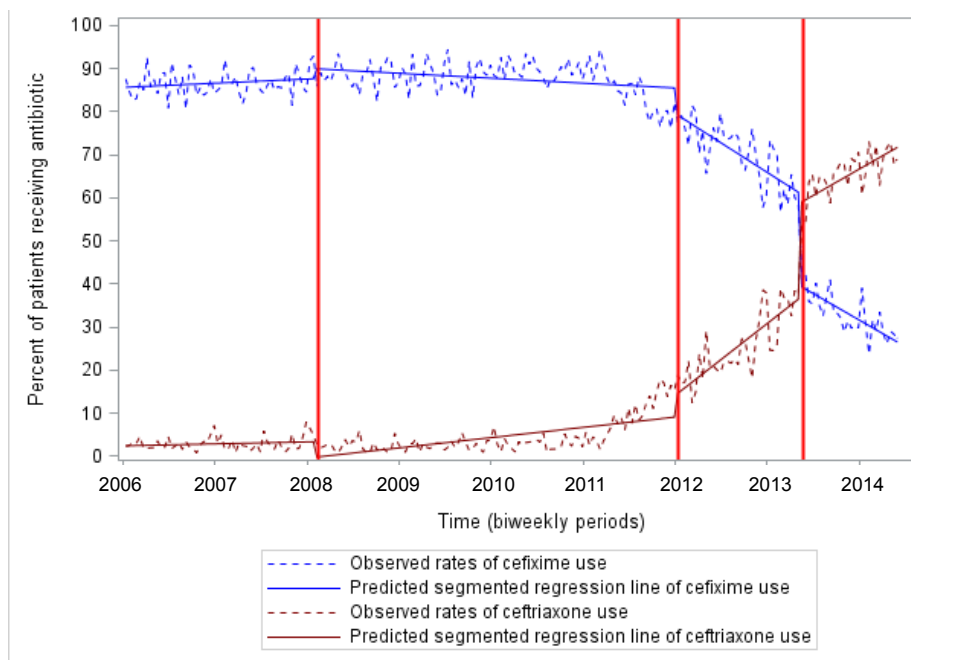
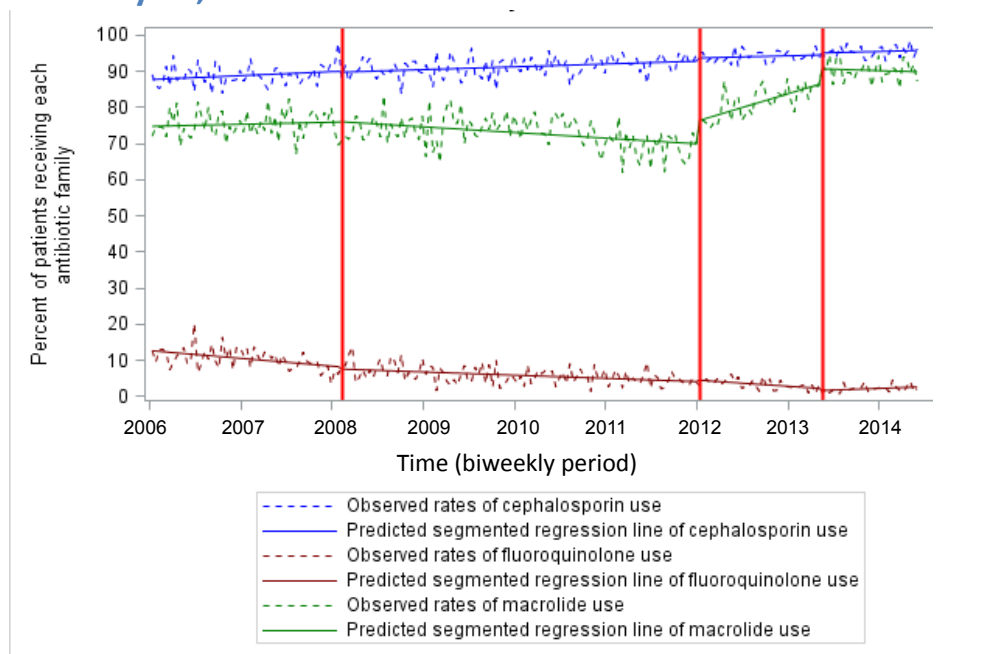


Figure 3-3: Percent of gonorrhea patients in Ontario receiving cephalosporins, macrolides, and fluoroquinolones over time from January 1, 2006 to May 31, 2014.



Supplementary Appendix for Chapter 3

Box S3-1: Criteria used to define adherence to first-line treatment recommendations.

A patient was considered to have received first-line treatment if the patient was:

- Reported to public health before February 3, 2008 and their treatment included one dose of either cefixime 400mg PO, cefixime 125mg IM, ciprofloxacin 500mg PO, or ofloxacin 400mg PO.
- Reported to public health between February 3, 2008 and January 1, 2012 and their treatment included one dose of cefixime 400mg PO.
- Reported to public health between January 2, 2012 and May 5, 2013, was not identified as a man who has sex with men (MSM) (this included both males identified in iPHIS as having sex with members of the same sex as well as males with rectal infections), did not have a lab-confirmed pharyngeal infection, and their treatment included one dose of azithromycin 1g PO plus one dose of either cefixime 800mg PO or ceftriaxone 250mg IM.
- Reported to public health between January 2, 2012 and May 5, 2013, was identified as an MSM and/or has a lab-confirmed pharyngeal infection, and their treatment included one dose of azithromycin 1g PO plus one dose of ceftriaxone 250mg IM.
- Reported to public health on or after May 6, 2013, and their treatment included one dose of azithromycin 1g PO plus one dose of ceftriaxone 250mg IM.

Figure S3-1: Reported cases of gonorrhea in Ontario by month from January 2006 to May 2014.

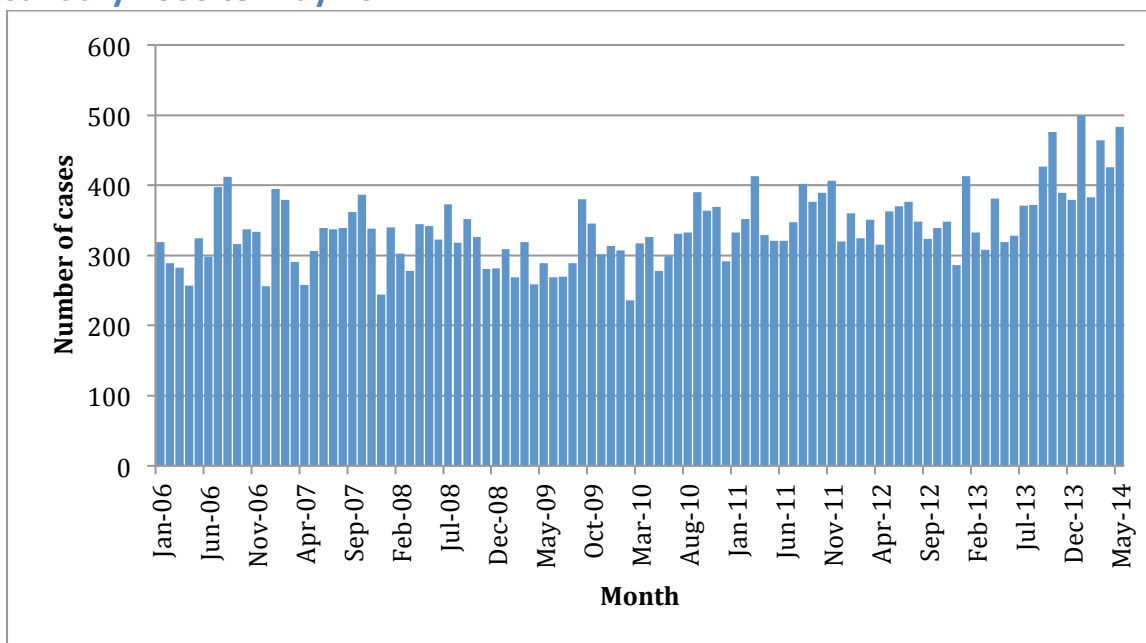


Table S3-1: Segmented regression analysis of percent use of cefixime and ceftriaxone, showing regression coefficient estimates, standard errors and p-values.

	Regression coefficient	Standard error	p-value
<i>Use of cefixime</i>			
2004 Canadian Guidelines on Sexually Transmitted Infections update (measured as of January 1, 2006)			
Intercept	85.5	1.29	<0.0001
Baseline trend	0.04	0.04	0.357
2008 Canadian Guidelines on Sexually Transmitted Infections update (January 2008)			
Level change after 2008 guideline change	2.32	1.55	0.134
Trend change after 2008 guideline change	-0.08	0.04	0.065
2011 Canadian Guidelines on Sexually Transmitted Infections update (December 2011)			
Level change after 2011 guideline change	-5.83	1.82	0.002
Trend change after 2011 guideline change	-0.48	0.08	<0.0001
2013 Guidelines for Testing and Treatment of Gonorrhea in Ontario (April 2013)			
Level change after 2013 guideline change	-21.5	2.28	<0.0001
Trend change after 2013 guideline change	0.05	0.13	0.698
<i>Use of ceftriaxone</i>			
2004 Canadian Guidelines on Sexually Transmitted Infections update (measured as of January 1, 2006)			
Intercept	2.23	1.31	0.091
Baseline trend	0.02	0.04	0.667
2008 Canadian Guidelines on Sexually Transmitted Infections update (January 2008)			
Level change after 2008 guideline change	-3.63	1.54	0.020
Trend change after 2008 guideline change	0.07	0.04	0.099
2011 Canadian Guidelines on Sexually Transmitted Infections update (December 2011)			
Level change after 2011 guideline change	4.92	1.79	0.006
Trend change after 2011 guideline change	0.55	0.08	<0.0001
2013 Guidelines for Testing and Treatment of Gonorrhea in Ontario (April 2013)			
Level change after 2013 guideline change	22.1	2.18	<0.0001
Trend change after 2013 guideline change	-0.17	0.13	0.203

Table S3-2: Segmented regression analysis of percent use of cephalosporins, fluoroquinolones, and macrolides, showing regression coefficient estimates, standard errors and p-values.

	Regression coefficient	Standard error	p-value
<i>Use of cephalosporins</i>			
2004 Canadian Guidelines on Sexually Transmitted Infections update (measured as of January 1, 2006)			
Intercept	87.5	0.64	<0.0001
Baseline trend	0.04	0.02	0.037
2008 Canadian Guidelines on Sexually Transmitted Infections update (January 2008)			
Level change after 2008 guideline change	-0.25	0.78	0.747
Trend change after 2008 guideline change	-0.01	0.02	0.568
2011 Canadian Guidelines on Sexually Transmitted Infections update (December 2011)			
Level change after 2011 guideline change	0.86	0.92	0.349
Trend change after 2011 guideline change	-0.006	0.04	0.871
2013 Guidelines for Testing and Treatment of Gonorrhea in Ontario (April 2013)			
Level change after 2013 guideline change	0.56	1.18	0.638
Trend change after 2013 guideline change	0.002	0.07	0.977
<i>Use of fluoroquinolones</i>			
2004 Canadian Guidelines on Sexually Transmitted Infections update (measured as of January 1, 2006)			
Intercept	12.5	0.51	<0.0001
Baseline trend	-0.08	0.02	<0.0001
2008 Canadian Guidelines on Sexually Transmitted Infections update (January 2008)			
Level change after 2008 guideline change	-0.64	0.62	0.305
Trend change after 2008 guideline change	0.05	0.02	0.005
2011 Canadian Guidelines on Sexually Transmitted Infections update (December 2011)			
Level change after 2011 guideline change	0.42	0.74	0.569
Trend change after 2011 guideline change	-0.03	0.03	0.323
2013 Guidelines for Testing and Treatment of Gonorrhea in Ontario (April 2013)			
Level change after 2013 guideline change	-0.61	0.97	0.532
Trend change after 2013 guideline change	0.10	0.06	0.069
<i>Use of macrolides</i>			
2004 Canadian Guidelines on Sexually Transmitted Infections update (measured as of January 1, 2006)			
Intercept	74.6	1.01	<0.0001
Baseline trend	0.02	0.03	0.491
2008 Canadian Guidelines on Sexually Transmitted Infections update (January 2008)			
Level change after 2008 guideline change	0.14	1.22	0.907
Trend change after 2008 guideline change	-0.08	0.03	0.017
2011 Canadian Guidelines on Sexually Transmitted Infections update (December 2011)			
Level change after 2011 guideline change	6.19	1.45	<0.0001
Trend change after 2011 guideline change	0.35	0.06	<0.0001
2013 Guidelines for Testing and Treatment of Gonorrhea in Ontario (April 2013)			
Level change after 2013 guideline change	4.32	1.87	0.022
Trend change after 2013 guideline change	-0.32	0.11	0.003

Box S3-2: Summary of Canadian and Ontario news items and major medical journal publications released in the three months before and after each guideline update was released.

2008 Canadian Guidelines on Sexually Transmitted Infections update:

- Some material on antimicrobial resistant gonorrhea was published in the medical literature, including a summary of the new at the time US recommendations that removed fluoroquinolones as a first-line treatment option in American Family Physician.⁹⁷

2011 Canadian Guidelines on Sexually Transmitted Infections update:

- A news story on the emergence of drug resistant gonorrhea was printed in The Globe and Mail.⁹⁸
- Material in the medical literature included updates on new US and UK recommendations,^{81, 100} studies demonstrating the presence of quinolone resistant gonorrhea in Canada,^{101, 102} and an editorial in the Canadian Medical Association Journal on the need for new strategies to address antibiotic resistance in gonorrhea.⁶⁹

2013 Guidelines for Testing and Treatment of Gonorrhea in Ontario release:

- Several articles were printed in Ontario and Canada-wide newspapers regarding antibiotic resistance in general^{99, 103-105} and one article specifically addressed the new guidelines.¹⁰⁶
- In the medical literature, around the time of the release of the 2013 Ontario guidelines, there were three articles in JAMA on cephalosporin resistant gonorrhea,^{5, 8, 9} including one paper on resistance trends in Toronto,⁵ as well as reports on the new European guidelines,⁸⁰ and the update of the US CDC's gonorrhea treatment guidelines.¹⁰⁷

Chapter 4 - Using process mapping to identify opportunities to improve the management of gonococcal infections in Canadian public health settings

Abstract

Objective: To explore the use of process mapping and routine data to model the local management of gonorrhea and identify deficiencies that could be changed to improve patient care.

Methods: Process mapping is used in business analysis to map out steps and decision points within a larger complex system. With input from clinical experts, we developed a series of process maps depicting the possible treatment pathways that a patient treated in Ottawa might follow. We flagged steps that did not comply with clinical guidelines and where loss to follow-up could occur. As an exploratory activity, we populated the initial management process map with routine reportable disease data for all cases of gonorrhea reported in Ottawa residents from January 2011 to December 2013.

Results: We developed four process maps describing initial management, treatment, public health follow-up and long-term outcomes. We identified intramuscular antibiotics use as a risk for loss to follow-up if a patient was referred on or asked to return once the drug was ordered. Symptomatic cases and known contacts were less likely to receive treatment on speculation as per current guidelines if seen in the community (vs. the sexual health clinic run by local public health).

Discussion: Using process mapping, we described treatment pathways for local gonorrhea cases and used routine surveillance data to describe the initial management of cases. We identified that interventions targeting community physicians and promoting the use of treatment on speculation for symptomatic individuals and known contacts could improve patient care.

Background

Since 1997, rates of gonorrhea infections have been on the rise in Canada.³ Gonorrhea is often asymptomatic but can have severe consequences, such as pelvic inflammatory disease, epididymitis, infertility, and disseminated infection.^{2,3} Case detection and appropriate clinical management are key in preventing its transmission.^{17,79} Cases of gonorrhea may be managed in a variety of clinical settings: from family physicians' offices where a case may only be seen every few years, to public health run sexual health clinics where cases may be seen daily.

In Ontario, the clinical treatment guidelines for gonorrhea have changed three times in six years due to rapidly evolving antimicrobial resistance patterns, including major changes such as the doubling of antibiotic doses, the addition of azithromycin co-treatment and a shift from oral cefixime to intramuscular ceftriaxone.^{17,65,79,94} Our previous work has shown that while some Ontario clinicians quickly changed their behaviour, over a year after the release of the new *Guidelines for Testing and Treatment of Gonorrhea in Ontario*,¹⁷ only 60% of cases received the recommended first-line treatment. Given the wide range of settings where cases are managed, case management practice may vary immensely between physicians with different levels of experience treating sexually transmitted infections (STIs) and familiarity with current guidelines. As the management of an STI is often a multi-step process (e.g., an initial visit, following up with laboratory results, returning for treatment, test-of-cure), it is possible for individuals to fall through the cracks and become lost to follow-up or to further transmit the infection before receiving effective treatment.

Process mapping is a business analysis tool used to map out and visualize the smaller processes that make up a larger complex system.¹¹⁰ It can be used to help identify redundancies and inefficiencies, and revise processes in order to improve quality.¹¹¹ Similar to its use in business, a process map can be used in health care to map out the steps in the management of a particular illness and to identify potential weaknesses in the system or areas for improvement.¹¹²

In this paper, we explore the use of process mapping as a means to identify the treatment pathways that patients with gonorrhea may follow within a

geographic region (the City of Ottawa). We also explore the use of routinely collected public health reportable disease data to estimate the proportions of cases that follow each treatment pathway.

