Modelling of pandemic influenza in Canada: predicted burden and hospital-resource adequacy

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A thesis submitted to the
Faculty of Graduate and Postdoctoral Studies
In partial fulfillment of the requirements for the
Doctorate in Philosophy degree in Population Health

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For Mom and Dad — my first teachers —

And for Jane Reisman — my partner in everything that comes next

Abstract

For centuries, pandemic influenza has emerged at irregular and unpredictable intervals to cause widespread illness, hospitalization and death. Uncertainty surrounding the timing and severity of future influenza pandemics present challenges for preparedness and response efforts. The objective of this dissertation is to advance pandemic influenza knowledge and preparedness, through a series of interrelated articles that address the follow research questions:

1. What are the likely consequences of a pandemic flu event in Canada?
2. What do mathematical models tell us about preparing for such an event?
3. What is the best way to mitigate the consequences of an influenza pandemic?

Six articles were prepared for submission in scientific, peer-reviewed journals. The first is a historical review of the burden of pandemic influenza. The second and third are systematic reviews of the effectiveness of interventions to interrupt pandemic influenza transmission. The fourth and fifth are research papers presenting a novel mathematical model, assessing the preparedness of the Canadian hospital system to accommodate expected surges in patient demand and evaluating intervention strategies to mitigate impact. The sixth is a policy-oriented paper discussing pandemic policy options within the context of public health ethics and risk management principles.

Pandemic vaccination, antiviral treatment, voluntary isolation and personal protective measures were identified as the most cost-effective interventions available. Antiviral prophylaxis, community-contact reduction, school closure and quarantine were less effective, and tended to be associated with higher associated economic burdens. The timely implementation of layered intervention strategies appears likely to protect hospital-resource adequacy, though areas of Southwestern Ontario appear to be more vulnerable to surges in patient demand. However, the

potential for high health and economic burdens, coupled with the uncertain severity of future pandemics, necessitates a flexibility in preparedness and response plans.

Acknowledgements

I would like to take this opportunity to recognize and thank a few of the individuals that were instrumental in the development of this project. I am grateful to my supervisor, Dr. Daniel Krewski, for supporting this project while giving me the freedom to shape it in a way that I found interesting and meaningful. I would also like to express my appreciation to Dr. Robert Smith? and Dr. Lindy Samson, members of my internal thesis committee that were so generous in volunteering their time and expertise throughout this process. Thanks also go out to Dr. Raywat Deonandan and Dr. Mark Loeb for their insightful questions and comments during the thesis defense process.

I benefitted greatly from the contributions of Bryson Quinn Hayes, Dr. James Crispo, Lindsey Sikora and Jane Reisman, co-authors who contributed to various aspects of this work. I am extremely fortunate to have had the opportunity to work with such talented researchers, and greatly appreciate the time and effort they dedicated to this work.

I would like to thank the McLaughlin Centre, the University of Ottawa and the Ontario Ministry of Training, Colleges and Universities for recognizing the potential of this research and providing financial support during my doctoral degree.

Lastly, I would like to thank my family and friends for their support and encouragement over the past five years. To my dad, from whom I learned and grew in all aspects of life: thank you for reminding me that "a good thesis is a done thesis". I hope you see. I will be forever grateful for the support, motivation and inspiration I received from my mom, as well as my siblings Emma, Katie and Owen. A big thank you to Ron for giving me my first job, and for being kind enough to intersperse "smiley faces" with insightful critiques of my work. To Stella: you are a constant source of love and distraction, and the best officemate I could have hoped for. And, lastly, to my wife

Jane: I could dedicate the remainder of this dissertation to thanking you for all you have done for me. You walked every step of this process with me, and this thesis would not have been completed without you.

Co-authorship

This work benefitted from the contributions of several invaluable collaborators. Below is a list of author contributions for each of the six manuscripts prepared and presented in subsequent chapters of this dissertation.

For the historical review presented in **Chapter 2**, Patrick Saunders-Hastings conceived the project, carried out the research and drafted the article. Dr. Daniel Krewski provided comments and feedback throughout the process, and contributed to the finalization of the draft article. Both authors approved the final version of the manuscript.

For the systematic review presented in **Chapter 3**, Patrick Saunders-Hastings conceived the project, developed the search strategy and protocol, conducted article screening, data extraction and drafted the article. Jane Reisman contributed conducted article screening and data extraction, provided comments and feedback throughout process and contributed to the finalization of the draft article. Dr. Daniel Krewski provided comments and feedback throughout the process and contributed to the finalization of the draft article. All authors approved the final version of the manuscript.

For the systematic review presented in **Chapter 4**, Patrick Saunders-Hastings conceived the project, developed the search strategy and protocol, conducted article screening, data extraction, and meta-analyses, and drafted the article. Dr. James Crispo conducted article screening and data extraction, provided comments and feedback throughout process and contributed to finalization of the draft article. Lindsey Sikora reviewed the search strategy and contributed to finalization of the draft article. Dr. Daniel Krewski provided comments and feedback throughout process and

contributed to finalization of the draft article. All authors approved the final version of the manuscript.

For the research article presented in **Chapter 5**, Patrick Saunders-Hastings conceived the project, designed the model, conducted the analyses and drafted the article. Bryson Quinn Hayes contributed to model design, coded the model, conducted the sensitivity analysis and contributed to finalization of the draft article. Drs. Robert Smith? and Daniel Krewski provided supervision throughout the project and contributed to finalization of the draft article. All authors approved the final version of the manuscript.

For the research article presented in **Chapter 6**, Patrick Saunders-Hastings conceived the project, designed the model, conducted the analyses and drafted the article. Bryson Quinn Hayes contributed to model design, coded the model and contributed to finalization of the draft article. Drs. Robert Smith? and Daniel Krewski provided supervision throughout the project and contributed to finalization of the draft article. All authors approved the final version of the manuscript.

For the research article presented in **Chapter 7**, Patrick Saunders-Hastings conceived the project, carried out the research and drafted the article. Drs. Lindy Samson and Daniel Krewski provided comments and feedback throughout the process, and contributed to the finalization of the draft article. All authors approved the final version of the manuscript.

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Chapter 1. Introduction

Global outbreaks of disease have created illness and death for millennia. Their earliest recording dates back to 412 BC, while historians suggest that 12 worldwide disease outbreaks occurred between 1600 and 2000 AD [1]. Now, however, globalization processes are altering the social and physical environment in ways that are making humans more vulnerable to the emergence and spread of infectious diseases. Continued human-animal interaction, driven by farming practices, live animal markets and trade in livestock and pets, coupled with increasing viral diversity and international trade and travel, increase the risk of viral emergence and accelerate their movement across international borders [2, 3]. One of the diseases of greatest concern is influenza, which emerged to cause a global pandemic as recently as 2009. Fears also persist regarding the pandemic potential of avian influenza subtypes H7N9 [4, 5] and H5N1 [6, 7], both of which have been transmitted to humans but have yet to establish sustained human-to-human transmission.

A key element of Canadian pandemic planning is to maintain essential health services and minimize disruption of other health services while limiting influenza-related illness and death. In this dissertation, I seek to advance pandemic influenza preparedness by drawing on empirical data from past pandemics to inform the development and application of a novel mathematical model. Specifically, I seek to address three related research questions:

1. What are the likely consequences of a pandemic flu event in Canada?
2. What do mathematical models tell us about preparing for such an event?
3. What is the best way to mitigate the consequences of an influenza pandemic?

This dissertation is situated at the intersection of mathematical modelling and public health emergency management, presenting a new influenza model reflecting Canadian contexts. This age-structured, differential equation model combines disease transmission dynamics, empirical social contact data, evidence-based interventions and economic data to predict the potential severity of future pandemics in Canadian cities, using this as the foundation from which to assess health system preparedness for future outbreaks of unknown severity. It is the first known project of this scale to be conducted within a Canadian context. While evaluations and recommendations will apply specifically to Canada, it is expected that certain themes and principles can be applied more broadly to other developed countries.

This introductory chapter begins by providing a brief definition of population health and the relevance of improved pandemic influenza preparedness (**Section 1.1**). This is followed by a description of pandemic influenza (**Section 1.2**), the role of mathematical models in the control of emerging diseases (**Section 1.3**), a brief history of epidemic modelling **(Section 1.4**), an analysis of persisting gaps in pandemic influenza knowledge base **(Section 1.5)** and a summary of the chapters to follow (**Section 1.6**).

1.1 Population health

Population health is a broad, interdisciplinary field of research that has been defined as the study of the "health outcomes of a group of individuals, including the distribution of such outcomes within the group" [8]. These distributions may be based on geography, age, gender, socioeconomic status or a range of other characteristics. The defining characteristic of population health is a focus on collective well-being over the individual outcomes more commonly associated with clinical medicine [9]. Key elements of population health research involve efforts to optimize allocation of

resources to effectively link health determinants with health outcomes [8]. This involves comparative cost-effectiveness of resource allocation strategies.

From this definition, it becomes clear that efforts to advance public health emergency preparedness will depend on — and advance the field of — population health science. In fact, emerging infectious diseases were recently identified as one of the complex public health problems that could be meaningfully addressed by population health research [10]. There are three main reasons for this: infectious disease emergencies constitute situations where the collective good must be prioritized over individual well-being; it is important to study the patterns and distributions of disease burden, particularly as they relate to geography and age; and resource constraints in emergency situations necessitate optimally cost-effective intervention strategies. These themes are promoted throughout my analysis of the evolution of pandemic influenza in Canada and strategies to mitigate its impact. In this way, by combining mathematical modelling and infectious disease epidemiological approaches, I hope to advance the field of population health science.

1.2 Pandemic influenza

The disease of interest for this dissertation is influenza. Influenza is a highly infectious disease caused by the inhalation of droplets carrying viral particles that attack the respiratory system [1]. Influenza pathogenicity and symptom severity can vary, but can include systemic (fever, headache, myalgia), upper respiratory (sore throat, runny nose) and lower respiratory (cough and phlegm) symptoms [11]. While most people will recover on their own, complications most commonly related to lower respiratory tract infection (pneumonia, bronchitis, croup) and — particularly among pediatric cases — neurological problems (encephalopathy, encephalitis, transverse myelitis) can lead to hospitalization and death, and influenza is the most deadly vaccine-preventable disease in North America [12, 13]. High-risk groups include children, the elderly,

obese individuals, pregnant women, nursing home residents, immunocompromised individuals (such as HIV positive individuals or those on chemotherapy) and those with pre-existing conditions such as asthma, chronic lung disease, metabolic diseases, cardiovascular or neurological disease and renal disorders [14, 15].