Methods

Process mapping

Ottawa, Canada's national capital, is located in the province of Ontario with a population of over 950,000.¹¹³ Care for STIs is provided through Ottawa Public Health, one of Ontario's 36 local public health units but patients may also present to other clinical settings to receive care. Gonorrhea is both a nationally and provincially reportable infection. Laboratory-diagnosed cases of gonorrhea are reported to Ottawa Public Health and a public health nurse case manager follows up with the case and their care provider if the infection is being managed outside of Ottawa Public Health's sexual health clinic.

We developed a set of four process maps to illustrate the routes that an individual with gonorrhea might take to receive diagnosis and treatment. The process maps describe the initial management, administration of antibiotics, follow-up and outcomes of cases. Each process map consists of a series of steps (represented by rectangles) and decision points (represented by diamonds) leading to two or more branches of possible steps in the management of a patient.

An initial set of draft process maps was developed in consultation with STI content experts at both the local and federal level. We verified the draft with an Ottawa Public Health nurse who works as a gonorrhea case manager and adapted it based on her feedback. We designed the process maps to incorporate the two most recent clinical guidelines used in Ontario for the management of gonorrhea.^{17, 79} A summary of recent guideline recommendations is found in Table 4-1. Process map branches were colour-coded using a traffic light system: green indicates that current guidelines were followed, red indicates that current guidelines were not followed, and yellow indicates that management may have been in line with guidelines under certain circumstances (e.g., treatment on speculation is generally not recommended

for asymptomatic individuals if they are not contacts of known cases but could be recommended for a patient at high risk of exposure but unlikely to return for follow-up).⁷⁹ We also used traffic light colour-coding to highlight branches where an infectious case could be lost to follow-up (red) or not (green). Outcomes of re-infection, treatment failure and/or undiagnosed infection were colour-coded grey.

Populating first process map with data

We used local reportable disease data to show the numbers and proportions of cases in each branch of the first process map describing initial case management. We used data from the integrated Public Health Information System (iPHIS), Ontario's reportable disease database. Local public health units use iPHIS to manage reportable disease case information and to report cases to the province.¹¹⁴ We extracted data for all cases reported to public health between January 1, 2011 and December 31, 2013 with a home address within the City of Ottawa at the time of diagnosis.

We determined that a case was a known contact of another case if "contact tracing" was identified as a reason for testing in iPHIS.

If any symptoms were recorded, we identified a patient as symptomatic. We identified a patient as asymptomatic if they were identified as such in the symptom field. If no symptom information was provided, symptoms were classified as "unknown".

iPHIS captures all positive laboratory diagnostic tests for reportable communicable diseases that are reported to public health. Using this information, we classified cases according to site of infection. We classified patients as having a urogenital infection if a positive lab test from the cervix, genital tract, urethra, urine, or vagina was recorded. We also created variables to identify cases with rectal, pharyngeal (or throat), or other infections.

Microscopy with Gram stain is only considered as diagnostic for gonorrhea, and reported in iPHIS, for urethral infections in men due to its varied sensitivity in different samples.¹¹⁵ If an on-site laboratory is available, a male with a urethral infection can be diagnosed and treated at his initial visit. We considered all patients

with a urethral Gram stain or microscopy on the initial date of sample collection to have been diagnosed on initial presentation; if the patient received treatment on the same date, he was considered as “treated at time of contact”. Otherwise, we considered a patient as “treated on speculation” if the earliest sample collection date was either the same date as or after the earliest date treatment was provided.

In addition to microscopy with Gram stain, a patient can be diagnosed (or have diagnosis confirmed) with nucleic acid amplification testing (NAAT), bacterial culture or both tests. We classified patients as diagnosed by NAAT, culture, both, or neither.

We identified cases as lost to follow-up if their encounter status was either “open – lost to follow-up” or “closed – lost to follow-up”.

Most cases had provider information available. If the provider was either of the two physicians who were the sexual health clinic’s clinical director between January 1, 2011 and December 31, 2013, we classified the patient as seen at the sexual health clinic. If another provider name was listed, we classified the patient as seen in the community (this might include general practitioners’ offices, walk-in clinics, emergency departments, obstetrics and gynaecology practices, urologists’ offices, and HIV clinics). If no provider was listed, we classified the point of care as “unknown”.

Distributions were tabulated using STATA 13.0 to determine counts and proportions of cases along each process map branch. Once the count in any branch reached zero, subsequent sub-branches were left out. We also tabulated counts and proportions of cases lost to follow-up for each combination of contact/non-contact, symptom category, and point of care category. In each branch where culture or NAAT testing data was missing, the number of cases for which the data was missing was reported, noting whether the data was missing because only Gram stain with microscopy was done, a test was reported but type was missing, or no lab tests were reported.

Results

Process maps

The first process map (shown in Figures 4-1 and 4-2) describes initial management in terms of diagnostic testing and timing of treatment by whether the individual is a contact of a known case (Figure 4-2) or not (Figure 4-1), whether or not the individual is symptomatic, and the point of care where the individual is seen (i.e., the sexual health clinic or the community). We identified pathways as consistent with guidelines as follows:

- If symptomatic, treatment on speculation or following microscopy with Gram stain is recommended.^{17, 79}
- For known contacts, regardless of symptoms, treatment on speculation is recommended.^{17, 79}
- If asymptomatic and not a known contact, treatment on speculation is not recommended unless “the individual is at high risk of infection and follow-up is not assured”.⁷⁹

The process map in Figure S4-1 of the supplementary appendix describes treatment provided, considering treatment route (oral vs. intramuscular), treatment availability (i.e., treatment is provided at the point of care, the patient is referred elsewhere for treatment, or the patient is given a prescription), consistency of treatment with clinical treatment guidelines, whether or not the patient completed the full treatment course, and overall outcome (i.e., whether or not the infection was cured). Figure S4-2 of the supplementary appendix describes the case reporting to Ottawa Public Health, data entry into iPHIS and the follow-up by the public health case manager with the diagnosing physician and the patient. Figure S4-3 of the supplementary appendix describes test-of-cure, reassessment of returning or ongoing symptoms, and six month follow-up screening. This process map describes possible outcomes including cure, continued infection due to inadequate treatment or treatment failure, or re-infection. The process map followed undiagnosed re-

infected and treatment failure cases to determine if they were identified through follow-up screening at 6 months (recommended for all cases).^{17, 79}

Process map of initial management with local data

Overall descriptive data

The process map of initial management populated with data is found in Figures 4-3 through 4-8.

A total of 719 cases of gonorrhea were reported between January 1, 2011 and December 31, 2013. Of these, 697 (96.9%) cases had urogenital infections, 27 (3.8%) had rectal infections, 6 (0.8%) had pharyngeal infections, and 3 (0.4%) had other infections. Twelve (1.7%) had concurrent infections in two or more sites.

Seventy-seven (10.7%) were identified as contacts.

Of those with symptom status recorded (n=577), 75.4% were symptomatic including 80.7% of non-contacts and 37.1% of contacts with symptom information.

Of those with physician information (n=653), 31.4% were diagnosed at the sexual health clinic, including 30.7% of urogenital infections, 80.0% of pharyngeal infections, 76.0% of rectal infections, and none of the other infections.

Of the 75 cases diagnosed with urethral microscopy and Gram stain, 89.3% were treated the same day (one had missing information and the relationship between treatment and test date could not be determined).

Excluding patient diagnosed with a urethral microscopy or Gram stain, 36.2% of patients with testing and treatment dates recorded (n=613) received treatment on speculation. This included 54.1% of known contacts, 40.8% of symptomatic non-contacts and 6.1% of asymptomatic non-contacts.

A total of 134 patients (18.6%) were lost to follow-up, including 22.8% of patients treated in the community, 8.8% of sexual health clinic patients, and 21.2% of those missing provider information. Cases lost to follow-up included 24.7% of non-contacts, 9.1% of contacts, 6.3% of asymptomatic patients, 7.6% of symptomatic patients, and 64.8% of patients without symptom information.

Management of non-contacts

Among non-contacts, 63.7% were symptomatic (Figure 4-3), 15.3% were asymptomatic (Figure 4-4), and 21.0% were missing symptom information (Figure 4-5).

Symptomatic non-contacts seen at the sexual health clinic

Among symptomatic non-contacts, 34.2% were seen at the sexual health clinic. Nearly half of these (47.1%) were diagnosed by Gram stain with microscopy, almost all of whom (90.9%) were treated immediately, as per guideline recommendations.^{17, 79} In addition, 68.9% of the other cases received treatment on speculation, in line with clinical guidelines.^{17, 79} Of all these cases, 8.6% were lost to follow-up.

Symptomatic non-contacts seen in the community

More than half of symptomatic non-contacts were seen elsewhere in the community (56.2%). None had Gram stain with microscopy done, 31.3% received treatment on speculation, and 5.7% were lost to follow-up.

Symptomatic non-contacts without provider information

Among the 10% of symptomatic non-contacts missing provider information, 5 (12.8%) had a urethral infection initially diagnosed by Gram stain with microscopy, suggesting that they were likely seen at the sexual health clinic. Four of the five were treated immediately. Of those not diagnosed by Gram stain with microscopy, 44.1% received treatment on speculation. Five patients were lost to follow-up.

Asymptomatic non-contacts seen at the sexual health clinic

Among asymptomatic non-contacts, 20.4% were seen at the sexual health clinic, of whom 15.0% received treatment on speculation, which may be consistent with guidelines if the patient is at high risk for infection but unlikely to return for follow-up.⁷⁹ None were lost to follow-up.

Asymptomatic non-contacts seen in the community

The majority of asymptomatic non-contacts were seen elsewhere in the community (73.5%). The vast majority (95.8%) were not treated on speculation and 9.7% were lost to follow-up.

Asymptomatic non-contacts without provider information

Among asymptomatic non-contacts, 6.1% were missing provider information. One case (17.7%) received treatment on speculation. None were lost to follow-up.

Non-contacts without symptom information seen at the sexual health clinic

A small number of non-contacts without symptom information were seen at the sexual health clinic (9; 6.7%). One patient was diagnosed with urethral infection by microscopy with Gram stain; we could not determine if this patient received immediate treatment due to missing date information. Two cases not diagnosed by Gram stain with microscopy received treatment on speculation. Two patients were lost to follow-up.

Non-contacts without symptom information seen in the community

The majority of non-contacts missing symptom information (81.5%) were seen in the community. Of these, 29.1% received treatment on speculation, 58.2% did not, and for 12.7%, it could not be determined due to missing data. Over a quarter (27.3%) were lost to follow-up.

Non-contacts without symptom or provider information

Among non-contacts missing symptom information, 11.9% were also missing provider information. None were diagnosed by Gram stain with microscopy, 31.3% received treatment on speculation, 50.0% did not, and 18.8% were missing date information. Half of these patients were lost to follow-up.

Management of contacts

Among those who were known contacts of a case, 33.8% were symptomatic (Figure 4-6), 57.1% were asymptomatic (Figure 4-7), and 9.1% were missing symptom information (Figure 4-8). A larger proportion of contacts were seen in the sexual health clinic (46.8%) compared to non-contacts (26.3%).

Symptomatic contacts seen at the sexual health clinic

More than half (53.8%) of symptomatic contacts were seen at the sexual health clinic. Of these, 21.4% were diagnosed by Gram stain with microscopy and all received treatment immediately. Of those not diagnosed by Gram stain with

microscopy, most (81.9%) received treatment on speculation. Of all these patients, 14.3% were lost to follow-up.

Symptomatic contacts seen in the community

Just over a third of symptomatic contacts (34.6%) were seen in the community. Of these, 11.1% received treatment on speculation, and 11.1% were lost to follow-up.

Symptomatic contacts without provider information

Provider information was missing for 3 (11.5%) symptomatic contacts. None were diagnosed by microscopy with Gram stain. One patient received treatment on speculation. None were lost to follow-up.

Asymptomatic contacts seen at the sexual health clinic

Of asymptomatic contacts, 43.2% were seen at the sexual health clinic. None were diagnosed by microscopy with Gram stain. The majority (73.7%) received treatment on speculation, and 10.5% were lost to follow-up.

Asymptomatic contacts seen in the community

Among asymptomatic contacts, 54.5% were seen in the community. Of these, 37.5% received treatment on speculation. None were lost to follow-up.

Asymptomatic contacts without provider information

One (2.3%) asymptomatic contact was missing provider information. This individual received treatment on speculation, and was not lost to follow-up.

Contacts without symptom information seen at the sexual health clinic

Three (42.9%) contacts with missing symptom information were seen at the sexual health clinic. None were diagnosed by microscopy with Gram stain and two received treatment on speculation. None were lost to follow-up.

Contacts without symptom information seen in the community

Three (42.9%) contacts with missing symptom information were seen in the community. Two received treatment on speculation, and the third was missing date information. None were lost to follow-up.

Contacts without symptom or provider information

One contact was missing both symptom information and provider information. This individual received treatment on speculation, and was lost to follow-up.

Discussion

This study demonstrated how process mapping can describe potential paths followed for the management of gonococcal infection. This exercise can identify where there is a risk that patients will receive inappropriate care or be lost to follow-up, and can identify potential opportunities to improve quality of care. Using routine surveillance data, we demonstrated that guideline-recommended treatment on speculation for symptomatic patients or at first contact for known contacts^{17,79} is provided less frequently in the community compared to the sexual health clinic. Community providers may be uncomfortable prescribing antibiotics without laboratory confirmation (particularly in light of recent efforts to promote antibiotic stewardship), may not have enough information to know which STI to treat a patient who was a known contact for (whereas, sexual health clinic staff can check lab data on iPHIS), or may be unaware of recommendations to treat contacts prior to laboratory confirmation. Interestingly, in the community, symptomatic contacts were less likely than asymptomatic contacts to receive treatment on speculation. Loss to follow-up to public health was noted across most branches but did seem to occur more among cases with missing symptom or provider data. Missing data may be reflective of loss to follow-up (e.g., could not reach patient to confirm symptoms) or may impede follow-up (e.g., could not contact the unidentified treating physician).

Process mapping has been used in other clinical settings, usually looking at a single process in a single location (e.g. a single procedure in one clinic or hospital).¹¹⁶⁻¹¹⁸ Although the literature applying process mapping in health care is growing, there is little literature using process mapping to address public health issues. This study uses process mapping to illustrate the complexity of care for a public health problem across a variety of settings and validated the approach with

STI experts, including local providers, from a variety of fields (including a guideline developer, a clinician, a case manager, and an epidemiologist). We used data from the provincial surveillance system designed to capture clinical information on all laboratory diagnosed cases of gonorrhea and thus were able to populate our process map with a large and comprehensive local data set.

This study was designed as a demonstrative activity. A more extensive process could have been used to involve community clinicians and to break the pathways down further to look at different types of community practice (e.g., general practice, walk-in clinics, emergency departments, other specialists). Due to data limitations, we opted to only break down the process map into the categories of care settings for which we could provide data.

For our study's purposes, the iPHIS data set had some limitations. Only positive tests are captured, which means that there is no denominator available to calculate percent positivity, or to appreciate the number of patients who returned for test-of-cure or rescreening that came back negative. iPHIS would also miss any contacts or symptomatic individuals who received treatment but either did not undergo testing or tested negative. iPHIS data is also limited to the information provided to the local public health unit and therefore information, such as follow-up treatment received if a patient is referred or recalled for retreatment, may be incomplete.

Currently, the province of Ontario is developing accountability agreements where public health units will be required to meet targets of percentage of gonorrhea cases receiving first-line treatment, even among cases seen in the community. In order to meet these targets, public health units will need to understand the care currently provided and identify where care can be improved. Through our exploratory work, we identified the community setting as an area where guideline adherence could be improved in Ottawa. Future public health activities targeting community practice could include targeting continuing education activities or individualized feedback to clinicians who recently managed a case of gonorrhea. Future research could further populate the maps using chart reviews or audits of clinical records, such as requests from community physicians for

ceftriaxone, in order to understand adherence to guidelines in other parts of the process maps. Process maps of STI management could also be used to conduct a critical incident analysis where specific patients are followed through the maps, identifying the paths they took, as well as issues in the process that led to delays in care, inappropriate care or loss to follow-up.

Table 4-1: Summary of gonorrhea management recommendations from the 2008 Canadian Guidelines for Sexually Transmitted Infections (with 2011 update) and the 2013 Ontario Guidelines for Testing and Treatment of Gonococcal Infections

Guideline	Diagnosis	Treatment on speculation	First-line treatment	Follow-up
<i>Canadian Guidelines on Sexually Transmitted Infections</i> – 2008 version plus December 2011 update 15, 16	Culture is recommended, if possible, to allow for antibiotic susceptibility information (recognizing that only nucleic acid amplification tests (NAATs) may be available in some jurisdictions). Culture specifically recommended for symptomatic MSM. Recommends urine NAAT if a patient resists pelvic examination or urethral swabbing. Urethral Gram stain in males is “generally diagnostic of gonorrhea.” (not recommended for other sites). “NAATs are not approved in Canada for oropharyngeal or rectal use.”	If mucopurulent discharge is present, “treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> if partner is infected with gonorrhea or if follow-up is not assured OR treat for <i>C. trachomatis</i> and consider treating for <i>N. gonorrhoeae</i> if local prevalence is high or sexual contact occurred in a region with high prevalence.” If no discharge is present, defer treatment until lab results are available unless “patient is at high risk for infection and follow-up is not assured or if partner is infected with gonorrhea.”	Ceftriaxone 250mg IM in a single dose (only first-line option if MSM patient or presenting with pharyngeal infection) + Azithromycin 1g PO single dose OR Cefixime 800mg PO in a single dose + Azithromycin 1g PO single dose	Test-of-cure if: the case was treated with quinolones and antimicrobial susceptibility testing was not done, treatment failure occurred previously, antimicrobial resistance to the treatment received is documented, compliance is uncertain, the case was re-exposed to an untreated partner, there is concern over a possible false-positive non-culture test result, infection occurs during pregnancy, PID or disseminated gonorrhea is diagnosed, or the patient is a child. Follow-up cultures for test-of-cure should be done 4-5 days after completion of therapy and should be done for all previously positive sites. NAAT is not recommended for test-of-cure, but if culture is not available, NAAT should not be done until 3 weeks after treatment to avoid false-positive results. Antimicrobial

Guideline	Diagnosis	Treatment on speculation	First-line treatment	Follow-up
				susceptibility is required for all from positive test-of-cure isolates and any presumed treatment failures. Repeat screening after 6 months recommended for all cases.
Ontario Guidelines for Testing and Treatment of Gonorrhea - April 2013 ¹⁷	Screening of asymptomatic individuals should be done using urine NAAT for males and cervical or urine NAAT for females. Testing of symptomatic individuals should be done using urethral culture or urine NAAT for males and cervical swab culture or cervical NAAT for females. Microscopy with Gram stain has a relatively high sensitivity and specificity for the diagnosis of gonorrhea in men. Microscopy for gonorrhea is not recommended for women. To improve sensitivity, in addition to testing by microscopy, a separate sample should be tested by culture or NAAT. If microscopy is positive, culture is preferred as it can provide antimicrobial	“Indications for treatment: • Identification of Gram-negative intracellular diplococci by microscopy in male urethral samples • Confirmed culture or NAAT specimen for <i>N. gonorrhoeae</i> • Epidemiological link to a gonorrhea case • Based on clinical assessment and/or risk behaviours following testing but before results are available • Following sexual assault • Mother of neonate with confirmed gonorrhea” Sexual partners of cases should be assessed, counseled, tested and treated. Regardless of the test results, partners should receive empiric treatment as soon as possible to prevent further transmission.	Ceftriaxone 250mg IM single dose + Azithromycin 1g PO single dose	Test-of-cure is recommended if: first-line treatment is not used, the infection is pharyngeal or rectal, the patient is pregnant, there is suspected or confirmed treatment failure or the patient is a sexual contact of a suspected or confirmed treatment failure, a strain with reduced susceptibility to cephalosporins is detected or the case is a sexual contact of person infected with a strain with reduced susceptibility to cephalosporins, treatment failure has occurred previously, compliance is uncertain, there is re-exposure to an untreated partner, there is concern over a false-positive non-culture test result, PID or disseminated gonococcal infection is diagnosed, the case is a child under 12 years

Guideline	Diagnosis	Treatment on speculation	First-line treatment	Follow-up
	susceptibility results. “Culture is the only method currently available in Ontario for testing for <i>N. gonorrhoeae</i> from rectal and pharyngeal sites.”			of age. For any test-of-cure, the preferred testing method is culture after four days post-treatment. If culture is not locally available, NAAT testing is a second-line option, but should be performed at least two weeks post-treatment. Rescreening after six months, or when they next seek medical care within the next 12 months, is recommended for all cases. Health care professionals should report any suspected or confirmed gonorrhea clinical failures to the local medical officer of health.

Figure 4-1: Process map of the initial management of cases of gonorrhea in Ottawa, Ontario who are not known contacts of a case.

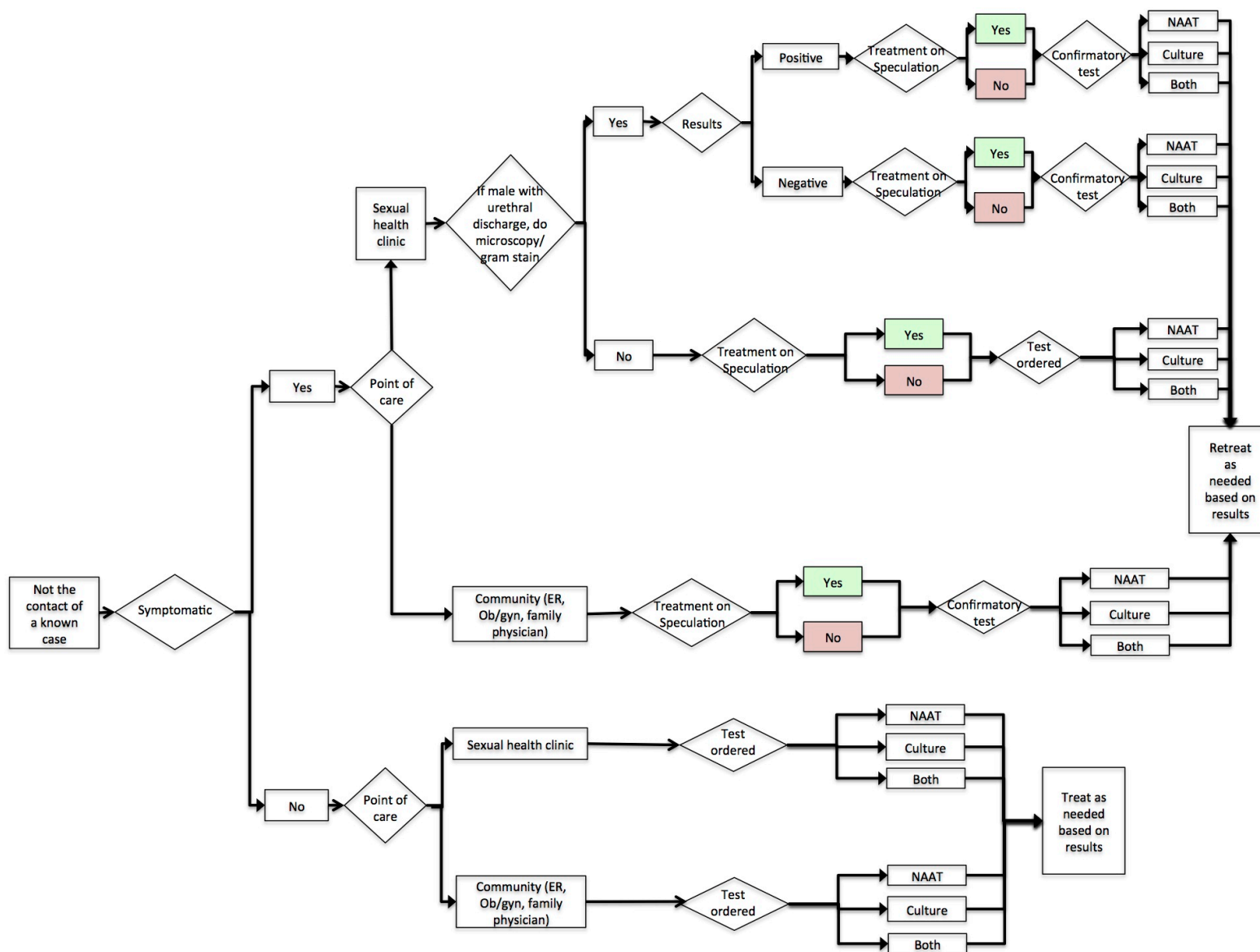


Figure 4-2: Process map of the initial management of gonorrhea patients in Ottawa, Ontario who are contacts of a known case.

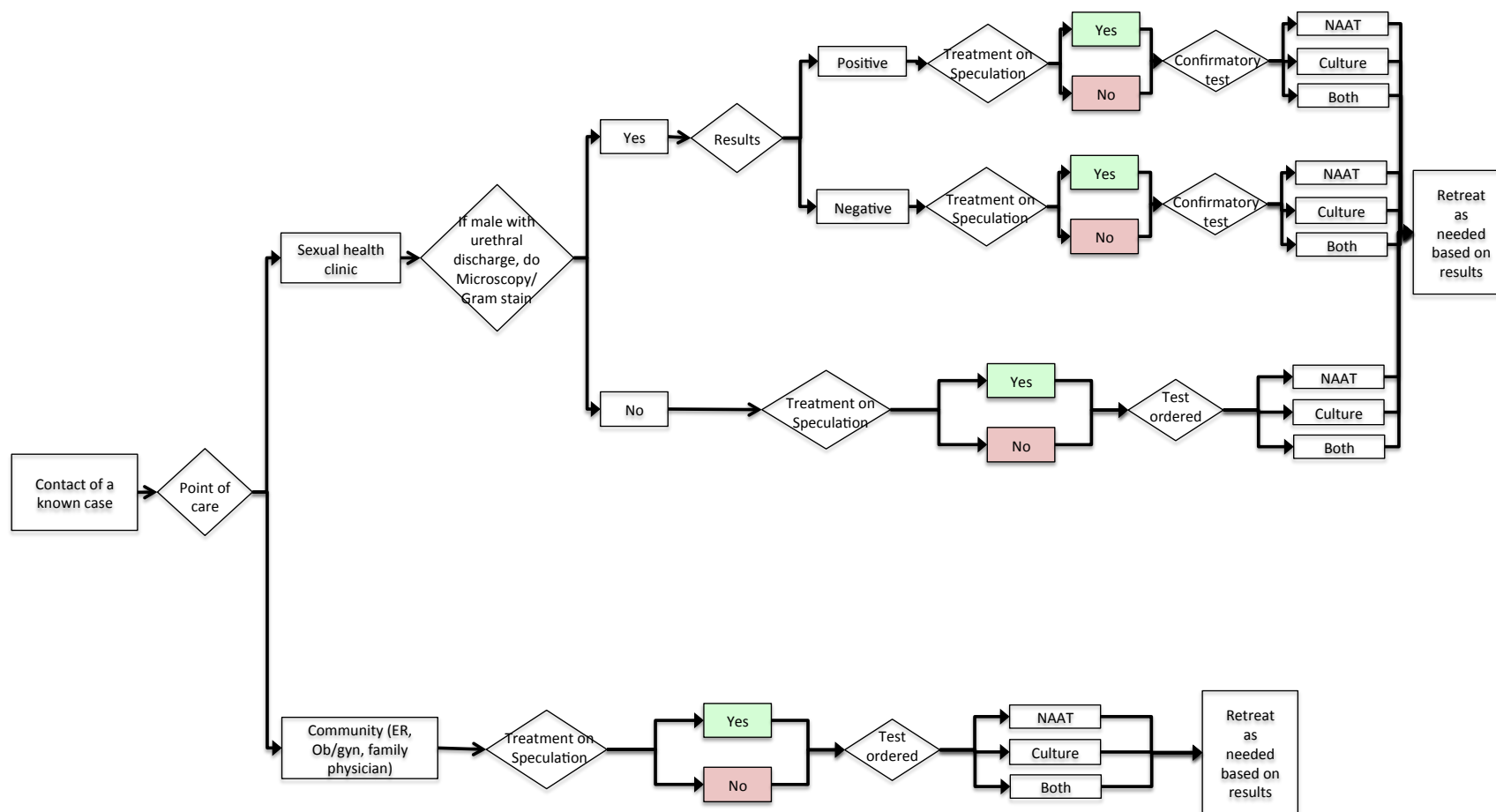


Figure 4-3: Process map populated with local data of the initial management of symptomatic cases of gonorrhea in Ottawa, Ontario who are not known contacts of a case.

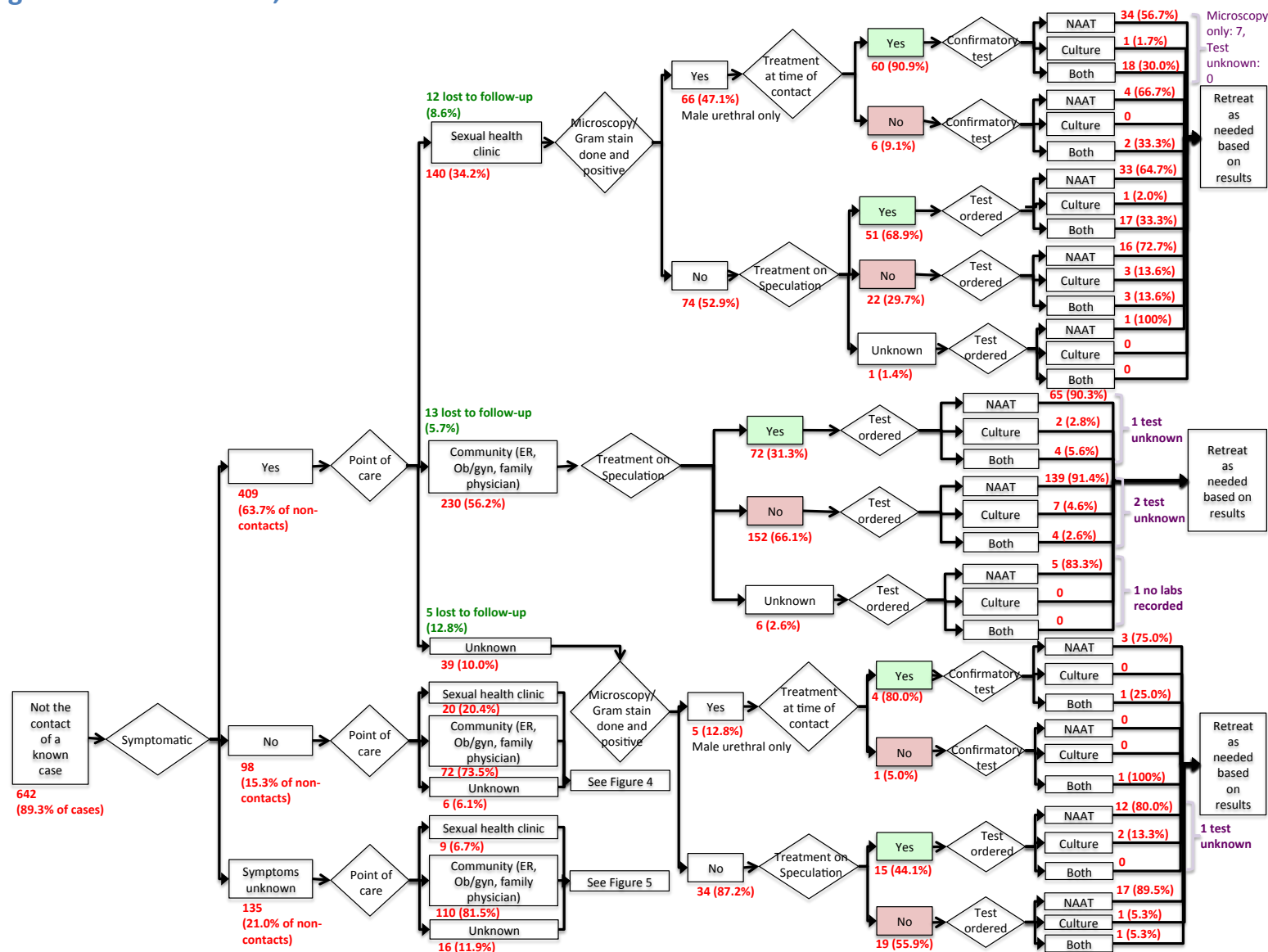


Figure 4-4: Process map populated with local data on the initial management of asymptomatic cases of gonorrhea in Ottawa, Ontario who are not known contacts of a case.