In the seven years since the concept was introduced, the World Health Organization has declared four Public Health Emergencies of International Concern (PHEIC): swine flu (2009), Poliomyelitis (2014), hemorrhagic Ebola Virus Disease (2014) and Zika virus (2016) [16, 17]. According to International Health Regulations, a PHEIC is defined as "an extraordinary event which is determined…to constitute a public health risk to other States through the international spread of disease and to potentially require a coordinated international response" [18]. This does not include other serious infectious disease outbreaks, such as the 2002–03 spread of SARS to 32 countries, as this occurred before the establishment of PHEIC [19, 20]. Further, it excludes outbreaks that were nearly declared PHEIC, such as Middle-Eastern Respiratory Syndrome [21], and circulating diseases with recognized pandemic potential, such as H5N1 avian influenza, despite both having case fatality rates of approximately 50% [22]. This trend of increasing viral emergence and geographical spread is concerning, and presents significant challenges for public health planning and response. This project seeks to contribute to this field of knowledge by presenting an innovative model of disease spread combining four layers of analysis: disease spread, hospital surge capacity, control measure impact and economic burden.

The study will focus on the threat of future pandemics in Canada. Though a developed country with a well-regarded health system, Canada does not perform as well as expected on several important health system indicators, especially when compared to other OECD countries. A 2007 study found that the Canadian health system performed poorly – relative to other Commonwealth

countries — across indicators such as same-day access to a physician and wait-times for hospital admission, tests and discharge [23]. A recent assessment of OECD primary health systems, conducted by the Commonwealth Fund, found that Canada consistently ranked among the worst developed countries in primary care performance indicators such as the proportion of medical practices with arrangements for after-hours access to a physician or nurse (43%) and the proportion of physicians using electronic medical records (37%) [24]. Recently, Canada has been exposed to several infectious disease outbreaks with pandemic potential. It was among the countries worst hit by the 2002 outbreak of severe acute respiratory syndrome (SARS) [25-27] and by the 2009 outbreak of H1N1 swine flu [28, 29]. Taken together, these findings suggest that the Canadian health system must improve and streamline processes to accommodate emergency situations involving surges in patient demand. Of concern, however, is that a lack of performance measurement within Canadian health systems has resulted in no comprehensive, independent assessment of the preparedness of the Canadian hospital and primary health care system to respond to, manage and mitigate the consequences of the next pandemic [23, 24]. This obstructs evidence-based risk management decision-making to prepare for, and react to, future pandemics. The goal of this dissertation is to address this knowledge gap.

1.3 Mathematical models

As the characteristics of a pandemic strain cannot be known prior to its emergence, there is a high degree of uncertainty in pandemic planning. Empirical studies, meanwhile, are often either infeasible or unethical in pandemic emergency situations. Further, is little time for indecision once an influenza pandemic has begun, so efficient and evidence-based protocols are required in advance of emergence.

Mathematical models have become vital tools in the preparatory and evaluative process in the inter-, pre- and post-pandemic periods. Models allow the synthesis of data and assumptions relating to a disease to produce rapid, inexpensive and quantitative assessments of likely epidemic evolution, burden and containment strategies [30, 31]. As data on the new disease becomes available, public-health practitioners benefit from the ability to make predictions regarding likely pandemic evolution, spread and burden.

Mathematical models can be categorized into differential equation and stochastic models [32]. Traditional differential equation models translate real-world assumptions into a system of equations that project the average transmission dynamics, and are most accurate in models of larger populations. Stochastic models introduce elements of randomness to account for uncertainty in disease transmission, and are particularly effective in charting disease transmission among small populations where randomness is a more dominant process. In a recent review of 91 influenza models, 58 were differential equation models. In this study, I developed and used a differential equation model, being most interested in macro-level transmission processes that would lead to large-scale increases in patient demand, thereby threatening the local health system. As such, it was reasonable to model the average transmission dynamics expected.

The most important transmission parameter for infectious disease models tends to be R_0, the basic reproductive number. This number represents the average number of new infections that would result from the introduction of an infectious individual into an entirely susceptible population. As a general rule, epidemic theory holds that if $R_0 > 1$ an outbreak will occur, while if $R_0 < 1$ an outbreak will die out. The problems associated with this simplified approach, and the next-generation operator approach used in my model, are discussed in detail in **Chapter 5**. However, this threshold parameter provides value in estimating pandemic influenza

transmissibility: most estimates of the R_0 for the most recent four influenza pandemics range from 1.3 to 2.3 [33].

1.4 History of epidemic modelling

Epidemiological models are crucial instruments to predicting the spread of infectious disease and assessing intervention plans to control outbreaks. While Bernouilli developed a simple model in 1760 for estimating the impact of inoculation on the smallpox-associated death rate in France [34], epidemiological modelling did not really emerge until the early 20th century [35].

There were some basic models developed before the 1918 pandemic, such as a discrete-time model Hamer developed to study measles epidemics [36]. However, progress in this field began in earnest in 1926, when Kermack and McKendrick published models demonstrating how the density of susceptible individuals in an area would impact infectious disease outbreaks [37, 38]. Modelling grew rapidly from this point through the middle of the 20th century, as described in detail in past reviews of modelling literature [35, 39-42]. Early iterations of infectious disease models were deterministic, compartmental models, which track the movement of populations through classes that include: Susceptible (S), Exposed (E), Infective (I) and Recovered (R). Popular variations of these models (illustrated in **Figure 1**) were selected based on the research questions and natural history of the disease of interest. These categories constitute the foundation of modern mathematical models in infectious disease epidemiology [35].

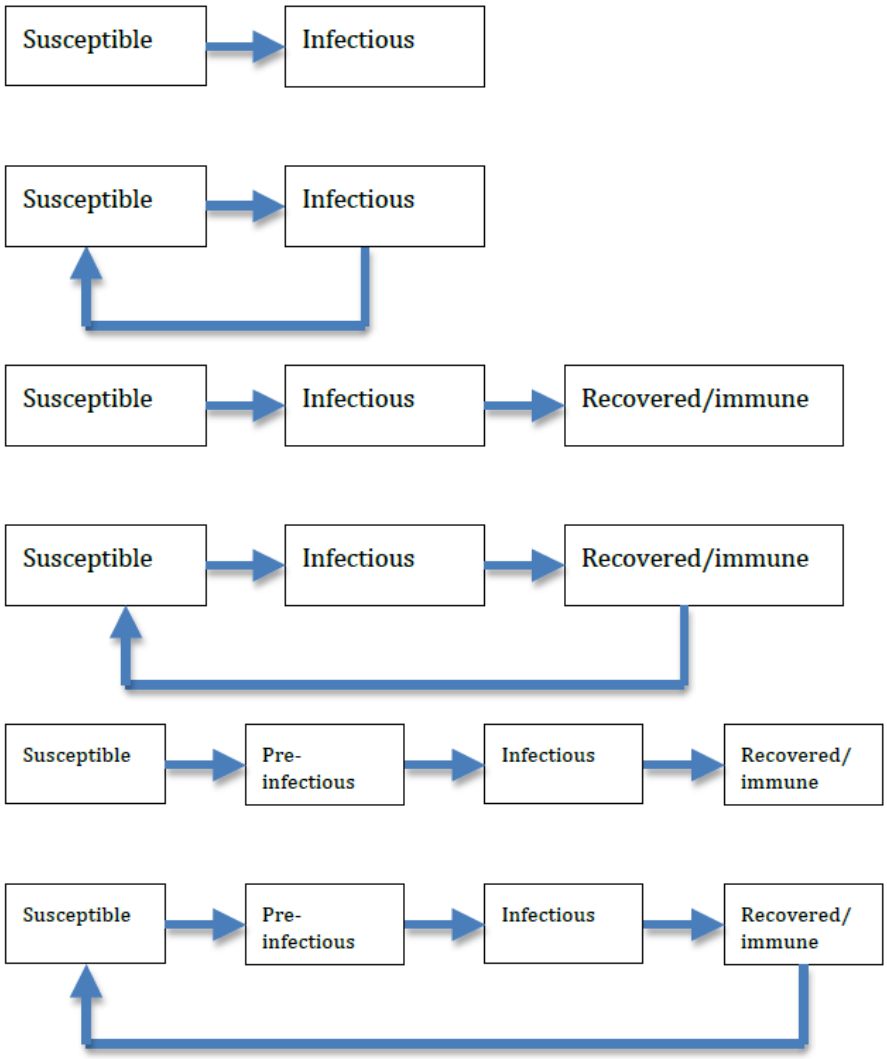

Figure 1. Common structures for compartmental models describing infectious disease transmission.

Around the same time, stochastic models were developed as a means of incorporating the randomness and uncertainty associated with real-world outbreaks [38]. More complex and less intuitive than deterministic models, these were slower to be popularized; it was not until 1949 that they would be mainstreamed [43]. Given the focus of this dissertation on assessing pandemic threats among large populations over the course of an outbreak — coupled with an emphasis on

model transparency and usability — I chose to use a deterministic, differential equation model. In the late 1940s, models were still simplistic and constrained by limited technological capabilities, and they were not yet used extensively to inform policy action. However, this period provided an important foundation to be built upon in the latter half of the 20th century.

The variety and use of epidemiological models to direct infectious disease control expanded rapidly in the second half of the 20th century [35]. This was driven in large part by the growing availability and functionality of computer technology. Though the first digital computer was built in 1946, it was not until 1969 that host computers would be connected on a common network, and not until 1991 that the World Wide Web was introduced [44]. New computer modelling capabilities allowed increased heterogeneity in model assumptions and areas of focus [41, 45-47]. Models were built to better reflect understanding of passive, acquired and waning immunity, stages of infection, age structure, mixing groups, spatial transmission dynamics and intervention impact, developing ways to express these concepts mathematically to inform and direct policy decisions [35]. The expanded functionalities provided more precise estimates of what might be reasonably expected from a future pandemic, as well as an assessment of potential intervention impact. Meanwhile, federal and regional health agencies scaled up surveillance practices, including household cohort studies that inform parameters for influenza transmission models [48-50]. Most surveillance, however, was based solely upon patients who sought medical care, thereby excluding asymptomatic or self-limiting infections, underestimating the burden of influenza and ignoring important routes of disease transmission [48]. Since the 2009 H1N1 pandemic, a wide array of models have been introduced to evaluate pandemic policies and planning strategies [32].

1.5 Outstanding knowledge gaps

Influenza pandemics occur at irregular and unpredictable intervals, making preparedness efforts of critical importance. Problematically, existing models tend to focus on predicting potential illness and death, with relatively little discussion of resource adequacy to respond to potential outbreaks. An important step is therefore to develop a model that better compares expected resource needs against current capacity. To date, there has been no known, comprehensive, independent assessment of the preparedness of the Canadian hospital and public health system to respond, manage and mitigate the consequences of the next influenza pandemic. This knowledge gap was noted at a recent gathering of public health experts, who concluded that modelling should better address issues relating to acute care service provision, particularly as it relates to hospital surge capacity [51]. This dissertation aims to fill this knowledge gap.

This dissertation also addresses identified gaps in the mathematical modelling of pandemic influenza. Recent reviews have identified several concerns and challenges relating to the use of pandemic influenza models [32, 52]. First, more sophisticated validation to support the credibility of model assumptions and results is needed, as too many models rely on the use of previously published model parameters that have not been validated by observed data [32]. My model relies on sophisticated parameterization with empirical pandemic data, alongside an assessment of its structural and predictive validity. Second, it has been suggested that models must better incorporate human behaviour, as this is commonly neglected [52]; using the next-generation operator approach, I include numerous measures of human behaviour as they relate to age- and location-specific contact behaviour, intervention adherence, and treatment-seeking behaviour. Third, recognizing that models provide approximations of expected behaviour, there is a need for models to be flexible and responsive to shifting assumptions as epidemiological data becomes

available in real-time, in order to provide rapid analysis to inform decision-making [51, 52]. The model presented herein is flexible to shifting assumptions as new data become available.