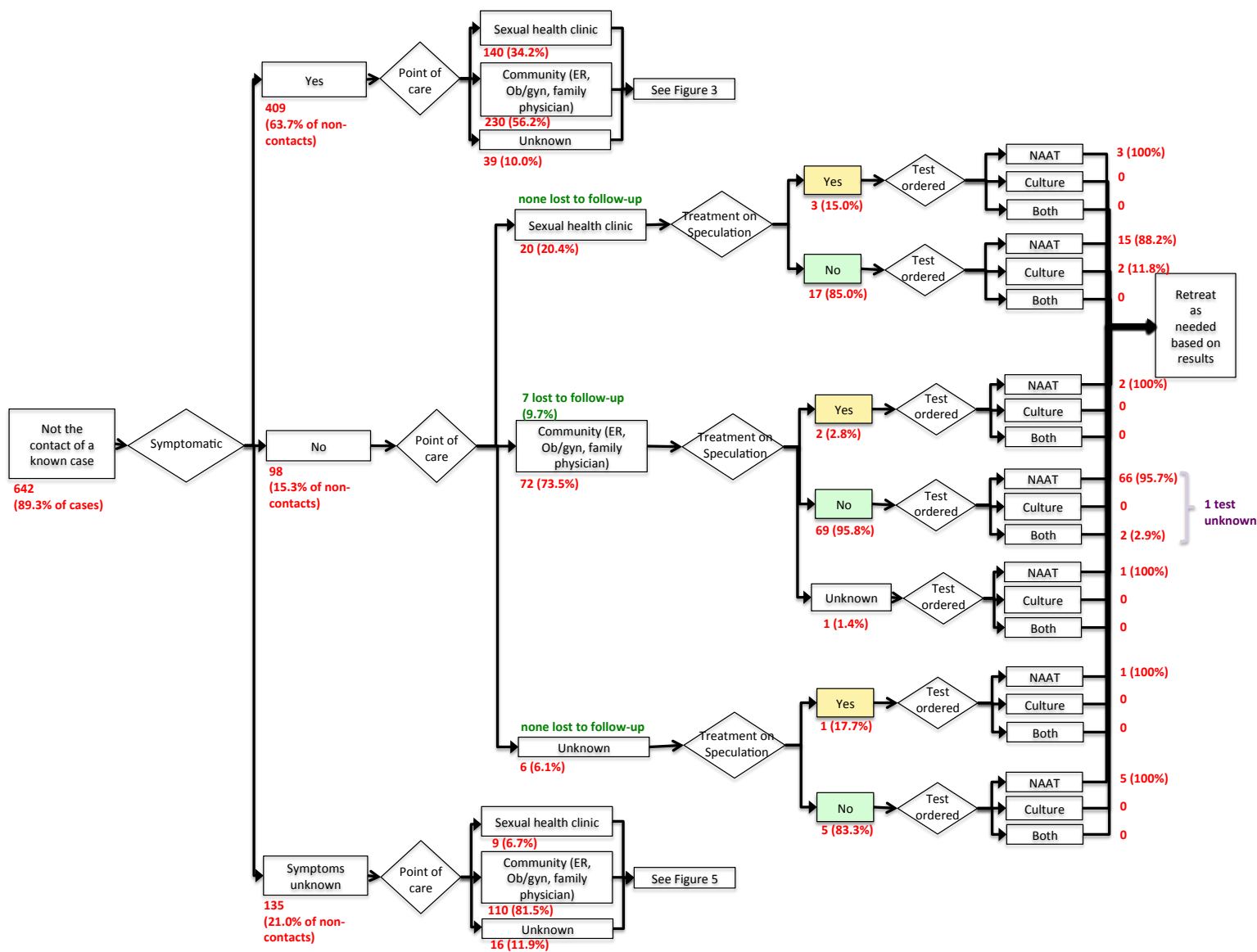


Figure 4-5: Process map populated with local data of the initial management of cases of gonorrhea with missing symptom information in Ottawa, Ontario who are not known contacts of a case.

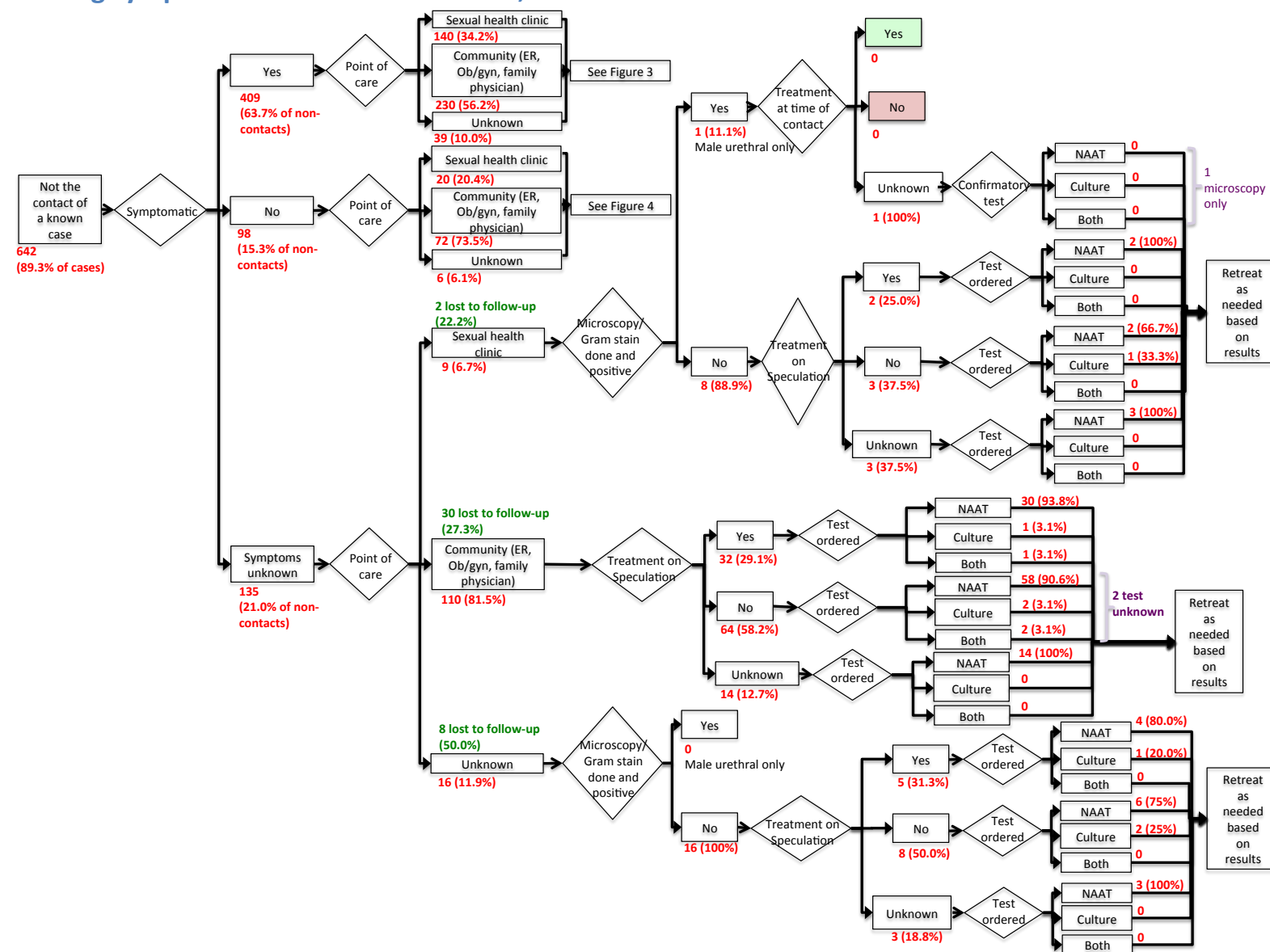


Figure 4-6: Process map populated with local data of the initial management of symptomatic gonorrhea patients in Ottawa, Ontario who are contacts of a known case.

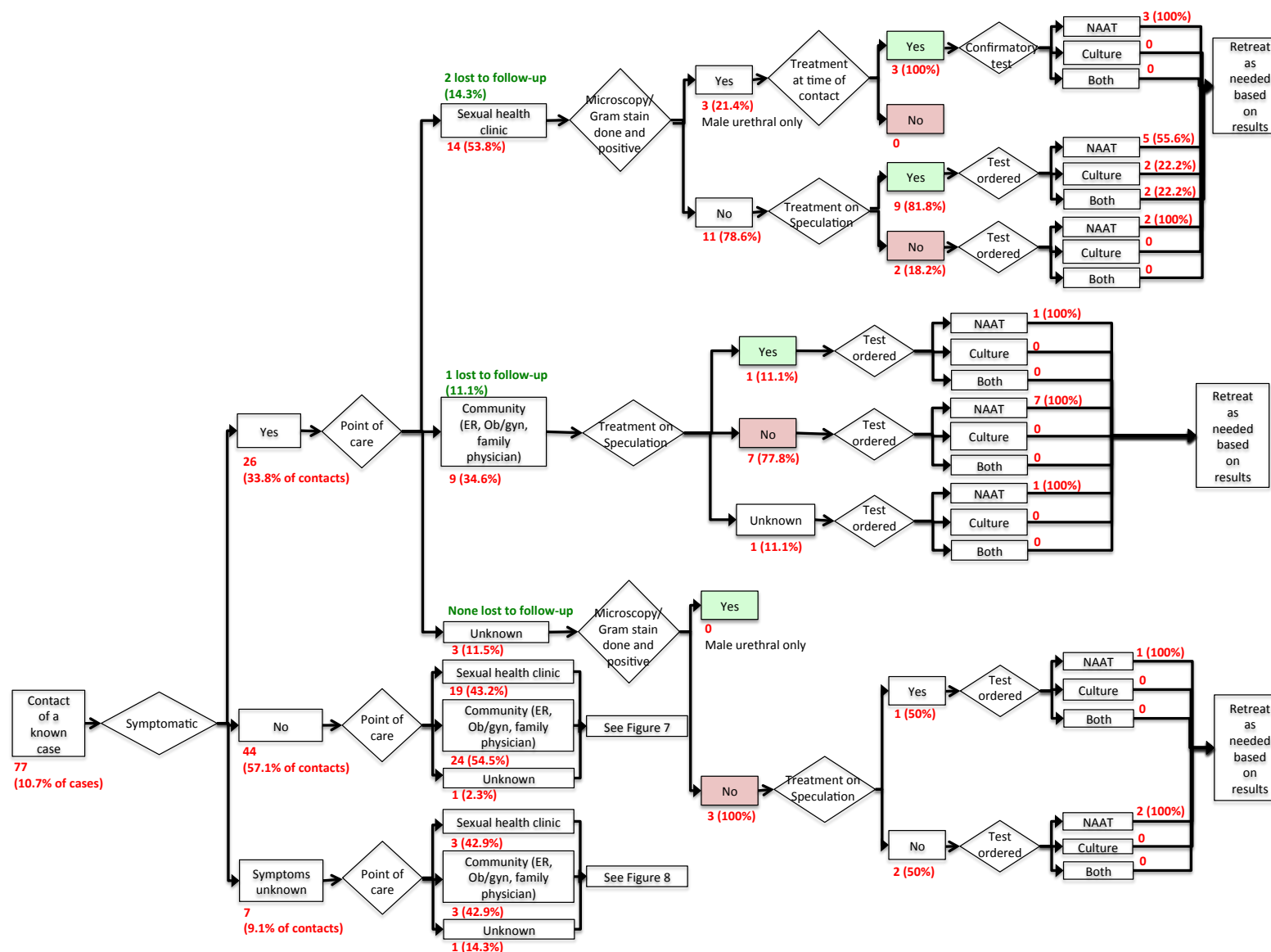


Figure 4-7: Process map populated with local data of the initial management of asymptomatic gonorrhea patients in Ottawa, Ontario who are contacts of a known case.

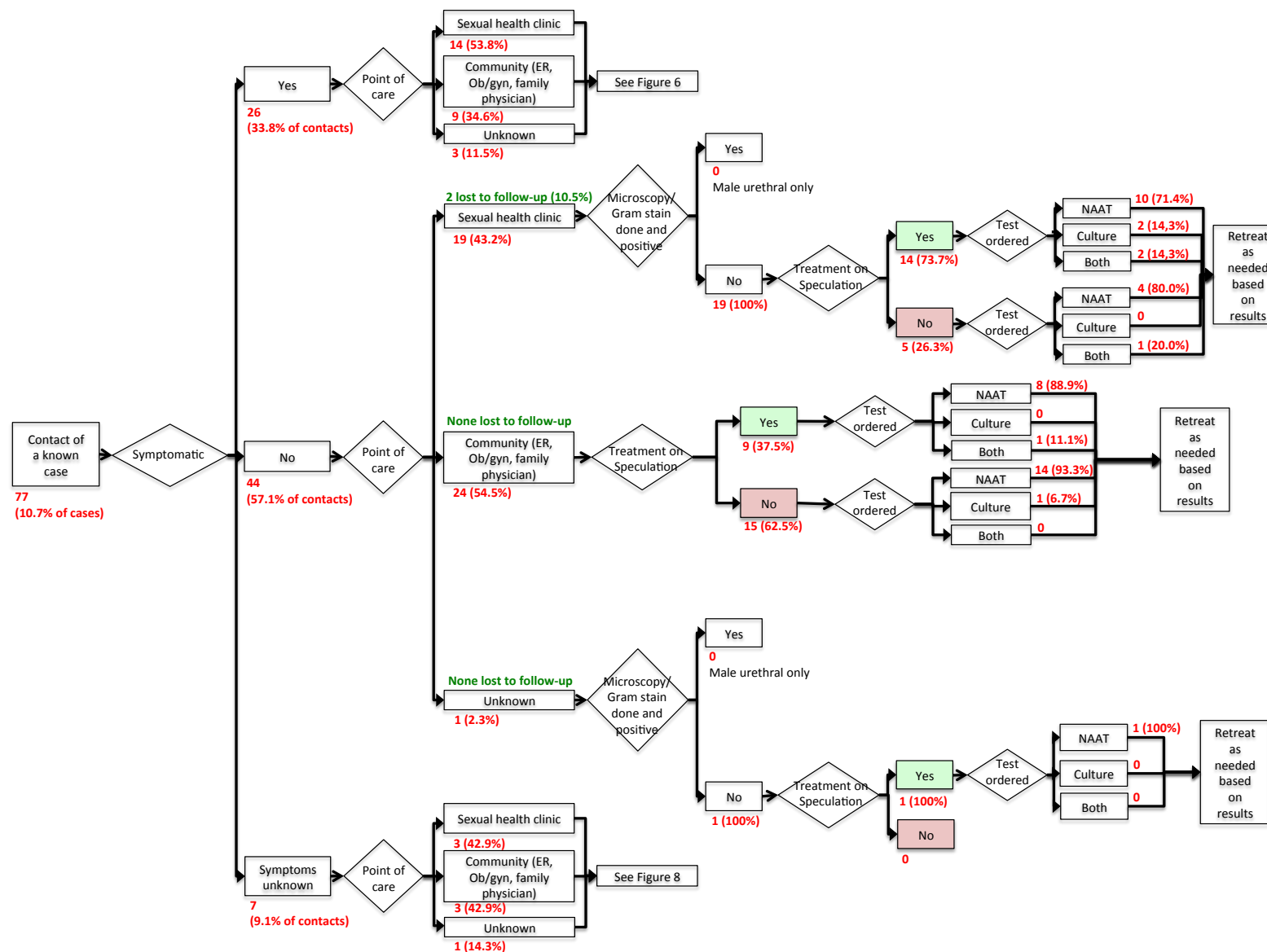
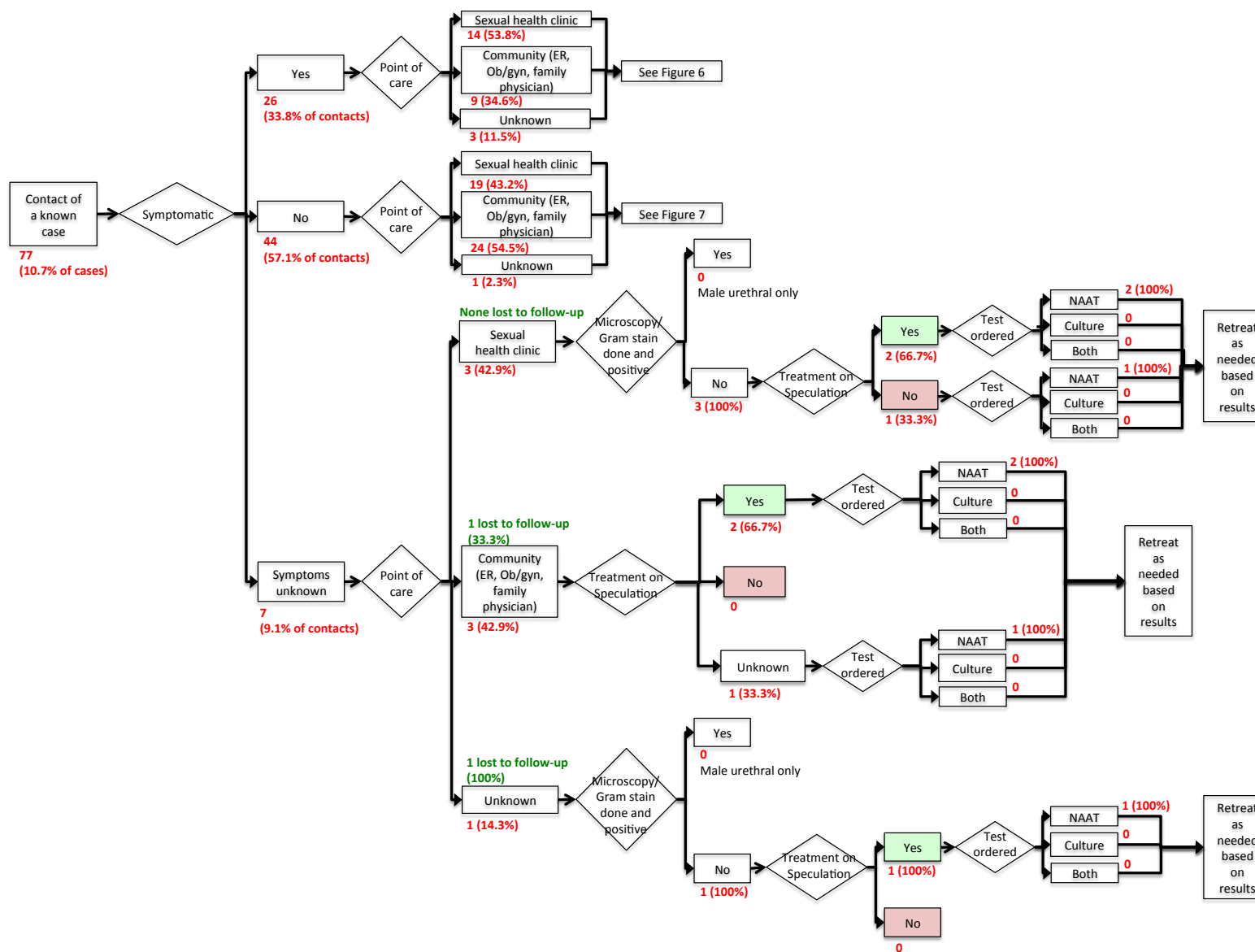


Figure 4-8: Process map populated with local data of the initial management of gonorrhea patients with missing symptom information in Ottawa, Ontario who are contacts of a known case.



Supplementary Appendix for Chapter 4

Figure S4-1: Process map of the treatment of individuals with gonorrhea in Ottawa, Ontario.

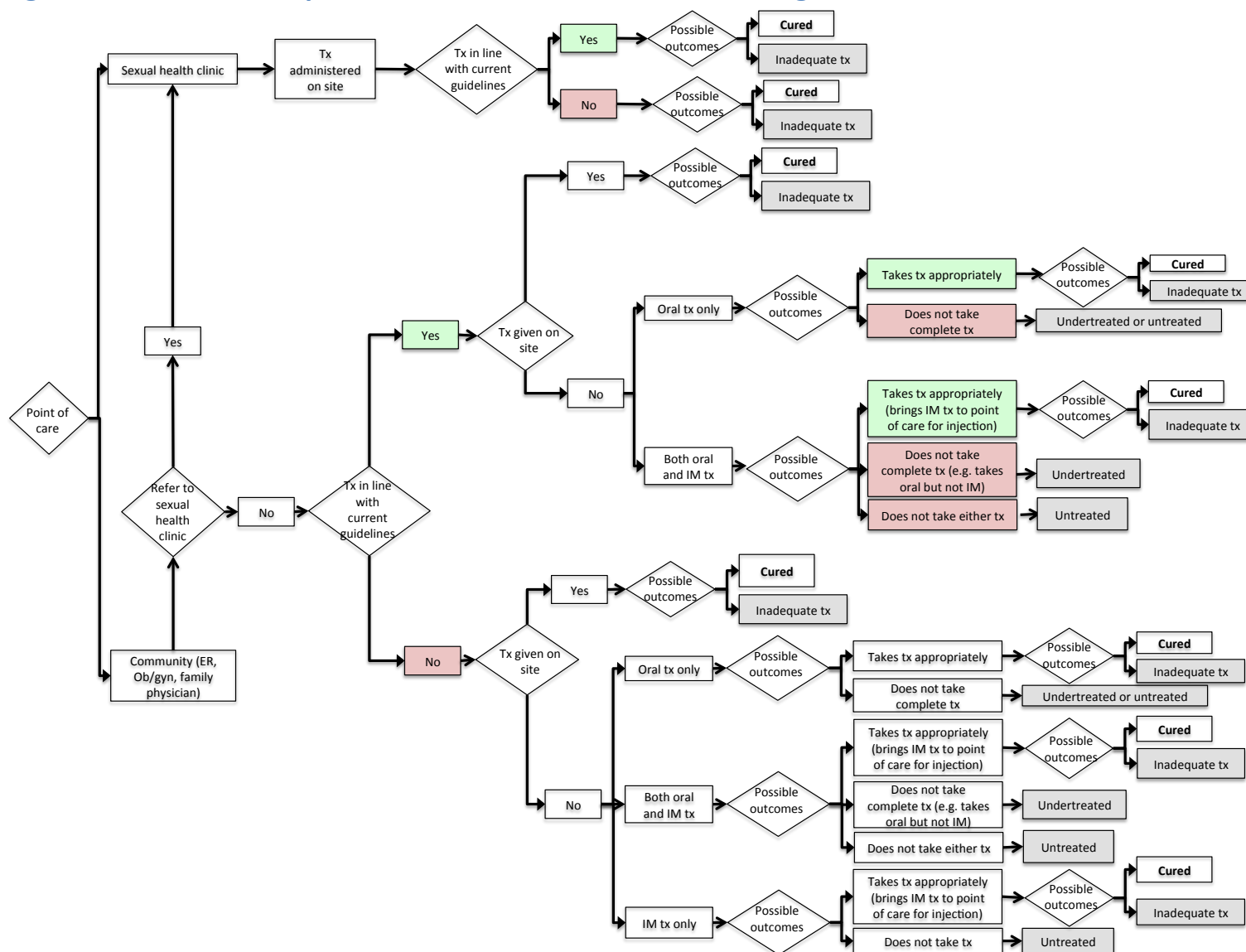


Figure S4-2: Process map of case reporting and follow-up by public health for cases of gonorrhea in Ottawa, Ontario.

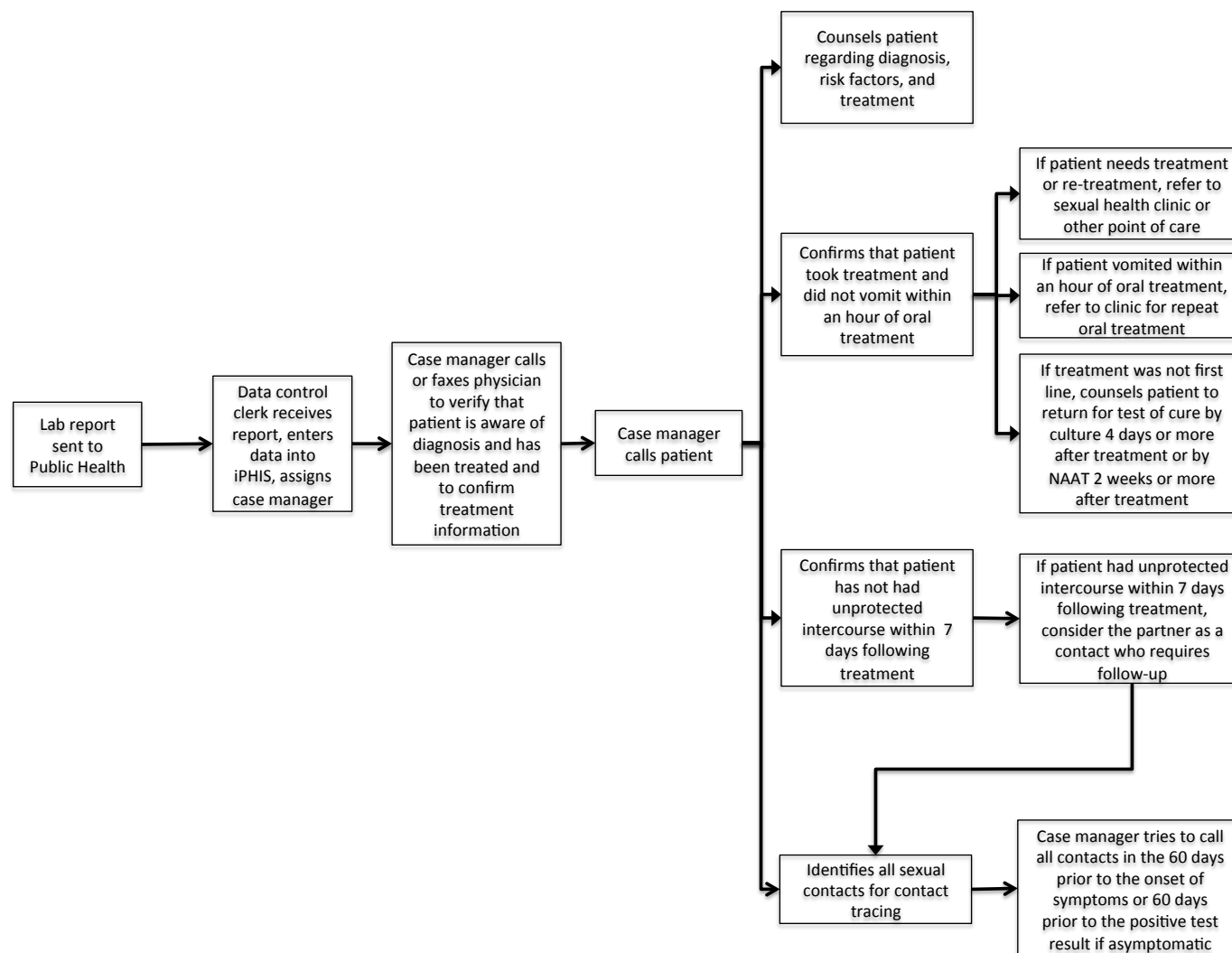
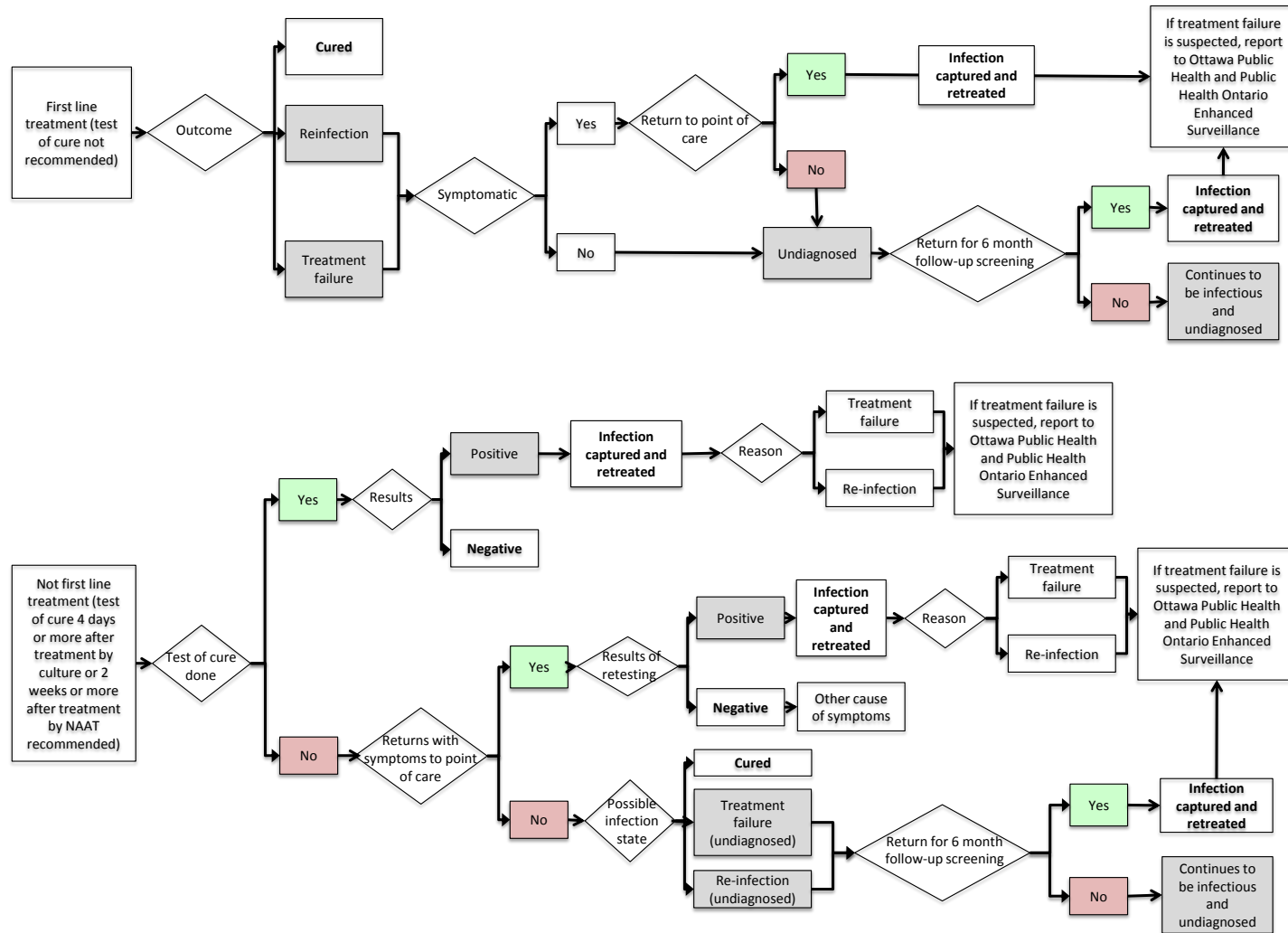


Figure S4-3: Process map of the reassessment and outcomes of individuals with gonorrhea in Ottawa, Ontario.



Chapter 5 - Conclusion

Since the introduction of antibiotics to treat gonococcal infections, *Neisseria gonorrhoeae* has developed and maintained resistance to each class of drug used to treat it.^{2, 4, 12} Case reports are starting to show treatment failure in cases treated with third generation cephalosporins, the current first-line treatment for gonorrhea.^{5-9, 108, 119} The pending loss of third generation cephalosporins as a treatment for gonorrhea would be a public health disaster as we are now running out of antibiotic treatment options.^{2, 4, 12, 93} Untreatable gonorrhea would lead to further spread of infection and an increase in complications such as pelvic inflammatory disease, epididymitis, male and female infertility, ectopic pregnancy, disseminated infection, and neonatal infections.¹

New antibiotics are under development that may provide future treatment options.^{2, 4, 12} However, as antibiotic development is a long process (and it will likely only be a matter of time before *N. gonorrhoeae* shows signs of developing resistance to the new treatment options), extending the amount of time that the current treatment regimen remains effective will be an important public health strategy. Clinical guidelines can help guide the appropriate care of patients with gonorrhea infection (cases). Cases should be treated early on after diagnosis or if clinical suspicion is high in order to prevent further transmission of infection. Cases should receive sufficient doses of effective antibiotics. Drug resistant cases should be identified either through culture or through test-of-cure following treatment as the more sensitive and convenient diagnostic test, the nucleic acid amplification test (NAAT), does not provide information on whether a *N. gonorrhoeae* infection is drug resistant. Treatment failure cases should be identified and re-treated.^{17, 79}

In order for clinical guidelines for the treatment of gonorrhea to be an effective public health tool in delaying the development of drug resistance, they must be developed in a way to ensure that they provide sound advice and are updated to keep up with changing resistance trends.¹²⁰ These recommendations must also be communicated to clinicians who would need to adhere to them.¹²¹ Guideline

adherence among clinicians has been shown in many areas of clinical care to be limited.^{19, 20} As the treatment recommendations for gonorrhea changed several times over the past decade, we anticipated that adherence to these guidelines could be particularly problematic.

In Ontario, unlike other types of infections with rapidly changing guidelines and concerns about changing resistance patterns, such as HIV or tuberculosis, many cases of gonorrhea are treated by general practitioners in the community. Gonorrhea may be seen and treated in a wide range of clinical settings including public health-run sexual health clinics, general practices, walk-in clinics, obstetrics and gynecology offices, emergency rooms, urology clinics, and HIV clinics. Depending on the setting, clinicians may see cases of gonorrhea at very different frequencies, may have different levels of familiarity with the current STI treatment guidelines, and may be more or less likely to look up the recommended treatment for any individual patient.

Previous studies on clinicians' adherence with gonorrhea treatment guidelines have shown that guideline adherence varied by type of practice (e.g., STI or genitourinary medicine clinics are more likely to adhere to guidelines),^{53, 54, 56, 59, 64} and number of gonorrhea cases treated at a location or by a provider.^{57, 59} Guideline adherence also varied by geographic location.^{22, 53, 56} This regional variation was demonstrated by comparing cities or regions within the same country. We can anticipate a greater variation in physician behaviour between countries due to the use of different guideline documents, the different settings where STIs are treated, and different medical education systems, limiting the generalizability of these previous studies to Ontario. In the United Kingdom, most gonorrhea cases are diagnosed and treated in genitourinary medicine (GUM) clinics where guideline adherence has been shown to be high, and thus overall adherence rates are high.⁶⁴ However, the small proportion of cases seen and managed in the community often received out of date treatment and a slow uptake of new STI treatment recommendations was noted among general practitioners treating gonorrhea.⁶⁴ Studies looking at ceftriaxone use for the treatment of gonorrhea in the United States found high physician adherence to the new American guidelines.^{53, 56, 57, 59} However, in the studies that assessed the effect of the US CDC guideline change that made

ceftriaxone part of the only first-line treatment option,⁷⁸ baseline rates of ceftriaxone use were higher than our Ontario baseline rates (generally more than half of cases were already receiving ceftriaxone^{53, 56, 59} compared to Ontario where rates of ceftriaxone use, though already increasing, were low when the new guidelines were introduced). Cefixime availability in the United States has been more restricted than in Canada,^{122, 123} which has likely led to changes in prescription patterns favouring the use of ceftriaxone.

As we could not locate any recent publications on gonorrhea management and adherence to clinical guidelines in Ontario or Canada, we developed this thesis to address this knowledge gap, working and consulting with STI experts at the federal, provincial and local level. This work is intended to provide useful information to those working in the area of STI at these multiple levels in order to improve the management of gonorrhea and to ultimately prevent treatment failure and complications of infection.

In order to look at how guideline development, dissemination and uptake can be improved to prolong the use of current antibiotic regimens as effective treatment for gonorrhea infections in Ontario, this three-part thesis looked at:

- Gonorrhea treatment guideline development,
- Gonorrhea treatment guideline uptake at the provincial level, and
- Gonorrhea management at the local level.