Perhaps most fundamentally, there have been repeated calls for mainstreaming of pandemic modelling in policy decision-making [31, 51]. Shortcomings to date are due in part to a lack of accessibility of relevant models, coupled with a lack of model literacy among public-health practitioners who are unlikely to have formal training in the field [52]. Another challenge is the computational burden of many pandemic models; this has impeded operability on personal computers and scalability to different population groups [52]. Taken together, the result has been a disconnect between mathematical modelling and pandemic decision-making in Canada, and a failure to optimize an effective response to public health emergencies through the combined, synergistic expertise of modellers, planners and policymakers [51]. In this dissertation, I introduce a novel mathematical model that is based on realistic, evidence-based assumptions and can be made accessible to policy-makers through a General User Interface; it is both scalable and operable on a personal computer. In this way, I seek to bridge the fields of mathematical modelling and pandemic planning to advance our capabilities in infectious disease emergency response.

1.6 Chapter summary

This dissertation is presented in a series of sequential, inter-related articles that have been submitted for publication in public health journals. **Chapter 2** provides a history of pandemic influenza, examining the global and Canadian experience with respect to the health, social and economic burdens of the four influenza pandemics to occur in the past century. I discuss how the parallel processes of globalization and public health advancement have created an environment in which humans are at greater risk of viral emergence, but are better prepared to mitigate its consequences.

Chapters 3 and **4** present two systematic reviews of pandemic influenza intervention effectiveness. **Chapter 3** constitutes a systematic review and narrative synthesis of existing systematic reviews, as a means of efficiently synthesizing existing knowledge, informing pandemic planning and parameterizing my mathematical model. **Chapter 4** is a systematic review and meta-analysis, filling the knowledge gap relating to effectiveness of personal protective measures in preventing pandemic influenza transmission, noted in **Chapter 3**.

Chapter 5 combines findings from the previous three chapters with a sophisticated review of modelling methodology to present the novel mathematical model. Taking the Ottawa–Gatineau Census Metropolitan Area as a study population, I provide a detailed discussion of the model structure and approach, and chart the likely burden of a future influenza pandemic across 192 intervention scenarios and multiple health and economic endpoints.

Chapter 6 provides a national-level assessment of Canadian pandemic preparedness, by conducting simulations across all 33 Census Metropolitan Areas. Under four scenarios of varying influenza transmissibility and pathogenicity, I identify areas at greatest risk of high pandemic-associated burden, where hospital-resource capacity risks being overwhelmed by surges in patient demand. This is done in the context of optimal vaccine-allocation strategies in the inter-wave period.

Chapter 7 combines findings from previous chapters with principles of public health ethics and risk management to offer policy recommendations to improve pandemic preparedness. This involves a discussion of the tensions and trade-offs between different principles, and how their application can inform pandemic policy.

Chapter 8 provides a brief synthesis and concluding comments, contextualizing this dissertation within the existing knowledge base, establishing its knowledge contributions, evaluating the project limitations and mapping out avenues for future research.

Chapter 2. Reviewing the history of pandemic influenza: understanding patterns of emergence and transmission

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Publication Status Information

This manuscript was published in December, 2016 by *Pathogens* (Saunders-Hastings, P. & Krewski, D. (2016). Reviewing the history of pandemic influenza: understanding patterns of emergence and transmission. *Pathogens*, *5*(4), 66. doi:10.3390/pathogens5040066)

Abstract

For centuries, novel strains of influenza have emerged to produce human pandemics, causing widespread illness, death and disruption. There have been four influenza pandemics in the past hundred years. During this time, globalization processes, alongside advances in medicine and epidemiology, have altered the way these pandemics are experienced.

Drawing on international case studies, this paper provides a review of the impact of past influenza pandemics, while examining the evolution of our understanding of, and response to, these viruses.

This review argues that pandemic influenza is in part a consequence of human development, and highlights the importance of considering outbreaks within the context of shifting global landscapes. While progress in infectious disease prevention, control and treatment has improved our ability to respond to such outbreaks, globalization processes relating to human behaviour, demographics and mobility have increased the threat of pandemic emergence and accelerated global disease transmission.

Preparedness planning must continue to evolve to keep pace with this heightened risk. Herein, we look to the past for insights on the pandemic experience, underlining both progress and persisting challenges. However, given the uncertain timing and severity of future pandemics, we emphasize the need for flexible policies capable of responding to change as such emergencies develop.

2.1 Introduction

Influenza pandemics, distinguished from epidemics on the basis of their geographical spread, have caused significant illness, death and disruption for centuries. In recent decades, however,

globalization has driven social and economic changes that have enhanced the threat of disease emergence and accelerated the spread of novel viruses. Conversely, globalization has also facilitated international cooperation, promoting advances in disease research and surveillance. Collectively, these changes alter the way that pandemics originate and are experienced, understood and controlled. This paper examines how changes in human demographics, economic systems, medical capabilities and epidemiological practices have affected the consequences of pandemic influenza, and the approaches to, and challenges in, responding to outbreaks. In the past century, four novel influenza strains have emerged to cause a global pandemic. These pandemics are addressed in sequence, highlighting pandemic origins, responses and consequences. This review is complemented by an analysis of how change in the intervening years between pandemics — with respect to globalization processes and to infectious disease practices — impacted exposure to, and preparedness for, the subsequent pandemic. We begin with a brief discussion of the disease and a background on pandemics from the more distant past.

2.2 The disease

Influenza viruses are named for the Latin *Influentia*, or "influence" [53]. Belonging to the Orthomyxoviridae family, they have a genome made up of eight segments, which together code for ten proteins [54]. Strains can be separated into types A, B and C. The present review deals exclusively with influenza type A. While types A and B are responsible for the majority of morbidity and mortality, type A is the only one with pandemic potential [55]. This is because type A is the only strain with an animal reservoir. Aquatic birds and swine are important reservoirs for influenza A, presenting obstacles to eradication and providing opportunities for viral mutation and reassortment [56].

The highly variable nature of influenza genetic material prevents maintenance of an adequate immune response acquired from previous infections, leading to annual epidemics of "seasonal influenza" [57]. Associated lower respiratory infections cause between 28,000 and 111,500 deaths globally in children under five years of age alone [58]. While the focus of this work is on the more catastrophic potential of pandemic strains, the continued burden of seasonal influenza strains suggests that co-benefits of pandemic flu planning extend to seasonal flu preparedness, as well as to other infectious disease outbreaks.

Influenza virus subtypes are distinguished based upon the antigenic properties of two surface glycoproteins: hemagglutinin (H) and neuraminidase (N), which promote and coordinate host cell entry and exit, respectively. The United States Centers for Disease Control and Prevention identifies 18 H subtypes and 11 N subtypes, for a theoretical total of 198 strain variations [59]. However, only H1, H2 and H3 are known to have achieved substantial human-to-human transmission [60].

Antigenic *drift* — a result of mutations in the genes encoding the H and N antigens — occurs continuously and drives the evasion of host immune system response that produces outbreaks of seasonal influenza [61]. This is the result of the RNA stranded genome, which lacks the ability to correct mistakes during replication. Antigenic *shift* is far rarer, and arises from the viral reassortment of two different influenza viruses that co-infect the same host, creating a new virus [61]. If the novel virus has the ability to infect humans and achieve human-to-human transmission, and possesses virulence for humans, a pandemic may arise, as humans are unlikely to have appreciable immunity to the novel strain. Within the past one hundred years, four pandemics have resulted from the emergence of a novel influenza strain for which humans possessed little or no immunity: the H1N1 Spanish flu (1918), the H2N2 Asian flu (1957), the H3N2 Hong Kong flu

(1968) and the H1N1 swine flu (2009). These are summarized in **Table 1**. Most of our understanding of pandemics has arisen in this period, and is the primary focus of this article; however, a brief discussion of more ancient pandemics is included for historical context.

Table 1. Summary of the key characteristics of influenza pandemics from the past one hundred years.

Pandemic Name	Year	Strain	Suspected Origin of Outbreak	Approximate Number of Deaths
Spanish flu	1918–1920	H1N1	China	40–50 million
Asian flu	1957–1958	H2N2	China	1–2 million
Hong Kong flu	1968–1970	H3N2	China	500,000–2 million
Swine flu	2009–2010	H1N1	Mexico	Up to 575,000

2.3 From ancient times to the machine age

Influenza epidemics and pandemics have been occurring for centuries. Epidemics result in local spikes in infection incidence, and tend to be driven by seasonal influenza strains, whereas pandemics are epidemics that spread globally. Greek writings from 412 BC describe what medical historians believe may have been an influenza outbreak [1, 62]. However, because the virus was not isolated and identified until the twentieth century, medical historians are restricted to searching for known signs and symptoms of influenza infection. An overall lack of data up until 1500 precludes significant analysis of the influenza outbreaks of the more distant past [63].

There is general agreement that an outbreak in 1580 represents the first influenza pandemic [63, 64]. It is likely that the strain emerged that summer in Asia, spreading by land routes to Asia Minor and North Africa before moving across Europe and into North America [65]. Disruption, illness and death were widely reported [66]. The first reference to "influenza" in scientific literature appeared in 1650 [63]. From this date, the history of pandemics is more reliably documented.

The first pandemic of the eighteenth century began in the spring of 1729 in Russia, spreading across Europe during the ensuing six months and around the globe over the next three years [65, 67-69]. As with more recent pandemics, the outbreak occurred in multiple waves, with higher associated morbidity and mortality in later stages [66, 68]. The second pandemic of that century appears to have begun in China in the autumn of 1781 [65, 69]. It spread through Russia and Europe over a period of eight months, with a particularly high attack rate among young adults [70].

The major pandemic of the nineteenth century began in the winter of 1830 in China [63]. Reported to be of similar severity to the 1918 Spanish flu pandemic, it spread across Southeast Asia, Russia and Europe, and into North America by 1831 [65, 66, 68]. Despite a high illness attack rate, associated mortality was low [63]. In the winter of 1889, another pandemic emerged in Russia, spreading by rail and sea across Europe and North America [65, 68]. With an estimated case fatality rate in the range of 0.1%–0.28%, the outbreak killed about one million people globally [71]. This pandemic spread at a faster rate than previous ones, and may provide the first indication of the accelerated spread of emergent diseases as a result of progress in transportation technology.

There remains considerable uncertainty over when and where influenza pandemics have emerged in the past four hundred years [63, 64]. It is worth noting, however, that in each of the ten pandemics where data on emergence is available, either China, Russia or, more broadly, Asia

have been identified as the likely point of origin [63]. Scholars tend to give a fairly consistent estimated interval of 10–50 years between influenza pandemics [1, 63, 64]. This is a very broad window, suggesting that pandemics occur with an irregularity that prevents accurate prediction of emergence.