Highlights of findings

Chapter 2 of this thesis describes a systematic review of current gonorrhea treatment guidelines and reviewed the quality of these guidelines using the AGREE II critical appraisal tool. We included 10 current gonorrhea treatment guidelines from North America, Europe and Australasia.

In appraising the guidelines with the AGREE II tool, we observed substantial variation in quality between the guidelines. Most guidelines scored quite high in the *Scope and Purpose*, *Stakeholder Involvement* and *Clarity of Presentation* domains. However within the *Stakeholder Involvement* domain, only one guideline made any mention of consulting patients or the public regarding the guideline. Most of the

guidelines scored quite poorly on the *Rigour of Development* domain which is often considered most important as it determines whether all the relevant information and existing research was used to develop recommendations and to ensure that they are up to date. The *Rigour of Development* domain also assesses whether the guideline development process used is likely to minimize biases in the guideline's recommendations. Most guidelines also did not score well in the *Applicability* domain – for example, most recommended changing antibiotics to an intramuscular regimen but did not address the practicalities of administering injections in different clinical settings. Guidelines also tended not to score well in the *Editorial Independence* domain, as in most guidelines, little information regarding editorial independence and the management of potential conflicts of interest was available.

Two Canadian guidelines were included in this review: *The Canadian Guidelines on Sexually Transmitted Infections* and the *Guidelines for the Testing and Treatment of Gonorrhea in Ontario*. Both of these guidelines scored above 50% in the *Scope and Purpose*, *Stakeholder Involvement*, and *Clarity of Presentation* domains but like the majority of guidelines reviewed, had room for improvement in the *Rigour of Development*, *Applicability*, and *Editorial Independence* domains.

This finding that most current gonorrhea treatment guidelines do little to address the logistics of switching treatment regimens to include an intramuscular injection and the possibility that the lack of information on the rigour of the guideline development process used and on the level of the guideline's editorial independence may affect users' trust of the guideline recommendations brings into question how well these guidelines are being followed.

Chapter 3 of this thesis addresses the question of physician adherence to current gonorrhea treatment guidelines using an interrupted time series design to examine changes in Ontario physician guideline adherence across three changes in local gonorrhea treatment recommendations between January 2006 and May 2014. Guideline adherence started off high with over 90% of cases receiving treatment in line with the current guidelines. A minor change in recommendations in 2008, where one infrequently used drug option was dropped, had little effect on adherence. Major guideline changes in late 2011 and 2013 were followed by large drops in adherence.

In 2011, the *Canadian Guidelines on Sexually Transmitted Infections* doubled the recommended doses of cefixime and ceftriaxone, recommended ceftriaxone for all pharyngeal infections and for all cases in men who have sex with men (MSM), and added azithromycin as recommended dual treatment for all cases. At the time of this guideline change, modeled adherence levels dropped from 82.3 (95% confidence interval (CI): 79.3-85.2) to 21.9 (95% CI: 17.5-26.4). In early 2011, ceftriaxone use increased slightly prior to upcoming guideline changes but was still quite low at the time of this change: 8.9% in the model (95% CI: 7.0-10.7) prior to the change and 14.5% (95% CI: 11.5-17.5) immediately following the change. Modeled adherence increased gradually over time, reaching 58.3% (95% CI: 53.7-62.8) by the time Ontario introduced their new guidelines in 2013. The new Ontario guidelines were another major change as intramuscular ceftriaxone plus oral azithromycin were made the first-line treatment recommended for all cases of gonorrhea. Following the introduction of these new guidelines, adherence dropped to 46.2% (95% CI: 41.4-51.1) in the model. Another gradual increase in adherence was seen following this change. However, this increase occurred slowly and, over a year after the most recent guideline was released, adherence had only reached 59.1% (54.1-64.2) in the model meaning that approximately 40% of cases were not receiving first-line treatment.

By the end of the study, around 70% of cases were receiving ceftriaxone and around 95% were receiving some sort of cephalosporin, suggesting that a large number of patients not receiving guideline-recommended treatment were receiving cefixime instead of ceftriaxone. Others did not receive the full dose of ceftriaxone (remembering that the recommended dose was doubled in late 2011) or did not receive azithromycin with the ceftriaxone. Some recent publications have suggested that dual treatment of either cefixime or ceftriaxone plus azithromycin or the second-line doxycycline provides greater coverage than single treatment and presents less risk of treatment failure.^{2, 12, 124} We repeated our analyses, this time looking at the proportion of cases receiving dual treatment of either cefixime or ceftriaxone plus either azithromycin or doxycycline. Figure 5-1 shows the observed and model-based adherence rates. The results of the segmented regression analysis

are presented in Table 5-1. At the start of the study, rates of dual treatment use were already high (77.5%, 95% CI: 70.6-84.3) likely because dual treatment was already recommended for all cases that might have a chlamydial co-infection (i.e., for all cases unless a negative lab test for chlamydia was available). Sudden increases in the use of combination therapy were observed after both the introduction of the 2011 and 2013 new recommendations that a two-drug regimen be used regardless of chlamydial infection status. By the end of the study, approximately 90% of cases were receiving a combination of cefixime or ceftriaxone plus doxycycline or azithromycin.

This study looked at overall adherence patterns in Ontario across all treatment settings and clinical presentations. Previous studies have shown differences in guideline adherence between different practice settings. To understand how these differences play out locally, in Chapter 4, we used process mapping and Ottawa-specific data to follow cases with different clinical presentations (known contact vs. not and presenting with symptoms vs. asymptomatic) presenting to different clinical settings (Ottawa Public Health's Sexual Health Clinic vs. elsewhere in the community).

We developed the process maps with input from people who worked in the area of STIs at both the federal and local levels, considering the possible pathways that a patient with gonorrhea may take to be diagnosed and treated as well as potential follow-up and outcomes. We then determined whether or not each pathway was in line with current guidelines and used local surveillance data to demonstrate the proportions of patients who followed each pathway according to the different clinical presentation categories as well as by clinical setting.

In this study, we found that symptomatic cases or cases that were known contacts seen in the community were less likely to receive guideline-recommended treatment on speculation or at first visit than patients seen at the Sexual Health Clinic. Symptomatic known contacts seen in the community were even less likely than asymptomatic known contacts seen in the community to receive treatment at the time of their first visit. Some long delays before treatment were noted for some of these cases, which could allow for further transmission of gonorrhea to others.

We also noted that cases of treatment failure may be over-reported. Positive tests among those returning for test-of-cure were most often tested by nucleic acid amplification test (NAAT) prior to the recommended 2-3 week time delay following treatment.⁷⁹ Without the time delay, false positives may occur because NAAT detects the presence of the organism but cannot differentiate between a dead organism that has been killed by the treatment but not yet fully cleared from the body and a live organism, which would suggest either treatment failure or that the person has been re-infected by a sexual partner still carrying the infection.

Study strengths and limitations

Overall

This thesis tried to systematically examine current practice in the management of gonorrhea as well as gaps in gonorrhea treatment guideline development and adherence in Ontario. We conducted three studies in order to address this issue. Other work will be needed to fully understand and enrich the understanding of this issue (see Implications for further research below).

Through the use of provincial reportable disease data, our studies are population-based, which help us to understand overall trends across the province. This is one of the first recent Canadian studies to look at gonorrhea treatment and guideline adherence.

Much of our work is specific to Ontario (or even specific to the management of gonorrhea infections in the City of Ottawa) and its applicability to other settings is uncertain.

A systematic review of the quality of guidelines for the management of gonococcal infections (Chapter 2)

This was the first systematic review that we could find assessing the quality of STI treatment guidelines. We searched an extensive number of databases as well as the grey literature in order to identify as many gonorrhea treatment guidelines as possible. The AGREE II tool is an instrument that has been validated with a variety of

types of clinical guidelines and can be used to guide the development of clinical guidelines as well as for their evaluation.^{70, 86, 87}

Our analysis was limited to English language guidelines (we identified but excluded one guideline written in German)⁹² and publicly available information. Limiting our analysis to publicly available information allowed us to assess the information that is reported transparently to the medical community but did not allow us to differentiate things that were done but not reported from things that were not done. For example, many of the guidelines did not provide information on the process used to develop their recommendations. It is possible that a full systematic review was conducted but we do not have any evidence to support it nor any means to differentiate between what is done and not reported and what is not done. Upon presenting preliminary results to Public Health Agency of Canada employees, they identified that there was a system in play with their Expert Working Group members to identify and address members' potential conflicts of interest when developing recommendations for the *Canadian Guidelines on Sexually Transmitted Infections*. However there is currently no information on the process available on the guidelines' website (but this information may be made available in the future). Although we attempted to identify all publicly available material on each guideline through searching multiple databases and within each guideline and its website, it is possible that we missed some material. However, with our extensive search, we have likely identified the material that a general guideline user is likely to access and work with.

The antibiotic management of gonorrhea in Ontario following multiple changes in guidelines: An interrupted time series analysis (Chapter 3)

Shadish, Cook and Campbell identify the interrupted time series design as "one of the most effective and powerful of all quasi-experimental designs."⁹⁵ Similarly, the interrupted time series design has been described as "the strongest quasi-experimental approach for evaluating longitudinal effects of interventions".⁹⁶ The interrupted time series design is used to study the effect of an event or the introduction of an intervention, particularly in situations where a controlled trial is

not feasible or ethical.⁹⁵ This design compares a series of outcome measurements taken at several time points over a period of time before and after the time that the intervention of interest was introduced.

The interrupted time series design can assess both immediate effects (changes in level) as well as longer-term changes in trend (changes in slope) following the intervention.⁹⁵ By including multiple measures following the introduction of the intervention, the interrupted time series design can be used to describe the rate of change of the outcome following the intervention as well as the effect size and the persistence of the effect (i.e., looking at whether the change remains over time). The interrupted times series design has the advantage of being able to account for underlying trends in the data, such as seasonal trends and autocorrelation (i.e., the relation between an outcome measure at a single time point and the outcome measures from time points just prior), in order to measure an estimated effect of the intervention. By including multiple pre-intervention measures, the interrupted time series design allows for the establishment of a baseline that accounts for existing trends (such as an increase or decrease already occurring over time, and other changes in the outcome measure not associated with the time of the intervention of interest).⁹⁵ Collectively, this information reduces the uncertainty that the relation between the intervention of interest and the effects observed is causal.⁹⁵

We did not anticipate that seasonality would be seen in gonorrhea treatment patterns (though seasonality was observed in the incidence of reported cases). However, we assessed for seasonality by testing each model for stationarity using the Engle-Granger cointegration test. Based on the results of these tests, we did not adjust for seasonality in our models.

We did, however, anticipate seeing autocorrelation in our models, as one's prescribing behaviour is likely dependent on one's recent behaviour. We tested for autocorrelation using the Durbin-Watson statistic^{96, 125, 126} and adjusted the segmented regression model by including an autocorrelation parameter estimated through backwards elimination to fit the most parsimonious model (starting with a

third order autocorrelation parameter and removing an order of autocorrelation until the highest order included in the model is statistically significant).¹²⁵

Another benefit of the interrupted time series design is that it gives a graphical representation of the results that can make it easy to identify any changes through visual inspection.⁹⁶ These changes can then be confirmed statistically (we used a segmented regression analysis). The graphical representation makes the results simple to understand for lay people and decision makers who may not be comfortable interpreting statistics.

Interrupted time series designs are based upon the following assumptions that if violated would threaten the internal validity of the study:

1-) The outcome follows a linear trend both before and after the intervention. Many trends do not follow a linear pattern, particularly over the long term.⁹⁶ We used a linear segmented regression model, as has been described elsewhere,^{96, 125, 126} that expressed changes as absolute differences in percentage for simplicity of interpretation. Because we were working with data expressed as proportions, we did have some concerns with our choice of an additive model that assumes a linear trend over time. In order to address these concerns, we examined the fit of the models using log-likelihood ratio tests, histograms of residuals, normal probability plots, and partial autocorrelation function plots. To account for potential non-linear trends over time and/or deviations from the normal assumption, we repeated the analyses on the log-odds (logit) scale, with changes expressed as relative differences. Our tests of fit revealed no major departures from the modeling assumptions. The substantive conclusions of our initial analyses did not change when we repeated our analyses on the log-odds scale. Thus, we were comfortable keeping our original linear regression model.

2-) Changes will begin to occur immediately following the intervention (i.e., change of level and change of slope at time point of interruption).⁹⁵ In reality, guideline dissemination and uptake occurs over a period of time. In our model, by using the first time point in the month following the guideline release as the interruption, we did account for a small delay before clinicians would start to use the new recommendations. We pre-specified these time delays prior to inspecting the

data. Inspecting the raw data from 2013, the jump in ceftriaxone use and drop in cefixime use corresponded with our selected time point for the interruption, suggesting that our selected time delay was appropriate at least for the 2013 guideline release. We used the interrupted time series design to model guideline adherence over time; this model illustrated the gradual uptake of these guideline recommendations by Ontario clinicians over time. At the time when the two most recent guidelines were introduced, adherence dropped quite dramatically, suggesting that most physicians were still following old recommendations. The gradual upward slopes that followed represented gradual changes in practice as physicians slowly changed their practices.

3-) Changes observed at the time of the intervention are related to the intervention of interest (i.e., the changes in guideline recommendations).⁹⁵ Since the intervention is not in a controlled setting, we needed to consider that other factors may affect the outcome of interest (i.e., physicians' treatment choices for the management of gonorrhea). In order to address this, we considered several plausible rival explanations, such as other interventions or other events occurring at the same time as the clinical guideline changes that could have influenced physicians' prescribing behaviours.¹²⁷

We searched Pubmed and Canadian Newstand, looking for articles in major medical journals and news stories on gonorrhea in the three months before and after each recommendation was released. Publications found in both medical journals and national or Ontario-based newspapers highlighted antimicrobial resistance trends and likely would have, if anything, promoted current guideline use.

In early 2011, a decline in guideline adherence and an increase in ceftriaxone use, not related in time to a guideline change, were noted. To investigate these changes, we searched the same databases between November 1, 2010 and June 30, 2011. Case reports of treatment failure with in patients treated with cephalosporins in Europe and Japan^{6, 7, 10, 108} were published during this time. In addition, cases of cefixime treatment failure in Toronto were reported in early 2011.⁵ Some clinicians may have been aware of these cases and preemptively changed their prescribing behaviour.

We also looked at the release dates of updates to gonorrhea treatment guidelines from other jurisdictions as they could also potentially influence clinical practice. The Centers for Disease Control and Prevention (CDC) updated their guidelines to remove cefixime from first-line treatment in August 2012.⁷⁸ The British Association for Sexual Health and HIV (BASHH) updated their guidelines similarly in October 2011,⁸¹ and the International Union for Sexually Transmitted Infections (IUSTI) updated their European guidelines in November 2012.⁸⁰ These release dates make it unlikely that these new guidelines had much influence on the observed trends of changing gonorrhea treatment patterns in Ontario.

Another possible cause for changes in prescribing behaviours is a drug shortage. Members of the thesis committee alerted us to a Canadian shortage of cefixime, which could have led to physicians either increasing their use of ceftriaxone or switching to the second-line option of 2 grams of azithromycin. This shortage, however, occurred after May 2014 and is thus not reflected in our results.¹²⁸

Segmented regression analysis generally uses aggregated data. In our analysis, we aggregated individual treatment data to calculate biweekly proportions. In using aggregate data, we are not able to control for individual-level characteristics (such as patient or clinician characteristics) that might influence treatment selection and that we would likely wish to include in a cross-sectional analysis such as a logistic regression model.⁹⁶ However, as this was an analysis of population-level data, confounding by individual-level variables (such as patient and clinician characteristics) does not introduce serious bias unless these variables change at the same time as the interventions of interest (e.g., suddenly, a larger proportion of cases are seen at public health-run sexual health clinics or a higher proportion of cases begin to refuse intramuscular injections).⁹⁵

Much of the literature on interrupted time series analyses recommends including a control group that has not experienced the intervention of interest in the analysis.^{95, 125} Due to the numerous clinical guidelines available and the limited data that we had available to us, it would be challenging to identify a control group with similar baseline rates that would not have been influenced by other interventions during the time period we were studying. Thus, we decided that including a control

group was beyond the scope of this thesis. However, as the *Guidelines for the Testing and Treatment of Gonorrhea in Ontario* recommending only ceftriaxone plus azithromycin were only released for use in Ontario, the rest of Canada would still be following the *Canadian Guidelines for Sexually Transmitted Infections*. The Canadian guidelines' gonorrhea chapter was updated in 2013 but the treatment recommendations remained the same as in the 2011 update notice. Treatment patterns from another Canadian province could potentially have been used as a control group to look at the effect of the most recent change in recommendations on prescribing practice in Ontario.

4) An interrupted time series analysis is dependent on the quality of the data used. The iPHIS data set that we used enabled us to conduct a population-based analysis studying a large number of cases (over 32,000) over a long period of time (over eight years). This allowed us to assess changes in clinician behaviour following the introduction of three new sets of treatment recommendations for the management of gonorrhea. The long time period and large number of cases allowed to include a large number of time points (219 biweekly time points between January 2006 to May 2014) with a large number of cases within each time point in our interrupted time series analysis. We met Shadish, Cook and Campbell's recommendation that an interrupted time series analysis include at least one hundred time points in order to correctly model autocorrelation.⁹⁵ The biweekly measures also allowed for sensitivity in detecting temporal trends⁹⁵ (such as changes in prescribing behaviour shortly after the guideline changes as well as the increased use of ceftriaxone in early 2011 prior to it being reintroduced as a first-line treatment recommendation).