Several patterns emerge in examining early pandemics. The first is an overall lack of quality, rigour and validity in the available evidence. Inconsistencies in disease recognition and reporting make it difficult to estimate with certainty the attributable health burden of these disease outbreaks. The second pattern is the relationship between the rate of disease spread and the transportation revolution of the eighteenth and nineteenth centuries. Influenza outbreaks in an area tend to last between six and ten weeks, and were previously contained to spreading along commercial trading routes, whether by foot, horse or downstream by boat. However, the industrial revolution led to the expansion of road systems and the advent of the steam engine, along with the promotion of steamboats and railroads for trade and travel. These technological advances led to major increases in human mobility, both within and across countries, and quickly became the primary vector of disease spread throughout the world.

Public health practice in the time of these pandemics was still rudimentary, and knowledge of disease prevention and management was poor. Vaccinations, antivirals and antibiotics to treat secondary infections had yet to be developed, and systematic response plans are not evident. Progress in both public health practice and infectious disease management would quickly become a priority, driven in part by the devastation wrought by the 1918 Spanish flu pandemic.

2.4 1918–1920: Spanish flu

In 1918, an H1N1 influenza strain emerged to cause the Spanish flu pandemic, a disaster that has been called the ‘greatest medical holocaust in history’ [72]. While the timing and number of

waves was not consistent globally, the pandemic is generally viewed to have had three distinct waves: the spring of 1918, the fall of 1918 and the winter of 1918–1919 [73, 74]. While the first and third waves were fairly mild, the second wave resulted in catastrophic global losses, with deaths reaching into the tens of millions. Global death toll estimates have been revised upwards in the decades since the pandemic. Initial assessments in the 1920s estimated deaths at around 21.5 million; this was subject to a recalculation in 1991 to between 24.7 and 39.3 million [75, 76]. A 2002 estimate put deaths at around fifty million, with an upper limit as high as a hundred million deaths [74]. More recent estimates tend to fall in this broad range, with 40–50 million deaths being most commonly reported [54, 64, 73, 77, 78]. Most of these deaths occurred over a four-month period in the autumn of 1918 [79].

Despite poor or absent data for many countries, the virus is believed to have infected over half of the world's population at the time [63]. Social and economic disruption was also prevalent, as absenteeism led to shutdowns of schools and businesses (many of which went bankrupt) [80]. Claims against life insurance policies soared by as much as 745% [80]. The pandemic strain differed from seasonal epidemics in terms of its disproportionate burden among young people, particularly previously healthy individuals between 18 and 40 years of age [64, 73, 74]. While the reasons for this are poorly understood, one possible explanation relates to the role of infection in turning the immune system against itself, triggering a dangerous and potentially deadly cytokine storm [78]. Consequently, those with the most robust immune systems may have been at greatest risk. This shift in mortality risk towards younger age groups may also have been due to prior exposure to a genetically similar strain among older age groups [81].

More specific accounts of the experience of particular regions are broadly available, including for North America [65, 75], Africa [82], Europe [83] and Australia [84]. However, many of these

accounts have not been subjected to peer-review, and reports, observations and conclusions often rely on assumptions and estimates made necessary by limited or unreliable data. This tends to be the greatest challenge associated with analyzing pandemics that occurred before the advent of systematic disease surveillance and reporting. Nevertheless, while the broad estimated mortality range highlights problems with data collection, missing records and misdiagnosis, it still provides a sense of the severity of the pandemic.

The origin of Spanish flu has been subject to uncertainty and debate, with proposed origins tending to center on the United States and China [63, 79, 80]. Recently, Humphries reviewed evidence of early outbreaks of unidentified, virulent respiratory diseases shortly before the emergence of the 1918 flu [73]. Despite limited availability of epidemiological evidence to confirm the theory, he presents data from several countries which suggests that the origin of the first wave of Spanish flu was an outbreak in China that was misidentified as pneumonic plague. It then would have spread across the globe through the Chinese Labour Corps (CLC), a group that, from 1916 to the end of the First World War, sent over 100,000 laborers to Europe to support the Allied war effort [85]. Originally reaching Europe via checkpoints in Singapore, Durban, Cape Town or North Africa, workers were later redirected to Vancouver, to be brought by train to Halifax and sent across the Atlantic [73]. In April 1918, a transport of workers experienced an outbreak of supposed plague; shortly after, the program was cancelled for fear of transporting infected workers. However, during this time, there was a spike in influenza cases reported among Canadian soldiers assigned to guard and transport the Chinese workers [73]. The argument for a Chinese origin is supported by observations of a (relatively) milder second wave in both China and Chinese populations in Canada, suggesting they may have been subject to previous exposure

to the virus [73, 86]. Alternatively, Cheng and Leung argue that China's escape from a more severe pandemic was due to the role of traditional Chinese herbal medicine [87].

The origin of the second wave of Spanish influenza, which would go on to produce the majority of infections and deaths associated with the pandemic, is more generally agreed upon. It emerged in Southern England, specifically in Plymouth and Devonport [73]. From the harbour town of Plymouth—a popular arrival site for CLC workers—the merchant ship *Mantua* transported the virus to Freetown, Sierra Leone [88]. Also a popular harbour town, the Freetown outbreak would spread the second wave of influenza across Africa, as ships would make port to refuel before traveling further South [73]. Meanwhile, New Zealand soldiers sailing to and from the War in Europe were also infected when they stopped in Freetown on their way; over 8,500 New Zealanders would die from influenza and pneumonia in just six weeks [88]. Around this time, a boat from Plymouth landed in Boston, seeding the infection in North America. Over the following four months, as many as 675,000 Americans, 300,000 Mexicans, and 50,000 Canadians would die from infection [74, 80].

In terms of overall illness and death, the Spanish flu pandemic is among the greatest public health disasters in recorded history [72]. It was the result of a highly pathogenic, transmissible strain of influenza that emerged in a time when populations that previously would have had limited contact with one another were brought together by World War I (WWI). While previous pandemics travelled mostly along trade routes and communication lines, the spread of the 1918 outbreak was accelerated by the military context in which it developed. Meanwhile, trench warfare in Europe provided ideal conditions—poor sanitation, overcrowding, and limited health services—to facilitate disease transmission [73].

At the same time, these problems were compounded by a public health system that was unprepared for an influenza strain of such pandemic potential. In 1918, experts still believed that influenza was caused by the *Bacillus influenzae* bacterium, though doubts were raised when physicians were unable to find any bacilli during autopsies [89]. Doctors also had a difficult time diagnosing influenza infection, often mistaking it for the common cold, cholera or bubonic plague [80]. They did recognize, however, that the routes of influenza transmission were via infectious respiratory droplets from the nose and throat. Further, though at this time some countries did have regulations for reportable diseases, influenza was not one of them [79]. As such, early stages of local outbreaks tended to be largely ignored, and action was often not taken until it was too late to achieve containment. Influenza would become a reportable disease early in the second wave of the pandemic, but not until infection was so widespread as to preclude accurate record keeping [80].

In 1918, effective vaccines and antibiotics to prevent influenza and treat secondary bacterial pneumonia were still decades away. Meanwhile, medical personnel were in short supply due to WWI. Hospital beds were also limited, and community centers and local schools were repurposed as surge centers. People who fell ill would turn to a range of ineffective drugstore and home remedies, such as topical creams or a mixture of water, salt and coal oil [80]. Some doctors even prescribed alcohol consumption as a means of infection prevention; this produced little more than a surge in liquor demand [80].

Efforts to control outbreaks had to rely on non-pharmaceutical interventions (NPIs), such as quarantines, school closure, banning public gatherings and infection prevention practices like cough and sneeze etiquette and use of facemasks [90]. Interventions were of variable effectiveness. For example, the gauze facemasks would have been effective in preventing bacterial infection, but were too porous to stop viral penetration, and many resisted their use regardless. Governments

issued directives on the dangers of influenza, but these were often poorly understood or ignored [80]. A recent analysis of NPI strategies implemented in the United States during the second and third wave in 1918, however, found that they were significantly associated with reductions in mortality and delays in reaching pandemic peaks [90]. The most effective strategies combined different types of NPI in a layered approach, with a combination of school closure and banning public gatherings being found to be the most successful [90]. Interventions implemented early and for longer duration also had a greater impact. NPIs alone are unlikely to prevent or contain a pandemic, as they do not affect susceptibility to, or infectivity from, viral infection. It is for this reason that, if NPIs are discontinued prematurely, infection may quickly return to its normal transmission patterns, leaving the ultimate impact of the outbreak unchanged. However, if implemented properly, NPIs have the potential to delay and flatten pandemic peaks in a way that reduces mortality and alleviates stress on the health care system.

Spanish flu brought illness, death and loss to tens of millions of people around the globe and is the worst pandemic in recorded history. However, it also brought a sense of urgency to improve public health, which led to advances in medical sciences, public health planning and international cooperation. It would be almost 40 years before another global influenza pandemic and, when it arrived, countries found themselves much better prepared.

2.5 1920s–1950s: Discoveries, vaccines and the WHO

In the years following the Spanish flu outbreak, the H1N1 virus continued to circulate, though it did not re-emerge to cause illness and death on a similar scale. In the decades before another pandemic strain emerged, global and public health would advance by leaps and bounds. With respect to pandemic influenza, three areas of progress may be highlighted: virus isolation and identification, the development of vaccines and the advance of global health diplomacy.

Richard Shope first isolated the influenza virus in the laboratory in 1931, extracting it from infected pigs [91]. Not long after, Smith, Andrewes and Laidlaw isolated the virus in humans, disproving the widely held belief that influenza was a bacterial infection [92]. This was a significant breakthrough for efforts towards diagnosis, surveillance and vaccine development. The first vaccine for the influenza virus was developed in parallel by multiple researchers during the late 1930s and early 1940s, with credit most often going to Jonas Salk and Thomas Francis [93, 94]. Vaccines in this period were not as safe as modern vaccines, and impurities would sometimes cause flu-like symptoms such as fever, aches and fatigue [54]. Meanwhile, poor surveillance capabilities made it difficult to properly match the vaccine with the circulating influenza strain. In 1947, for example, an epidemic emerged when antigenic drift resulted in changes to the hemagglutinin antigen such that the flu vaccine did not provide any protection against influenza [95]. Fortunately, the strain was not very severe, and a pandemic did not occur [96]. The discovery and isolation of the influenza virus would dramatically change the way societies approached flu prevention and control. Meanwhile, the discovery of penicillin in 1929 would provide health planners with an important tool for treating secondary bacterial pneumonia, the primary cause of death during influenza pandemics [97]. In addition, positive-pressure ventilators for use in intensive care units (ICUs) were developed in the 1940s; this would also improve health outcomes in complicated cases [98]. Taken together, these advances have helped prevent another pandemic with a case fatality rate similar to that of the Spanish flu.

During the Spanish flu pandemic, there was little meaningful coordination among jurisdictions. There were several reasons for this. First, meaningful international cooperation for the control of infectious diseases was still in its infancy. Beginning in 1851, a series of International Sanitary Conferences began to bring countries together to address infectious disease control;

however, the early treaties arising from these conferences, with their focus on sanitation, proved of limited use during an influenza pandemic [99]. Meanwhile, international organizations with mandates to coordinate and inform infectious disease response were inadequate. International bodies such as the Pan American Sanitary Bureau (which would later become the Pan American Health Organization) and the Office International d'Hygiène Publique (in Paris, France), were founded in the early twentieth century, but did not have the size, range or expertise to effectively contribute to the Spanish flu response [99]. Meanwhile, the League of Nations, arguably the first global political system, was founded in 1919, establishing a health organization in 1923 (replaced by the World Health Organization in 1948) [99, 100]. These international bodies would play an important role in later pandemics. Further, many national health institutions did not yet exist, and provincial/state health departments were small [101]. In Canada, largely as a result of the disorganized response to Spanish flu, legislation for the establishment of a federal health department was introduced in March 1919 [101]. In the United States, the Communicable Disease Center (now the Centers for Disease Control and Prevention) was not formed until 1946 [102]. The result was that states planned and implemented very different control strategies, often with little insight from the experience and best practices of other states [90]. In the absence of these national and international coordinating bodies, a lack of communication and reporting between jurisdictions impeded more effective responses. The size and responsibilities of local, state, provincial and federal health departments expanded over the upcoming decades.

In the inter-pandemic period between 1918 and 1957, the world experienced massive growth in population, trade and travel. In 1918, the global population was around 1.8 billion; by 1957 that figure had risen to 2.8 billion [103, 104]. Meanwhile, international travel for both business and leisure had been increasing steadily for years. However, with the arrival of commercial jet aircraft

in the 1950s, the number of international travelers began to climb rapidly [105]. A similar trend is apparent in international trade, which has grown 140-fold from the industrial revolution of the nineteenth century to the twenty-first century [106]. Though the globalization of trade stalled from 1914 to 1945—limited by WWI, the Great Depression and WWII—it, too, would re-emerge in the 1950s, initiating what has been called the "second age of globalization" (the explosion of trade, capital and migration during the industrial revolution is considered the first) [106]. The beginning of this second age may be traced to the 1944–1947 establishment of the United Nations and three multilateral economic institutions known collectively as the Bretton Woods system: the World Bank, the International Monetary Fund and the General Agreement on Tariffs and Trade [106]. These organizations set the stage for unprecedented international trade cooperation and liberalization, catalyzing the formation of multinational institutions and the international movement of goods, services and information on a scale wholly different from that seen before the First World War. Therefore, while three decades of advances in medical sciences, public health practice and international political cooperation may have improved preparedness for pandemic influenza emergence, three decades of population growth and the globalization of trade and travel increased the risk of disease emergence and spread. This contributed to the emergence of two global, albeit mild, influenza pandemics within a decade of each other.

2.6 1957–1958: Asian flu

After almost forty years of H1N1 being the only influenza strain in circulation, a new strain emerged to cause another influenza pandemic. In February 1957, a new influenza strain was detected in the Yunnan Province of China [65]. Humans under 65 possessed no immunity to this H2N2 strain, suggesting prior viral circulation and exposure at some point in the late nineteenth century [107]. The virus spread to Hong Kong in April, then to Singapore, Taiwan and Japan,

before spreading globally throughout the summer of 1957 [107]. By June, it was reported in twenty countries [108]. In the United States, it was first reported on naval bases, again suggesting the role of military routes in global disease diffusion [102]. The pandemic was spread primarily via land and sea routes, with air travel playing only a small part in disease spread [65]. The majority of global transmission occurred over land routes from Russia to Scandinavia and Eastern Europe and at an international conference held in Iowa [109, 110]. As with the 1918 Spanish flu, Asian flu would reappear in successive, unpredictable waves, with the second wave being more severe than the first [111]. Although the virus was circulating during the summer, community-wide transmission was limited; it was not until schools re-opened in the fall that broader transmission was triggered, with clinical attack rates in schools of 40–60% [112].

The strain came to be known as the Asian flu, and was a comparatively mild influenza pandemic. With a maximum case fatality rate estimated to be about 0.67%, it caused between one and two million deaths worldwide [77, 111-113]. A recent study by Viboud and colleagues used historical mortality data from 39 countries to estimate an average pandemic-associated excess respiratory mortality rate of 1.9 per 10,000 people [113]. Excess pandemic-related mortality between 1957 and 1959 in the United States was estimated to be 0.83/10,000, compared to 1.79/10,000 over the same period in Canada. As with Spanish flu, the mortality curve shifted towards younger age groups, a distinguishing characteristic of influenza pandemics [114]. Younger age groups dominated in terms of attack rates, suggesting pre-existing immunity in older groups [115].

There was some societal disruption due to school and workplace absenteeism, though this was mostly concentrated among children, school teachers and healthcare workers [116]. During the pandemic peak, work absenteeism was in the range of 3–8% in the United States [116]. The

economic impact was small, with the pandemic reducing industrial production by about 1.2% in Canada during the peak and reducing GDP in the United States by about 1% [112]. Economic recovery following tapering off of the pandemic was almost immediate. Meanwhile, though hospital admissions in North America did increase during the pandemic, hospitals were able to accommodate surges in patient demand through repurposing beds, reassigning physicians and cancelling elective surgeries [112]. This was complemented by a concerted effort to promote homecare for uncomplicated cases [112]. In the United Kingdom, these efforts were compromised by a regulation that individuals required a signed doctor's note to qualify for sickness benefit [115].

The Asian flu was the first pandemic to occur in an environment with the global surveillance systems and laboratory capabilities in place to study it. In 1957, a worldwide network of laboratories was linked to the Influenza Research Center based in London, and investigators from Melbourne to Washington were able to study the strain soon after it emerged [115]. This was the first time that comprehensive surveillance was used to track the spread and burden of the disease, although expertise and methodological rigour were still lacking in this area [102]. It was also the first chance to study the response of an immunologically naïve population to influenza vaccination campaigns [96]. Development and distribution of vaccines was slow, and they were in only limited circulation by August 1957 in North America, and by October in Europe [115]. Vaccine allocation in the United States was based upon population size, with priority given to high risk individuals and essential personnel, an allocation strategy commonly employed today [112]. Prioritization was important, for by the end of the pandemic, only thirty million vaccine doses (enough to cover 17% of the American population at the time) had been distributed globally [117]. Despite a heavy focus on vaccination campaigns and a vaccine efficacy of 53–60%, inadequate coverage prevented vaccination from having a significant impact on pandemic trends [112, 117]. Antivirals had yet to

be developed. Physicians took variable approaches to treatment with antibiotics, with some prescribing antibiotics to all cases and others only to the seriously ill [115]. While this might have helped reduce the burden of secondary bacterial infections, antibiotics are not effective against viral infection, and should not have been used to treat uncomplicated influenza. There was little use of non-pharmaceutical interventions, such as school closure, travel restrictions, banning of mass gatherings or quarantine [116]. Quarantine, in particular, was considered inappropriate due to the mild nature of symptoms and the large overall number of infections. Though a mild influenza pandemic, the Asian flu provided a reminder of the persisting threat of the global spread of emergent diseases.

2.7 1968–1970: Hong Kong flu

It would be only a decade before the next global influenza pandemic, during which time there were few developments of note in terms of either medical science or globalization. This inter-pandemic period from 1959–1968 is not further addressed here, as it represents more of a continuation and expansion of past developments than a shift in how influenza was understood or addressed. One exception of note is that the Hong Kong flu was the first virus to exhibit an accelerated spread due to extensive air travel [118, 119].

Ten years after its appearance, the Asian flu strain underwent an antigenic shift, reassorting to H3N2 and emerging as a new pandemic known as the Hong Kong flu. Despite being highly transmissible, this strain was even milder than the Asian flu. Estimates suggest that Spanish flu resulted in global excess all-cause mortality of 598 deaths per 100,000 people per year, whereas the same approximation for Asian flu was only 40.6; excess mortality during the Hong Kong flu was 16.9 [120]. However, methods for calculating these estimates varied across the three pandemics and may not be directly comparable. First reported in Hong Kong in July 1968, the virus spread

was driven in part by Vietnam War veterans returning to the United States [118, 121]. The infection was isolated in the United States and Japan in August; England, Wales and Australia in September; Canada in December; and France in January 1969 [114].

Again displaying the characteristic shift in mortality towards younger populations, the highest case fatality rates were reported among children [122]. A unique feature of this pandemic was that the majority of influenza-related deaths in the United States (70%) and Canada (54%) occurred in the first pandemic wave, whereas countries in Europe and Asia experienced 70% of deaths associated with the pandemic during the second wave [114]. This was likely due to an antigenic drift between waves resulting in geographic variation in infection rates, but stands in contrast to the previously observed uniformity of a more severe second wave. The health burden was also two to five times smaller in North America than elsewhere [114].

Similar to the Asian flu, the Hong Kong flu is estimated to have caused between 500,000 and two million deaths worldwide [77, 123]. Mortality rates were low, which may have been due to pre-existing immunity to the neuraminidase antigen (N2), the same as the previously circulating influenza strain. Still, during the two pandemic waves, the United States experienced a 47% increase in mortality related to pneumonia and influenza and a 6.6% increase in all-cause mortality; in Canada, these figures were somewhat lower at 43% and 3.6%, respectively [114]. However, the pandemic burden was higher in other countries, with increases in excess all-cause mortality of 9.1% (Australia), 11.9% (France), and 13.0% (England and Wales) over the previous year's baseline [114]. These differences indicate the geographic heterogeneity of pandemic impact.

The social and economic burden of the Hong Kong flu was small, particularly in North America. There was some direct economic impact related to higher school and workplace absenteeism, but there was a rapid recovery after infection rates declined [112]. Low disease

severity and mortality rates meant that more costly non-pharmaceutical interventions, such as school closures or quarantines, were unnecessary [124].

Instead, infection control measures emphasized a combination of vaccination, hospitalization for complicated cases and antibiotics to treat secondary (bacterial) pneumonia. In most countries, vaccines were not available until after the pandemic had peaked [125]. Meanwhile, surges in hospitalizations caused problems in some areas, with an excess hospitalization rate of 150% reported in Portland Oregon, for 1968–1969, relative to 1970–1971 [126]. Hospitalization was significantly more likely among the elderly, and occurred at a rate that would be impossible to accommodate today [127]. This is because, in general, hospital bed capacities have either decreased or not increased sufficiently to keep pace with population growth rates [128]. The characteristics of the Hong Kong flu pandemic indicated a lack of progress in public health intervention strategies and medical science between the 1957 and 1968 pandemics.