The iPHIS database was designed for administrative purposes and only includes information reported to public health. Treatment information may be incomplete if a patient is re-treated without notifying public health. Data are collected and entered locally, and data collection and entry methods may differ between health units.

As iPHIS was a fairly new system at the start of the study period in 2006 and as there may have been recent emphasis on gathering information on treatment used

to manage gonorrhea due to increasing concern regarding antimicrobial resistance, we were concerned that there might be more missing treatment data earlier on in the study period, which could introduce some bias. Therefore, we looked at the distribution of cases with no treatment data over time. The incidence of completely missing data was fairly evenly distributed over time, reducing our concerns regarding this potential source of bias. The distribution of the proportion of cases with no treatment data over time is shown in Figure 5-2.

In discussion with staff at Ottawa Public Health, they identified some concern with data entry with regards to antibiotic dosage – they report picking up on occasion that the new dose of cefixime (800mg) or ceftriaxone (250mg) was administered but that the previously recommended dose was entered into iPHIS (400mg ceftriaxone or 125mg cefixime). It is possible that this data entry error (or similar errors such as antibiotic name) was also made on other occasions but not caught. These errors would likely be more frequent shortly after the change in guidelines and could lead to an underestimation of the proportion of cases receiving guideline-recommended treatment. The frequency of these errors could also vary between public health units depending on the individual(s) entering the data.

iPHIS data is also limited to the information that is reported to public health. Generally, laboratory information confirming the diagnosis of a case is reported to public health. A public health case manager will follow up with the patient and treating physician to gather further information that is then entered into the iPHIS system. If the patient receives further treatment after the information is provided to public health, this new information may not be reported and entered into the iPHIS system.

In setting up our data set, we did not consider treatment dates when determining whether a case had received first-line treatment. Some cases received multiple courses of treatment and were considered as having received first-line treatment if they received the appropriate dose(s) of antibiotics at any point. The proportions of cases who received first-line treatment would have been lower had we only considered those who initially received the recommended treatment or who

received both combination therapy drugs at the same time as having received the first-line treatment.

We were provided with a data set with a limited number of variables and were thus unable to conduct stratified analyses by geographic region, clinical setting, or physician's experience managing STIs.

Using process mapping to identify opportunities to improve the management of gonococcal infections in Canadian public health settings (Chapter 4)

This was a proof of principle study to demonstrate the value of process mapping in understanding the current treatment pathways followed for the management of gonococcal infection in order to identify the risk of guideline inappropriate care and potential opportunities to improve quality of care. Process mapping has been used very infrequently in the literature to address public health issues. We used process mapping to illustrate the complexity of managing gonorrhea infections across a variety of settings.

Process mapping is a useful tool as it can help visualize a complex series of processes and it forces the user to think closely of the processes and of how they work together. It can be used to identify weaknesses in the process such as unnecessary delays, the use of ineffective treatment choices, duplication of work (e.g., the repetition of lab tests), and wastage (e.g., unnecessary lab tests).¹²⁹ A process map can be populated with data in order to track the proportion of cases that follow each treatment pathway. This tracking can provide information for health planning purposes or can help identify where cases are receiving inappropriate care in order to take corrective measures.

Limitations of process mapping include the fact that it can be a time-consuming process. It can be challenging to ensure that all the relevant information required to map out all the possible pathways has been considered.¹²⁹ Process mapping can introduce a high level of complexity, which may be difficult to work with (such as our multi-page series of process maps) but more representative of the possible treatment pathways seen in the management of cases. Process maps can also be over-simplified, making the map easier to work with but not representative

of all cases ⁴¹ (e.g., process mapping may represent how cases are managed according to a protocol ¹²⁹ but may not include possible deviations from protocol which may occur in a real life setting). A process map may be challenging to populate with data because the data of interest may not be available or may be of poor quality. In our case, data availability dictated how we organized our process map. We had wanted to include a more granular breakdown of treatment settings (e.g. emergency department, walk-in clinic, general practitioner's office, obstetrics and gynecology practice) but because our data could only be broken down into seen at Ottawa Public Health's Sexual Health Clinic and seen elsewhere in the community, we opted to use this same breakdown in our process map.

As in Chapter 3, we used iPHIS data. However, the data set we used here was specific to the City of Ottawa and consisted of all cases with a home address within the City of Ottawa at the time of diagnosis. This data allowed us to look at the treatment pathways for all Ottawa cases of gonorrhea over a 3-year time period. For this study's purposes, the iPHIS data set had some limitations. iPHIS only records test results that confirm the diagnosis of gonorrhea, meaning that only positive tests are captured. Therefore, there is no denominator available to calculate percent positivity, or to appreciate the number of patients who were initially treated for gonorrhea only to test negative or patients who returned for test-of-cure or rescreening and tested negative. iPHIS does not include any contacts of a known case of gonorrhea who were treated but either did not undergo testing or tested negative. As described above, iPHIS data is also limited to the information provided to the local public health unit and thus there was missing information for many cases, including symptom information and/or care provider information. Additional information, such as follow-up treatment received if a patient is referred or recalled for retreatment, may also be incomplete.

Implications for policy and practice

The results of this thesis provide information that can help improve the management of gonorrhea infections in order to help slow the development of cephalosporin-resistant strains and prevent cases of treatment failure. With ongoing

concerns regarding antimicrobial resistance, recent case reports of treatment failure^{5, 7, 11, 108} and lab reports of resistance to current first-line treatment,^{6, 8-10, 101, 119, 130} we can anticipate that gonorrhea treatment guidelines will continue to be frequently updated and that clinicians will need to frequently change their prescribing behaviours. In order to increase the rates of adherence to current first-line treatment guidelines as well as to promote a more rapid uptake of future guidelines, we should consider the development and implementation of knowledge tools such as clinical guidelines.

The Knowledge to Action model (shown in Figure 5-3) was developed to describe how knowledge tools should be created and implemented.¹²¹ The central *Knowledge Creation Funnel* describes how knowledge is collected, synthesized and adapted into knowledge tools (e.g., a clinical guideline for the treatment of gonorrhea) that are meant to be concise and geared towards the needs of the user. The quality of a practice guideline both ensures that all relevant information is considered in making appropriate recommendations and may also improve end-user trust of the guidelines and recommendations, increasing the likelihood that a physician will follow the recommendations. Guideline developers may want to consider using the AGREE II tool⁷¹ or the Guidelines 2.0 checklist¹²⁰ as a guide as they develop new guideline documents or update current ones. The Guidelines 2.0 checklist is more extensive than the AGREE II tool and includes 18 topics and 146 items, guiding developers from initial planning all the way through to guideline evaluation and updating.¹²⁰

The results of our systematic review suggest that to improve the quality of their gonorrhea treatment guidelines, guideline developers may want to focus on *Rigour of Development, Applicability* and *Editorial Independence*, as these are domains that many guidelines did not score well on when assessed using the AGREE II tool.

The Guideline Implementability for Decision Excellence Model (GUIDE-M)¹³¹ is an evidence-informed model designed to assist guideline developers to create clinical recommendations that can more readily be implemented into practice. GUIDE-M consists of 3 core tactics, 7 domains, 9 subdomains, 44 attributes, and 40

subattributes and elements. The three core tactics consist of: (i) *Developers of Content*, (ii) *Creating Content*, and (iii) *Communicating Content*.¹³¹

Developers of Content identifies the importance of including a comprehensive range of experts, ensuring that developers are knowledgeable and credible, and that potential conflicts of interest in individuals involved with the guideline development are addressed.¹³¹

Guideline developers should involve a large multidisciplinary team to participate in guideline development. Gonorrhea is managed in a variety of settings, often by primary care physicians or emergency medicine specialists who may not have the same degree of STI knowledge or access to resources as physicians working in a sexual health clinic. Therefore, in order to improve applicability, primary care physicians and emergency doctors should be consulted about their needs in order to develop future gonorrhea treatment guidelines that address these needs and to create an implementation plan that will address challenges to clinicians, such as the administration of intramuscular antibiotics.

Policies should be in place to ensure that guideline recommendations are created independently of the influence of all funders. Any potential conflicts of interest of individuals involved in the development of recommendations should be declared and a policy should be in place to address these potential conflicts.

Creating Content consists of evidence synthesis as well as deliberations and contextualization.¹³¹

Evidence synthesis refers to how the evidence is collected, compiled and accurately used.¹³¹ Guideline developers should use systematic reviews to gather the evidence informing their guidelines. Developers should use tools such as GRADE¹³² to qualify the strength of evidence behind each recommendation. Plans should be made to update this evidence base regularly and to revise the recommendations as needed.

Deliberations and contextualization use the evidence base to develop recommendations that are feasible, clinically applicable, acceptable, and in line with clinicians', patients', and society's values.¹³¹ Guidelines could identify areas where a clinical recommendation may be challenging to follow (e.g., drug allergies, settings

where intramuscular antibiotics provide extra challenges such as correctional facilities, or patient refusal of injections) and offer strategies for managing these challenges and/or alternative treatment regimens.

Communicating Content includes both language and format.¹³¹ The language of a clinical guideline should be clear, simple, and persuasive in that it frames the recommended actions by highlighting their importance or benefits. Format includes the layout of the document as well as the modalities used. There could be a benefit in developing both print and electronic versions of the guidelines, developing a quick reference version that just highlights key recommendations, or developing guidelines for specific clinical settings, such as emergency departments or prenatal visits, or patient populations, such as pregnant women, sex trade workers, or transient populations.

All of these processes described above should be documented and available to guideline users to allow for better transparency. Guideline users should have access to the information needed for them to understand the guideline development process and appreciate the quality of the guideline.

The *Action Cycle* of the Knowledge to Action model describes the process by which knowledge should be implemented and involves seven steps:¹²¹

1-) *Identify the Knowledge-To-Action Gaps*: a needs assessment is conducted to determine where and how practice differs from the current knowledge in order to identify action(s) to target (e.g., our studies have demonstrated gaps in the treatment of gonorrhea suggesting the need for further actions to improve physician adherence to current treatment guidelines);

2-) *Adapt Knowledge to Local Context*: the knowledge tool is adapted to the local context of users (e.g., adapted to better meet the needs for users in a region, such as a remote setting where access to labs or specific drugs may differ, users in a specific setting such as an emergency department where follow-up protocols may need special consideration, or for users in a specific organization such as Ottawa Public Health's Sexual Health Clinic to align the guidelines with the organization's processes, resources, and personnel);

3-) *Assess Barriers to Knowledge Use*: potential barriers that may limit the uptake of the guidelines are identified (the COM-B framework to classify such barriers is described below);

4-) *Select, Tailor, Implement Interventions*: these knowledge translation interventions should be tailored to address the identified barriers (the Behaviour Change Wheel described later on in this section helps to identify the types of interventions that would be suited to address each of the COM-B barriers);

5-) *Monitor Knowledge Use*: this can either be done by testing knowledge (e.g.: testing clinicians with STI case vignettes and asking them how they would manage the case) or by assessing how cases have been managed (e.g. looking at antibiotic prescription information for the treatment of gonorrhea over time);

6-) *Evaluate Outcomes*: this is looking at the impact of the knowledge use: it can be assessed through looking at health impacts (e.g., the reported numbers of cases of treatment failure and changes in drug resistance patterns over time – keeping in mind that even with adherence to current treatment recommendations, we still anticipate that drug resistance will eventually develop and cases of treatment failure will occur, though we hope to see resistance develop at a slower rate), or clinician and/or patient satisfaction with the guidelines (here we anticipate that many clinicians and patients will not be happy with the change from oral to intramuscular antibiotics so perhaps it would be better to assess satisfaction with efforts to address this barrier rather than satisfaction with this recommendation);

7-) *Sustained Knowledge Use*: this refers to continued use and uptake of new knowledge. As gonorrhea treatment recommendations are expected to change again in short order in order to keep up with evolving antibiotic resistance trends, strategies to implement new recommendations must be considered along with strategies to promote continued use of current guidelines.

Guideline development and implementation is a complex process. There are often different players involved with and responsible for the development and implementation steps. In Ontario, the latest gonorrhea treatment guidelines were developed at the provincial level. Local public health is held accountable for local physicians' adherence to the current gonorrhea treatment guidelines through the

introduction of accountability agreements where funding transfers from the province are tied to a series of local public health performance measures including the rate of local adherence to the first-line treatment recommendations in the *Guidelines for the Testing and Treatment of Gonorrhea in Ontario*. However, although public health can reach out to local physicians and ask them to change their practice or contact cases to ask them to come in for re-treatment as part of the follow-up of reported cases of gonorrhea, they have limited influence on clinician and patient behaviour. Ultimately, local clinics and physicians are responsible for actually making the changes to their practices in order to follow the new guideline recommendations (e.g., ordering ceftriaxone and having sufficient staff on hand who can provide an intramuscular injection).

Our second study shows that change in clinical practice takes time, especially if it is a major change. In May 2014, over a year after the introduction of the *Guidelines for the Testing and Treatment of Gonorrhea in Ontario*, around 40% of cases did not receive first-line treatment. Guideline developers and policy makers need to consider ways to encourage the change to happen more rapidly to keep up with drug resistance patterns and current clinical guidelines. The limited adherence to the most recent guidelines may be due to lack of awareness of the change in recommendations but there may be other factors that are impeding the uptake of the most recent clinical practice recommendations. For example, because ceftriaxone is administered intramuscularly, it may not be convenient to administer in some clinical settings as it needs to be available on site and reconstituted just prior to injection. In addition, patients may refuse an injection and insist on receiving a second-line oral treatment. Patients may also have drug allergies or other medical conditions that impede the use of a cephalosporin or azithromycin or may take medication that is contraindicated for use with one of the first-line drugs.

Michie et al.'s Behaviour Change Wheel framework (shown in Figure 5-4) can be used to address the *Assess Barriers to Knowledge Use* and *Select, Tailor, Implement Interventions* steps of the Knowledge to Action model. This framework can be helpful in identifying why there are gaps in the use of current treatment guidelines as well as to identify interventions and policies to address these gaps. According to the

Behaviour Change Wheel, three conditions are required for a behaviour to occur: capability, opportunity, and motivation (COM-B). Capability refers to possessing the physical and psychological ability to undertake the desired behaviour, including knowledge and skills. Opportunity refers to factors in the physical and social environment that enable or prompt the behaviour. Motivation refers to how brain processes drive behaviour: this includes habit, emotions and analytical decision-making. Motivation is further broken down into reflective processes (e.g. conscious decision-making) and automatic processes (e.g. innate emotional responses).¹³³ The Behaviour Change Wheel identifies types of behaviour change interventions (environmental restructuring, restrictions, education, persuasion, modelling, enablement, training, coercion, and incentivisation), as well as categories of policies that could facilitate the interventions (fiscal measures, guidelines, environmental/social planning, communication/marketing, regulation, service provision, and legislation). The model identifies the types of interventions that are suitable for influencing each condition and the policy categories that could influence each type of behavior change intervention.¹³³

In identifying tools to assist with clinician behaviour change, one can determine which conditions out of capability, opportunity, and motivation are interfering with the adherence to current treatment guidelines and need to be influenced and then identify interventions and policies that are suitable for the factor(s) that we are looking to influence.

In terms of capability, clinicians may lack the knowledge of the new Ontario guidelines and may be continuing to follow the recommendations from the *Canadian Guidelines on Sexually Transmitted Infections* (which are still relevant in Ontario for the management of all STIs except for gonorrhea). As part of a green initiative and to allow for an evergreen version of the document to be readily available, the current version of the *Canadian Guidelines on Sexually Transmitted Infections* is only available electronically. Previously, hard copies of these guidelines were distributed to clinicians. Some clinicians may be continuing to use these hard copies, not realizing that they are out of date. Clinicians may lack the skill to provide intramuscular injections or may not have skilled support staff (e.g., a clinic nurse) who can provide

the injection. Educational programs or the promotion of new guidelines at conferences or medical events would enhance knowledge, as would feedback from local public health on the management of a recent case. Training in the administration of intramuscular injections as well as practice opportunities could improve skills.

With regards to opportunity, the clinical environment may make the use of ceftriaxone challenging. If cases of gonorrhea are infrequently seen, a clinical manager may be reluctant to stock ceftriaxone as it is likely to reach its expiry date before it is used. Some local public health units, such as Toronto Public Health and Ottawa Public Health, will deliver ceftriaxone to a physician's office on request either to manage a specific patient or to keep on hand (especially for clinics that see a high number of cases, such as university clinics or specialized clinics for men who have sex with men (MSM)). In more remote areas (e.g. northern Ontario where STI rates are similar to large urban centres¹⁷), the local public health department's offices may be quite far away and ordering ceftriaxone from local public health will require more coordination to ensure that it is delivered in a timely matter (e.g., if it is ordered from local public health after a lab diagnosis is made, waiting for delivery would delay treatment). In addition, there may be some factors in the social environment that may interfere with the adoption of the current gonorrhea treatment recommendations. Patients might refuse intramuscular treatment and insist on receiving cefixime or may avoid going for STI screening in order to avoid receiving intramuscular treatment. There may also be some settings, such as correctional facilities, where there may be safety concerns around the use of treatment by injection. Delivery systems can be improved to get ceftriaxone to community clinics in a timely manner. Ceftriaxone could be included as part of immunization deliveries since in Ontario, vaccines are provided to community health care providers through local public health. In remote areas with high rates of gonorrhea, keeping a small local stockpile of ceftriaxone (e.g., in a designated hospital or clinic) may allow for more timely access to first-line treatment.