2.8 1970s–2000s: Computers, drugs and the WTO

Despite two global pandemics in a decade, popular opinion in 1970 was that societies had figured out how to prevent, treat and control infectious diseases [129]. This may have been partly due to the less severe nature of the Asian and Hong Kong flus, which simplified responses and masked inefficiencies. Confidence was further fueled by the success of vaccines in reducing morbidity and mortality from both smallpox and poliomyelitis, particularly in Western countries. In 1969, the United States Surgeon General declared it was time to '…close the book on infectious diseases, declare the war on pestilence won' [130]. In time, this optimism would be challenged by outbreaks of various infectious diseases, including influenza, HIV/AIDS and SARS. In fact, Jones and colleagues reported the emergence or re-emergence of several hundred new infectious diseases between 1940 and 2004, most of which have appeared since 1970 [131]. This points to a trend of

increasing exposure to emerging infectious diseases, driven by globalization processes, that has been balanced, to some degree, by an increasing capacity to control infectious disease outbreaks, driven by advances in public health advances.

In 1977, H1N1 re-emerged for the first time since before the 1957 pandemic to cause a "pseudo-pandemic" known as the Russian flu, which spread through the Soviet Union, Hong Kong and China [54]. Disproportionately affecting those born after 1957, but not resulting in a significant increase in illness and death, it did not spread widely enough to produce a pandemic [64, 124, 127]. Though it is not clear how H1N1 re-emerged, it is suspected to have arisen from a laboratory accident [54]. Notably, this was the first time that two distinct influenza strains produced persistent co-circulation, as neither H1N1 nor H3N2 were displaced [127]. Both remain dominant sources of global influenza infection today. Later on, 1997 would mark the first case of human infection with H5N1 avian influenza, sparking fears of another pandemic from a pathogenic influenza strain [64]. However, in the twenty years since its emergence, H5N1 influenza has failed to achieve substantial human-to-human transmission. This may be because the virus attaches to — and replicates in — cells of the lower respiratory tract, in contrast to most influenza strains which attach and replicate in the upper respiratory tract [64].

An important development in this time was the growing availability and functionality of computer technology. Though the first digital computer was built in 1946, it was not until 1969 that host computers would be connected on a common network, and not until 1991 that the World Wide Web was introduced [44]. In addition to allowing the expanded use of sophisticated predictive modelling programs, the rise of computers and the Internet also had significant implications for surveillance capabilities. The WHO had established a Global Influenza Surveillance Network in 1952 (renamed the Global Influenza Surveillance and Response System

in 2011) to facilitate monitoring of influenza infections throughout the world. It was not until the establishment of FluNet in 1996, however, that surveillance information became publicly available in near-real-time. Today, FluNet is made up of 138 National Influenza Centers, six WHO Collaborating Centres and four Essential Regulatory Laboratories [132]. This network monitors the influenza strains circulating in human populations, speeding up vaccine development and stockpiling, and acts as a warning system to inform other preparedness activities. Meanwhile, federal and regional health agencies scaled up surveillance practices [48, 50]. However, most surveillance is based solely upon patients who seek medical care, thereby excluding asymptomatic or self-limiting infections, underestimating the burden of influenza and missing important routes of disease transmission [48]. Moreover, parallel expansion of federal and regional health agencies was not accompanied by stringent protocols to facilitate inter-agency cooperation. This has led to a problematic lack of coordination in response to recent infectious disease outbreaks, such as the reaction to the 2002–2003 SARS outbreak in Canada [101].

During the late twentieth century, there were two particularly important medical advances: the purification of vaccines and the development of antivirals to treat influenza. Previously, impurities in influenza vaccines would sometimes cause flu-like symptoms, with a risk of more serious complications. In 1976, for example, influenza vaccination in the United States was linked with an increased risk of Guillain-Barré syndrome, a serious, though poorly understood, neurological condition that can lead to paralysis and death [54]. From forty million vaccinations, there were 532 cases and thirty-two deaths reported [133]. Side effects in more recent vaccines tend to be mild, with no significant increase in risk of Guillain-Barré syndrome having been reported since the 1976 vaccine [134]. Meanwhile, antiviral drugs were developed to combat influenza infection. In 1964, amantadine was reported as an inhibitor of influenza, and was particularly useful for

prophylaxis (infection prevention) [135]. Though this class of drug is susceptible to viral development of drug resistance, it also provided a basis for the more recent development of neuraminidase inhibitors (generic names zanamivir and oseltamivir), which can be effective in preventing influenza infection, as well as reducing the severity and duration of infection, particularly if administered within 48 hours of symptom onset [136]. Neuraminidase inhibitors are the class of antiviral most commonly used today: their development was an important milestone in increasing response capabilities to influenza.

Advances in technology and international economic cooperation dramatically increased the movement of people and goods across borders. The Boeing 747, the first "wide-body" passenger jet, was invented in 1969, and air travel became increasingly popular in the 1970s as its cost decreased [44, 137]. In the United States, for example, the number of annual foreign visitors grew a hundred-fold by the turn of the century [105]. By 2004, the number of people who crossed international borders that year (743 million) was 73% higher than in 1989 [138]. At the same time, the 1995 foundation of the World Trade Organization, a successor to GATT, heightened the pace of multilateral international trade [106, 137]. Over the following years the value of merchandise exports and commercial services trade increased by an average of 7.3% and 8.2% per year, respectively [106]. By the time swine flu emerged in 2009, global connectedness was of an entirely different scale than during previous pandemics. This would have important implications for disease emergence, spread, impact and surveillance.

2.9 2009–2010: Swine flu

The pH1N1/09 virus — also known as swine flu, Mexican flu, New flu and A(H1N1) — likely emerged from Mexico in April 2009 [139, 140]. It was first recorded in almost simultaneous outbreaks in Mexico and the United States [77]. Within weeks, the disease had spread across 30

countries [141]. On 11 June 2009, the WHO declared a global influenza pandemic [142]. The extent of global trade and travel allowed swine flu to spread as widely in six weeks as past pandemics had in six months. By July, infection was reported in 122 countries, with 134,000 laboratory-confirmed cases and 800 deaths [112]. In this case, the pandemic emerged as a result of triple viral reassortment between two influenza lineages that had been circulating in pigs for years [141]. The viral genes appear to have come from viruses found in North American and Eurasian swine, though it is unclear when and where reassortment occurred [77].

As with the pandemics of the twentieth century, the swine flu pandemic exhibited wave behaviour, with wave timing varying geographically. In Mexico, for example, a three-wave pandemic profile has been identified, with a spring, summer and fall wave [143]. Pandemic peaks in the rest of North America were more consistent with a two-wave profile, with a spring–summer (29 March–2 August 2009) and fall (2 August–31 December 2009) wave [144]. Elsewhere, the timing of pandemic waves was very different. In Europe, despite heterogeneity in pandemic timing, the general pattern was of an initial, generally mild wave in the spring and early summer of 2009, which subsided as the summer progressed, only to re-emerge with the re-opening of schools to produce a more severe second wave [145, 146]. India, meanwhile, experienced three wave peaks in September 2009, December 2009, and August 2010 [147]. The WHO declared the pandemic officially over in August 2010 [145]. After the pandemic, there were 18,500 laboratory-confirmed deaths globally, though mathematical models suggest that actual influenza-associated mortality was somewhere between 151,700 and 575,400, eight to thirty times the number confirmed in laboratory [148, 149]. It should be noted that the mortality estimates for twentieth century pandemics did not rely on laboratory-confirmed cases, but rather on statistical attribution of excess all-cause mortality [150]. The latter method is more inclusive, as the former risks

influenza-associated deaths being under-reported, due to misattribution of cause of death or the absence of laboratory confirmation of infection. As a result, the health burden of pH1N1, relative to past pandemics, may have been underestimated.

Again, pandemic infection resulted in a shift in mortality towards younger populations, primarily affecting children, young adults and pregnant women [151], with thirty-seven years being calculated as the average age for laboratory-confirmed deaths in the United States [150]. As a result, years of life lost were again disproportionately higher for the pandemic strain than seasonal influenza. It was estimated that, between May and December 2009, pH1N1-attributable illness resulted in between 334,000 and 1,973,000 years of life lost, figures that are comparable to a typical seasonal flu at the lower bound and to the 1968 pandemic at the upper bound [150].

The pandemic also caused societal disruption and a substantial economic burden, which was documented more comprehensively than for past influenza pandemics. However, the total global impact of the pandemic is not well understood [151]. First, direct costs related to treatment, with respect to drugs, outpatient visits and hospitalizations, were high. In Canada, total costs have been estimated at around CAD $2 billion, with the care of hospitalized patients alone estimated to be close to $200 million, as the cost of hospitalization for each H1N1-infected patient averaged about $11,000 [152]. Emergency department visits are estimated to have resulted in costs of another $50 million [152].

Overall, estimates of economic losses range from 0.5% to 1.5% of GDP in affected countries [153, 154]. Such calculations, however, tend to underestimate other, often longer-lasting impacts related infection prevention efforts, such as school closures, lost productivity from work absenteeism, shifts in consumer habits and reduced tourism. For example, although reactive school closures were implemented in many countries due to the high transmission rate in children [154],

associated costs are difficult to calculate, as such action also leads to work absenteeism and lost productivity [155], One study of the impact of school closure on households in New York City found that, in 17% of households, at least one adult had to miss work because of the closures [156]. Though estimates vary depending on the size of the affected population and duration of closure, school closures have been estimated to cost from tens to hundreds of millions of dollars [157]. The pandemic also negatively affected global tourism [158], with airlines reporting losses in the tens of millions [153]. It is difficult, however, to disentangle swine flu's role in this decline, as the global economic crisis of 2008 was occurring simultaneously.

The response to the 2009 H1N1 pandemic, particularly in North America and Europe, demonstrated a significantly improved level of preparedness relative to past pandemics. This was the result of emergency preparedness efforts catalyzed by the earlier SARS outbreak of 2002–2003 and persisting fears surrounding H5N1 avian flu. Containment efforts employed a combination of pharmaceutical and non-pharmaceutical interventions. In the United Kingdom, for example, an aggressive containment campaign combined school closure and voluntary isolation with antiviral treatment for suspected cases and mass prophylaxis of potential contacts; these interventions helped control the outbreak until more information could be gathered [159]. The swine flu pandemic also marked the first pandemic response combining both vaccination and antiviral use. In Canada, though an H1N1 vaccine was not approved until about six weeks into the second wave, the largest mass immunization program in the nation's history was carried out, with the federal government investing $400 million to purchase fifty million doses of the vaccine [160]. High priority groups were the first to receive vaccination, before it was expanded to all groups a few weeks later [161]. Between one third and one half of the population was vaccinated over the remainder of the pandemic [162]. Vaccination coverage was lower in the United States (with state

averages from 12.9% to 38.8%) [163], and much of Europe, with the exception of Norway (45%) and Sweden (59%) [164]. Unfortunately, there was little use of antivirals before September 2009, though awareness campaigns targeting primary care providers increased their use to treat patients later in the pandemic [152].

Non-pharmaceutical measures applied in response to past pandemics were again widely implemented to help contain the pandemic. The most common among these were recommendations for hand hygiene and voluntary isolation of symptomatic individuals [165]. Canada did not recommend school closures to mitigate the pandemic [166], but did benefit from closures for summer break during the first wave; estimates from Alberta suggest this reduced transmission among children by at least 50% [167]. Other countries — including the United States, United Kingdom and Australia — did recommend and implement school closures [156, 166, 168]. While there is uncertainty regarding the effectiveness of these interventions, research suggests strong compliance with, and public acceptance of, these measures [168].