With regards to motivation, clinicians may not believe that cefixime is any less effective than ceftriaxone or that treating a patient with a second line drug regimen

puts the patient at risk for treatment failure and selects for more resistant strains that can then be passed on to sexual partners. Social marketing campaigns to increase physician awareness around antimicrobial resistance and antibiotic stewardship may help motivate clinicians to adhere to the most current guidelines.

Our third study demonstrated how process mapping can be used to visualize how gonorrhea is managed in the City of Ottawa. This technique can also be used to evaluate other public health activities (for example, how tuberculosis cases in an urban setting are managed along the course of their treatment, or how a public health department inspects food establishments and how establishments that are not in compliance with public health regulations are managed). The process map can be used to identify when and where activities deviated from the intended process or where response times were slow or where policies or guidelines are unclear. By identifying where clinicians deviated from current clinical guidelines or communalities among clinicians who did not follow the guidelines, it is possible to identify and address why these deviations occurred.

In addition, our third study showed that by populating these process maps with routinely collected data, it is possible to identify target groups (such as community physicians as a whole) or target practitioners (if the process mapping drilled down to the individual practitioner level, we could identify specific physicians who have seen several cases but consistently do not follow current recommendations), or specific practices (e.g., treatment on speculation for symptomatic individuals or providing treatment to contacts of known cases before waiting for lab confirmation) to better focus knowledge translation efforts.

Implications for future research

Guideline compliance and STI management practices will likely differ between jurisdictions. Other studies have demonstrated differences in prescribing behaviour by geographic region, clinical setting, or physician's experience managing STIs.^{22, 53, 54, 56, 57, 59, 64} Further work should look at what is going on in the management of gonorrhea in other provinces or parts of Ontario where rates of

infection are high. In addition, sub-analyses could look at variations within a jurisdiction.

Given the importance of rapid guideline uptake, robust research on interventions to increase guideline uptake, such as the potential interventions discussed in the above *Implications for policy and practice* section would be valuable to inform both the further dissemination of current recommendations as well as the development and dissemination of future guidelines. The Behaviour Change Wheel Framework¹³³ can be used to design behaviour change interventions which can be implemented provincially. This intervention, or a collection of interventions could be developed to promote the current Ontario recommendations or could be launched with the next set of gonorrhea treatment recommendations. Following the release of the intervention, a study using our interrupted time series analysis methods could be used to assess any immediate changes in physician prescribing behaviour as well as more gradual trends following the release of the intervention in order to evaluate its effect.

Further work could be done to further populate the data in our set of process maps through chart reviews, records of Ottawa Public Health's distribution of gonorrhea treatment regimens to community settings, and laboratory data in order to include both positive and negative test results. Including all patients who presented for screening and test-of-cure, regardless of result, would also allow us to further expand on the number of potential pathways within the process maps. The process maps could also be evaluated for utility by conducting interviews or focus groups with local public health staff.

Future research could look at the applications of process maps more broadly, repeating the exercise to map out other public health activities or working with other public health departments to look at adapting this series of maps to depict the management of gonorrhea in other settings.

Summary

This thesis aimed to examine gonorrhea treatment guideline development, dissemination and uptake in order to identify potential means for improvement. The

widespread use of clinical guidelines based on up to date drug resistance patterns and evidence on effective antibiotic regimens will hopefully prolong the shelf life of currently available antibiotic regimens. To address these goals, this three-part thesis looked at:

- Gonorrhea treatment guideline development,
- Gonorrhea treatment guideline uptake at the provincial level, and
- Gonorrhea management at the local level.

Our studies found varied levels of guideline development and reporting quality in our systematic review of current gonorrhea treatment guidelines, delayed uptake of recent changes in gonorrhea treatment recommendations by Ontario physicians with approximately 40% of cases still not receiving first-line treatment over a year after the latest guidelines were released, and a higher frequency of missed opportunities for early treatment of gonorrhea in Ottawa community settings (in comparison to Ottawa Public Health's Sexual Health Clinic).

These findings can inform future guideline development, guideline dissemination, efforts by public health to work with community physicians to improve the management of gonorrhea, as well as future research on appropriate knowledge translation interventions.

Figure 5-1. Percent of gonorrhea patients receiving dual treatment of cefixime or ceftriaxone plus azithromycin or doxycycline over time from January 1, 2006 to May 31, 2014.

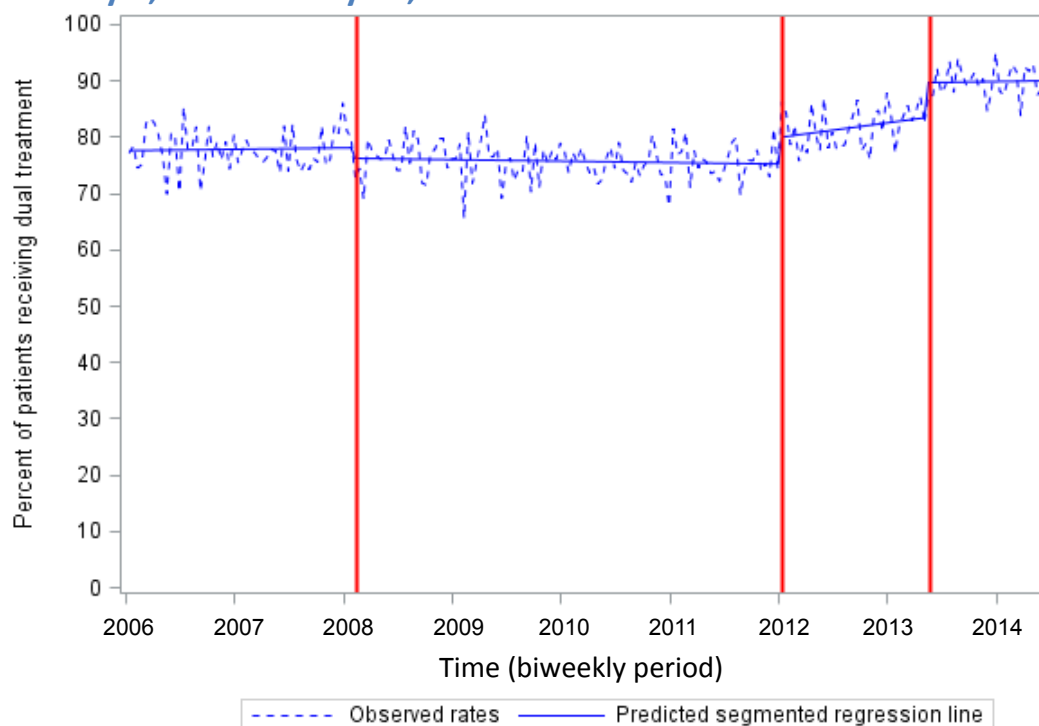


Table 5-1: Segmented regression analysis of percent treatment of gonorrhea with combination therapy of either cefixime or ceftriaxone plus azithromycin or doxycycline, showing regression coefficient estimates, standard errors and p-values.

	Regression coefficient	Standard error	p-value
2004 Canadian Guidelines on Sexually Transmitted Infections update (measured as of January 1, 2006)			
Intercept	77.5	0.92	<0.0001
Baseline trend	0.01	0.03	0.75
2008 Canadian Guidelines on Sexually Transmitted Infections update (January 2008)			
Level change after 2008 guideline change	-1.86	1.12	0.10
Trend change after 2008 guideline change	-0.02	0.03	0.54
2011 Canadian Guidelines on Sexually Transmitted Infections update (December 2011)			
Level change after 2011 guideline change	4.70	1.33	0.0005
Trend change after 2011 guideline change	0.11	0.06	0.06
2013 Guidelines for Testing and Treatment of Gonorrhea in Ontario (April 2013)			
Level change after 2013 guideline change	6.25	1.71	0.0003
Trend change after 2013 guideline change	-0.09	0.10	0.35

Figure 5-2. Percent of gonorrhea patients with no gonorrhea treatment data available over time from January 1, 2006 to May 31, 2014.

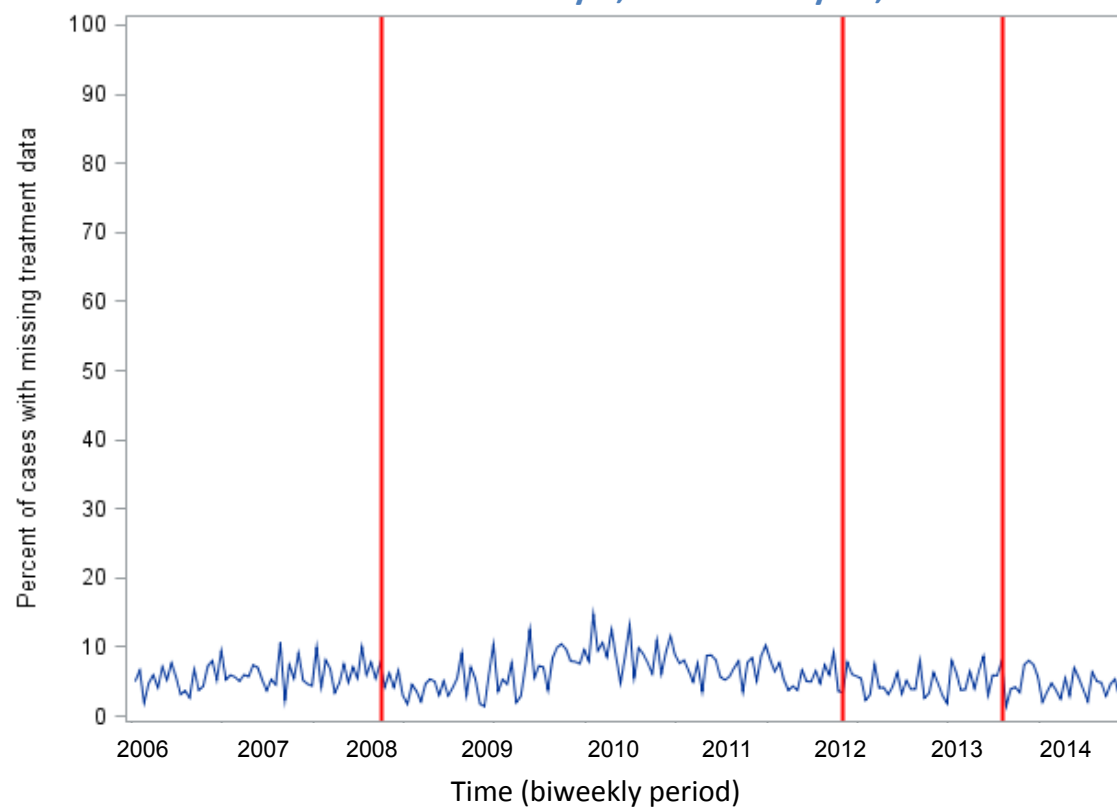


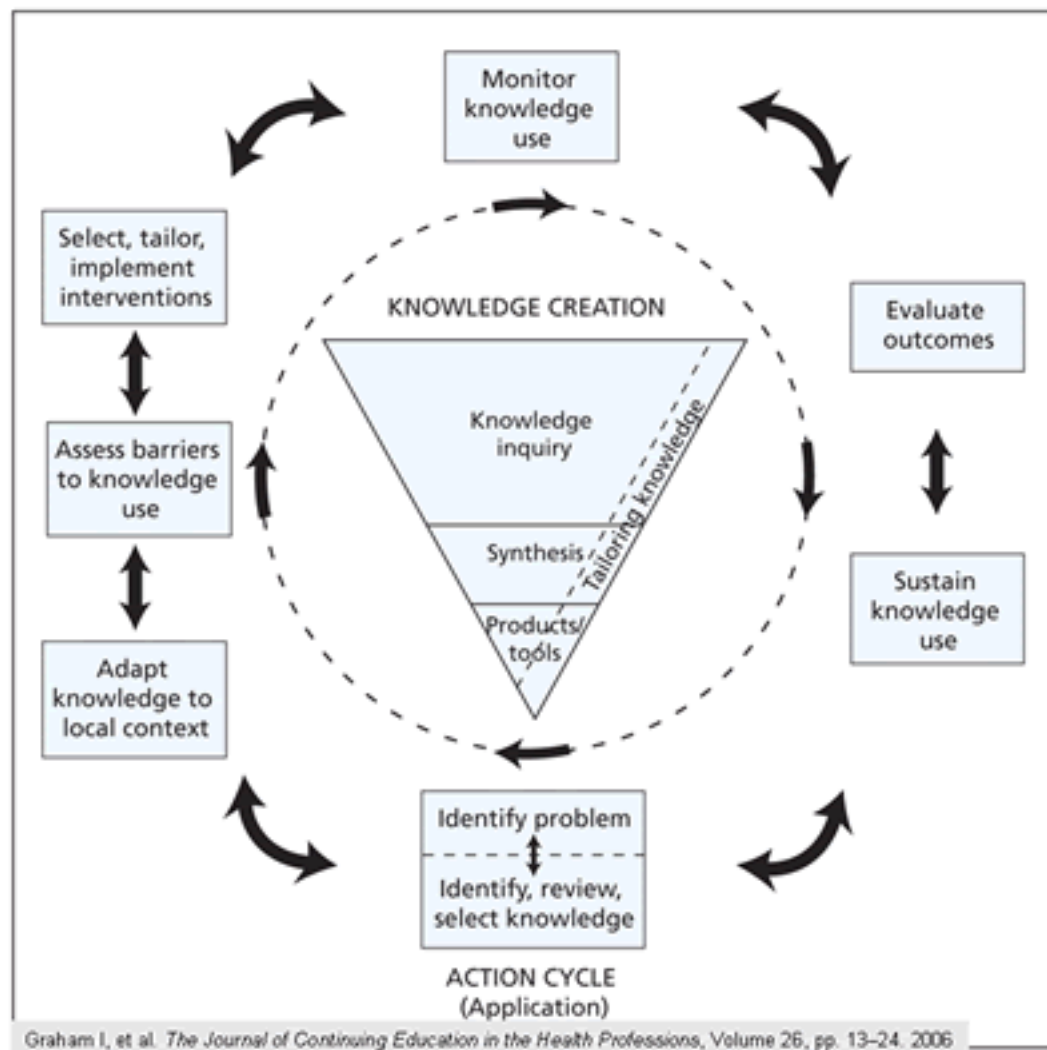
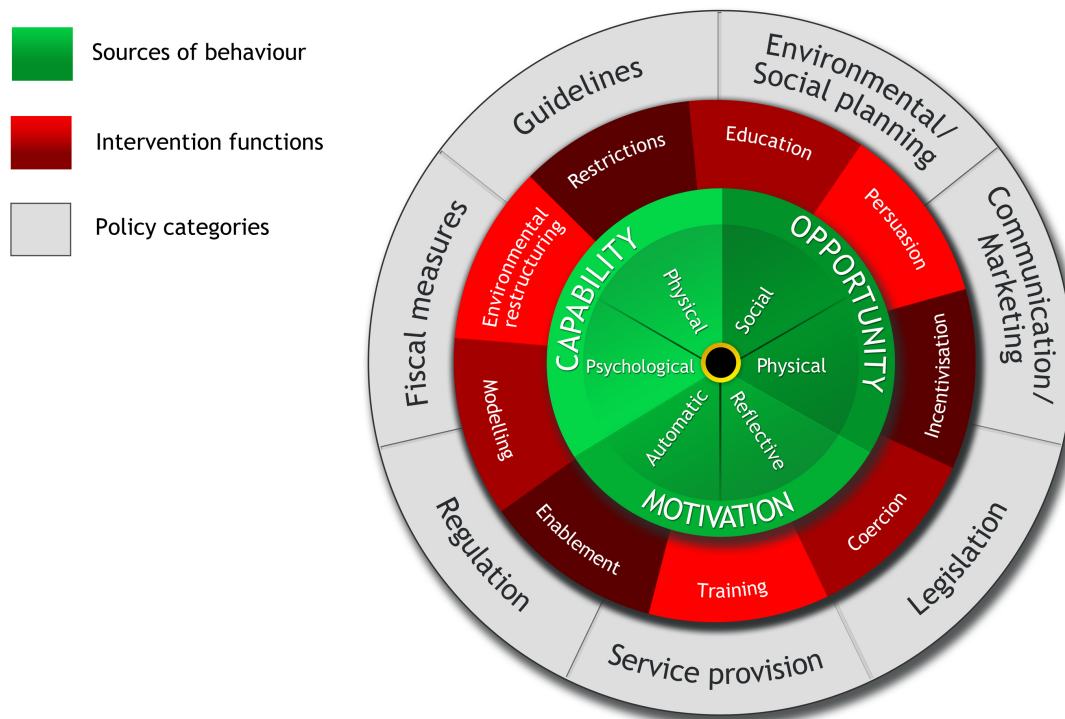
Figure 5-3: The Knowledge-to-Action Model ¹²¹

Figure 5-4 The Behaviour Change Wheel ¹³³

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