While understanding of the influenza virus's properties and transmission was by this point fairly advanced, weaknesses in maintaining consistent diagnostic protocols presented challenges for surveillance efforts [152]. Officials tracking data on hospitalization, intensive care admission and mortality struggled to generate relevant surveillance data to inform decisions in real-time [169]. Instead, summary data was made available after the fact. The Public Health Agency of Canada (PHAC) surveillance group, for example, consisted of only four people at the time of pandemic onset, making it difficult to produce, analyze, appraise and communicate relevant data in a timely fashion [169]. This was compounded by shortcomings in inter-agency coordination, highlighting a dual need for clarification of roles and responsibilities in planning and response,

and for a streamlined approach for the incorporation of evidence into decision-making processes [166].

Another important concern was the observed strain on public health, hospital and human resources during pandemic peaks [152]. While health systems were generally able to accommodate surges in patient demand, it is likely that an even marginally more severe pandemic would have resulted in harmful service disruption and the need to turn patients away [169]. This was, in part, due to the need for doctors to issue antiviral prescriptions, which has since been addressed by extending this authority to pharmacists. Overall, the 2009 pH1N1 pandemic was a mild — albeit costly — global virus. While it has reinforced optimism about pandemic preparedness, it should not necessarily be seen as predictive of future pandemic severity.

2.10 2010–2016 and Beyond

Since the 2009 pandemic, H1N1 and H3N2 have continued to circulate in the global population. However, the novel pandemic strain pH1N1/09 displaced the previously circulating H1N1 strain to begin producing seasonal outbreaks [170]. There have been reports of human infection with avian strains to which humans are immunologically naïve, particularly H5N1 and H7N9, but these infections have failed to achieve human-to-human transmission [4, 7]. Despite expansion of surveillance efforts, it is impossible to predict with certainty whether the next pandemic will arise from an antigenic shift in currently-circulating strains or a mutation that enables human-to-human transmission in one of the more lethal avian strains. Animal husbandry continues to increase contact between humans and animals, providing opportunities for both viral mixing between animal hosts and spillover to human populations. There have been massive increases in domestic animal populations, with poultry and swine being of particular relevance to influenza risk. Keeping animals at high population densities facilitates viral reassortment through

shared habitats and drinking water, as animal influenza is passed via the oral-fecal route [171]. There have recently been more frequent influenza outbreaks among domestic poultry populations [172, 173], and a greater diversity of influenza viruses circulating among pig populations [173, 174], both increasing the risk of another human pandemic. Most human infections with animal influenza arise from close, direct contact with poultry or swine [175]. Live poultry markets in particular have been identified as a major source of viral mixing, as well as human H5N1 infection [4, 176]. This suggests a need for international discussion and cooperation towards policy development to reduce live market practices and mitigate associated risks.

The year 2014 marked the first time that flights per day exceeded an annual average of 100,000, while 2013 was the first time that the number of annual passengers exceeded three billion [177]. Meanwhile, global population growth continues. When the 1918 pandemic occurred, the global population was around 1.8 billion [103]; as of July 2016, the World Population Clock estimates a global population of about 7.4 billion [178]. If a pandemic today were to kill the same proportion as in 1918, this would equal between 74 and 370 million people. Population growth, human mobility and greater proximity to animal reservoirs continue to increase both the risk of pandemic emergence and the speed with which such a pandemic could spread across the globe. Between 1700 and 1889, the average inter-pandemic period ranged from 50–60 years; since 1889 this period has shortened to 10–40 years [63]. While a pandemic one hundred years ago would take weeks or months to spread globally, an infection today could spread to every continent in days. This increased risk can only be addressed by a combination of local, national and international efforts to improve both mitigation and containment of future pandemics.

There is also a need for improved global surveillance capabilities of both human and animal populations. A weakness noted in the aftermath of the swine flu pandemic was the need for

stronger surveillance of swine populations [141, 169], with the same need holding for avian reservoirs. While recent efforts have yielded some results, more investment is needed to scale up animal surveillance in areas where viral spillover from animal to human populations is most likely to occur. Meanwhile, governments must increase global cooperation to advance early warning systems. This is because contact tracing for influenza is difficult and expensive, even in an outbreak involving a very small population [179]. As such, less developed countries may lack the resources to carry out consistent and sufficient disease surveillance; it becomes very challenging to trace contacts once the disease has spread internationally. An important effort will be to streamline the disease reporting process, shortening lag time between physician reporting and national and international evaluation. The fact that disease surveillance relies on hospital, outpatient and physician visit reporting means that outbreaks are reported, at the earliest, when an individual seeks care. In the case of influenza, this may be sufficiently rare to prevent detection before substantial community spread has occurred. It also ignores findings that a substantial health and economic burden associated with pandemic influenza arises from the morbidity from uncomplicated, self-limiting cases for which individuals do not seek treatment. As such, population-based surveillance should be strengthened, exploiting social media capabilities to obtain real-time data.

In short, while medical advances and past experience with less severe pandemics may lead some to a degree of complacency, globalization processes have increased the risk of emergence and spread of a novel influenza strains. Since the characteristics of such outbreaks are difficult to predict in advance, global capabilities must continue moving towards information provision in real-time, with data that can be streamlined into flexible models to inform policies and programs as the situation develops. In addition to enhanced surveillance capabilities, this effort requires

expanded availability of quick, affordable diagnostic tests, and a consistent approach to diagnostic reporting.

2.11 Conclusion

This review has examined the ways in which the understanding, experience and response to pandemic influenza has evolved over time. While significant progress in reducing pandemic impacts has been made, thanks in large part to advances in pharmaceutical interventions and surveillance, there is much about pandemic influenza that is still poorly understood. The emergence of pandemics has not adhered to typical influenza seasons, and can occur at any time. Meanwhile, though pandemics tend to occur in waves, it is difficult to predict why, how and when waves will occur in different countries. Increased human preparedness has been accompanied by an increased exposure to, and frequency of, pandemic spillover from animal to human populations. Pandemic transmission has always occurred along the dominant lines of movement and communication at the time. In the past, pandemics spread somewhat predictably along military passages or important trade routes, but globalization has multiplied and obscured the dominant routes. Given their sheer number, and the speed with which human and animal transmission vectors can move, there is no longer a single dominant pathway for the geographical movement and expansion of infectious diseases. Pandemics are inherently uncertain, necessitating policies that are flexible in responding to outbreaks as they develop. While insights can be gathered from past experiences of pandemic influenza, it is unlikely that the next event will mimic those of the past. Continued efforts are required to improve local, national and international surveillance, coordination and resource planning to most effectively mitigate and contain future pandemics. Despite all of the uncertainty surrounding pandemics, history has shown that influenza pandemics

occur in cycles — albeit unpredictable ones — and that it is not a question of whether another influenza pandemic will occur, but when.

Chapter 3. Assessing the state of knowledge regarding the effectiveness of interventions to contain pandemic influenza transmission: a systematic review and narrative synthesis

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Publication Status Information

This manuscript was published in December, 2016 by *PLoS ONE* (Saunders-Hastings, P., Reisman, J., & Krewski, D. (2016). Assessing the state of knowledge regarding the effectiveness of interventions to contain pandemic influenza transmission: a systematic review and narrative synthesis. *PLOS ONE*, *11*(12), e0168262. doi: 10.1371/journal.pone.0168262). A systematic review protocol was registered and published in *PROSPERO* in July, 2016 (Saunders-Hastings, P. Reisman, K., & Krewski, D. (2016). Assessing the state of knowledge regarding the effectiveness of interventions to contain pandemic influenza transmission: a systematic review of systematic reviews and meta-analyses. *PROSPERO* (registration number 42016039803)).

Abstract

Influenza pandemics occur when a novel influenza strain, to which humans are immunologically naïve, emerges to cause infection and illness on a global scale. Differences in the viral properties of pandemic strains, relative to seasonal ones, can alter the effectiveness of interventions typically implemented to control seasonal influenza burden. As a result, annual control activities may not be sufficient to contain an influenza pandemic.

This study seeks to inform pandemic policy and planning initiatives by reviewing the effectiveness of previous interventions to reduce pandemic influenza transmission and infection. Results will inform the planning and design of more focused in-depth systematic reviews for specific types of interventions, thus providing the most comprehensive and current understanding of the potential for alternative interventions to mitigate the burden of pandemic influenza.

A systematic review and narrative synthesis of existing systematic reviews and meta-analyses examining intervention effectiveness in containing pandemic influenza transmission was conducted using information collected from five databases (PubMed, Medline, Cochrane, Embase and Cinahl/EBSCO). Two independent reviewers conducted study screening and quality assessment, extracting data related to intervention impact and effectiveness.

Most included reviews were of moderate to high quality. Although the degree of statistical heterogeneity precluded meta-analysis, the present systematic review examines the wide variety of interventions that can impact influenza transmission in different ways. While it appears that pandemic influenza vaccination provides significant protection against infection, there was insufficient evidence to conclude that antiviral prophylaxis, seasonal influenza cross-protection or a range of non-pharmaceutical strategies would provide appreciable protection when implemented

in isolation. It is likely that an optimal intervention strategy will employ a combination of interventions in a layered approach, though more research is needed to substantiate this proposition.

PROSPERO Registration: 42016039803

3.1 Introduction

Each year, influenza infection is responsible for hundreds of thousands of hospitalizations, tens of thousands of deaths and billions of dollars in healthcare costs and lost productivity in the United States alone [180, 181]. At the same time, there is an ever-present threat of an antigenic shift occurring in the influenza virus, producing a new strain to which humans possess little or no immunity and causing an influenza pandemic with even more catastrophic potential. This has occurred four times in the past hundred years, at unpredictable intervals and with varying degrees of severity. The 1918 Spanish flu remains one of the worst public health catastrophes in recorded human history [72], resulting in between 20 and 50 million deaths globally [73-76].

Key concerns surrounding a future pandemic relate to surges in community illness attack rates and, by extension, hospitalization demand [182-184]. The just-in-time nature of resource delivery in hospitals could make it difficult to adapt to such surges [185, 186]. Taken together, these risks could lead to disruption of health services, compounding the social, economic and health burdens associated with a pandemic. The inherent uncertainty surrounding such pandemics presents challenges in mounting an appropriate and effective response. Integration of best practices as informed by past influenza pandemics may help in developing effective responses to future pandemics.

This study examines the effectiveness of any intervention to contain human transmission of influenza infection during a future pandemic of unknown severity. To accomplish this, we conducted a systematic review of existing systematic reviews (SR) and meta-analyses (MA) on pandemic influenza interventions. Recognizing that there is substantial variation in where, how and when interventions are implemented, we sought to better understand the impact of such interventions. Given continuing fears surrounding the threat of avian influenza virus (H5N1 and H7N2) infection in poultry and humans [187, 188], increasing viral diversity of influenza strains circulating in swine populations [174] and escalating human-animal proximity and interaction [189, 190], this article provides timely insight to support future pandemic planning efforts.

3.2 Methods

3.2.1 Overview

The review methodology was developed in keeping with PRISMA [191] guidelines for systematic reviews (**Appendix 1**); a protocol developed *a priori* is published in the National Institute for Health Research International Prospective Register of Systematic Reviews (PROSPERO). Briefly, we conducted a systematic review of existing SRs and MAs dealing with pharmaceutical and non-pharmaceutical interventions to interrupt pandemic influenza transmission and infection. Pharmaceutical interventions include vaccination policies and antiviral use. Non-pharmaceutical interventions include school and work closures, social distancing and contact reduction, use of masks, hand hygiene and cough etiquette. Where feasible and appropriate, differential effectiveness according to age was noted during data extraction.

3.2.2 Search strategy

Systematic literature searches were conducted on July 5, 2016 using PubMed (all dates), Medline (1946–present), Embase (1947–present), Cochrane Library (all dates) and the Cumulative Index to Nursing and Allied Health (CINAHL; all dates). The general search strategy is presented in **Table 2**, with database-specific variations documented in the supplemental material (**Appendix 2**).

Table 2. Systematic review search strategy as executed in Medline.

1	Influenza, human/
2	Exp Influenzavirus A/
3	1 or 2
4	Pandemics/
5	(pandemic* adj3 (influenza* or flu* or grippe)).tw.
6	4 or 5
7	3 and 6
8	Systematic review.tw.
9	Meta-analysis.tw.
10	Meta analysis.tw.
11	Or/8–10
12	7 and 11

The search excluded research on seasonal influenza and non-influenza disease outbreaks, which would both be of reduced applicability in studying interventions specifically targeting pandemic influenza. The search was conducted with no language or date restrictions. In cases where a full report was not available, we contacted the authors to request any manuscripts based on the identified abstract. The search was complemented by searching the reference lists of included reviews and *ad hoc* grey literature searches using Google Scholar.

3.2.3 Eligibility criteria and study inclusion

Articles were imported into Endnote X7.5™ and were subjected to blind title and abstract appraisal by two independent reviewers. Discrepancies automatically pushed articles to full review. Full texts were sought for articles retained for full review, and again subjected to blind review by two independent reviewers. Conflicts were resolved by consensus and third-party arbitration as necessary. Articles were excluded if they met one of the *a priori* exclusion criteria listed in **Table 3**. Studies were considered to address an influenza "pandemic" if they assessed an intervention implemented during the first or second wave of a pandemic, after which the annually circulating strain was viewed as a "seasonal" influenza.

Table 3. Exclusion criteria for systematic reviews and meta-analyses of pandemic influenza interventions.

Criterion	Rationale
Does not deal with human populations	Animal models may not give accurate representation of impact in humans
Does not include studies on pandemic influenza, but deals exclusively with seasonal influenza or other condition	Experience of pandemic influenza may not reflect that of seasonal influenza
Exclusively reviews in vivo and/or in vitro studies or mathematical modelling studies	Purpose of study is to examine the behaviour of influenza within human populations, rather than genetic considerations
Does not review an intervention to contain pandemic influenza infection	Purpose of this review is to quantify intervention effectiveness
Does not use infection/transmission risk/rate as an outcome measure	Purpose of this review is to quantify intervention potential to contain pandemic transmission
Only the abstract is available	Must be able to assess article in its entirety
Not a peer-reviewed systematic review or meta-analysis article	Seeking to compare over-arching intervention patterns across heterogeneous settings

3.2.4 Data extraction and analysis

Data from retained articles were extracted to a piloted Excel spreadsheet by two independent reviewers. Spreadsheet categories offer information pertaining to the study populations, interventions and outcomes. The principal summary measures of relative intervention effect are risk and odds ratios. Methodological heterogeneity of the included systematic reviews — particularly with respect to research questions, inclusion criteria, intervention specifics and outcome measures — precluded pooling of data for a new meta-analysis, as well as the use of funnel plots to assess the potential for publication bias. Instead, a narrative synthesis is presented for each of the interventions evaluated in a past review, highlighting current knowledge and unfilled data gaps.

3.2.5 Quality assessment

The quality of articles retained for data extraction was assessed by two independent reviewers using the AMSTAR tool (**Appendix 3**). The 11-item questionnaire was developed for application across a broad range of public health interventions [192, 193] and has been widely applied over the past decade [194, 195], including for reviews of seasonal influenza interventions [196-198]. An SR can achieve a maximum score of 10 and an MA a maximum score of 11. Following the approach set out in past publications [194, 196], reviews receiving a score of 9–11 were classified as high quality, 5–8 as moderate-quality and 0–4 as low-quality. Inter-reviewer disagreements regarding scoring were resolved by consensus only when they resulted in differential quality categorization (low, moderate, high). Although review quality was not used as an exclusion criterion, the level of evidence was noted and integrated into a discussion of results and formulation of conclusions.

3.3 Results

A total of 348 citations were retrieved from the execution of the search strategy discussed. Following the removal of duplicates, 185 articles were subject to title and abstract review, with 64 retained for full review. An additional 9 articles were identified from searches of reference lists and the grey literature; all were reviewed in full. Of these 73 articles, 17 were selected for quality assessment and data extraction. **Figure 2** summarizes the study selection process; articles omitted during full review are summarized in **Appendix 4**, along with the reason for their omission.

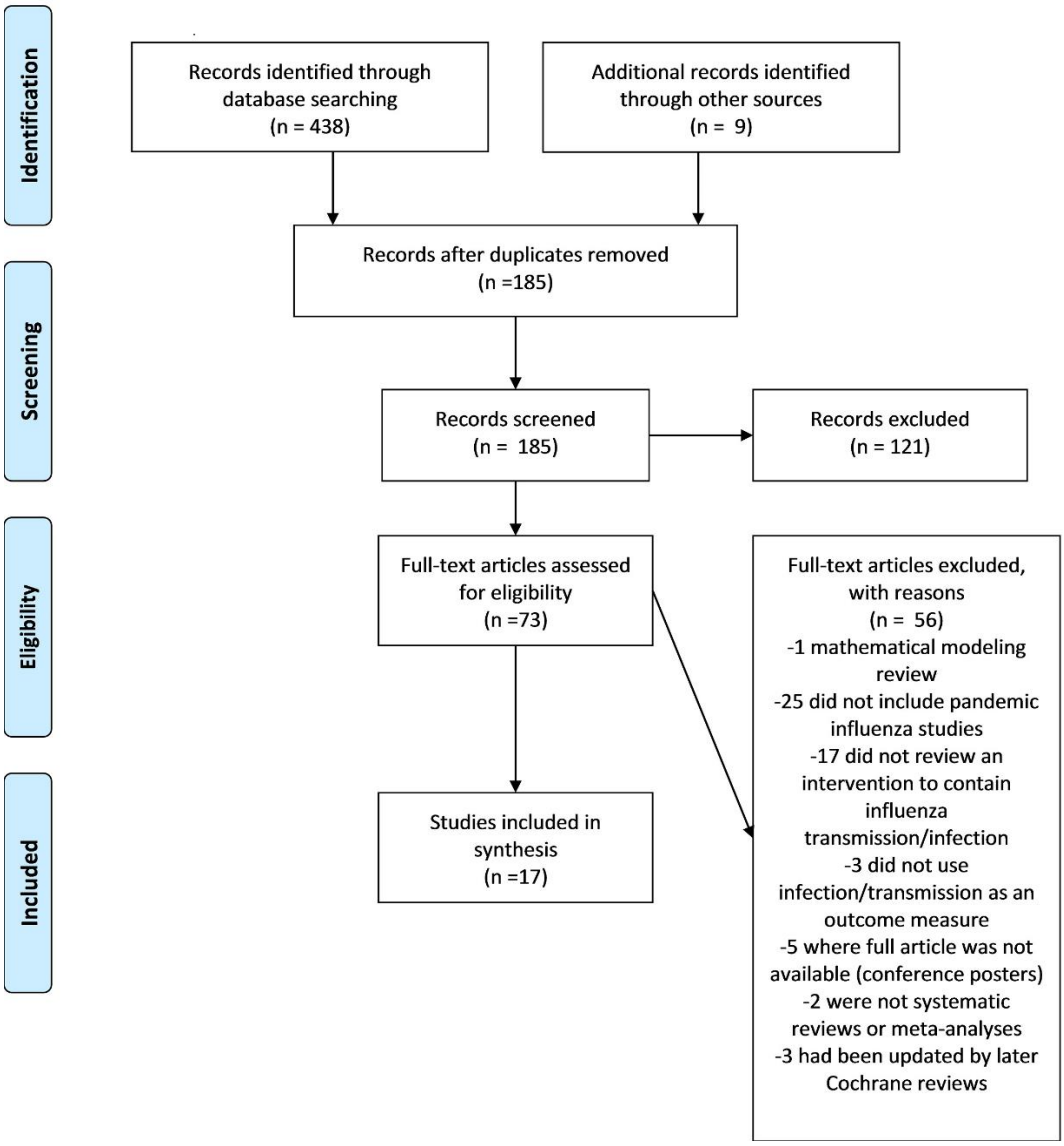

Figure 2. Systematic review flow diagram.

3.3.1 Included reviews

In total, 17 reviews were retained, covering six types of intervention to prevent pandemic influenza infection. Eight [199-206] review the effectiveness of pandemic influenza vaccine in preventing influenza and influenza-like illness (ILI); three [207-209] examine the impact of antivirals; two [205, 210] review the effectiveness of seasonal influenza vaccines in preventing

pandemic influenza infection; two evaluate the impact of personal protective measures (hand-washing, mask use) [211, 212]; one [213] analyzes the impact of school closure; and another [214] reviews the efficacy of traditional Chinese medicine (TCM). One review [215] evaluates the economic viability of a wide range of pharmaceutical and non-pharmaceutical measures, concluding that social distancing, antiviral prophylaxis, school closure and vaccination are likely to be cost-effective in all settings, while quarantine is never cost-effective. Across these reviews, 33 meta-analyses of intervention impact were conducted. The characteristics of individual reviews are summarized in **Table 4**, with results and associated implications for intervention impact described in subsequent intervention-specific subsections. Tables summarizing the results of the quantitative analyses performed in the included reviews are available in the appendices for pandemic vaccination (**Appendix 5**), antiviral prophylaxis and treatment (**Appendix 6**), seasonal influenza vaccination (**Appendix 7**) and personal protective measures (**Appendix 8**). Results from the reviews on school closure and TCM are not reported in tables, as only a single review was available for each.

Table 4. Summary of reviews included in the systematic review of pandemic influenza interventions.

Systematic Review	Population	Total Studies (N)	Pandemic Studies for Meta-analysis	Pandemic Meta-analysis Population Size (N)	Intervention	Outcome	AMSTAR Quality (low, moderate, high)	Quality of Evidence
Breteler et al., 2013	Schoolchildren in China during 2009 pandemic	41	1	95,244	Vaccination (two doses of PANFLU1)	Laboratory-confirmed influenza	High	Only a single study was retrieved
Chien et al., 2010	Civilian and military populations during 1918 pandemic	13	13	1,956,492	Mixed killed bacterial vaccines	Influenza incidence	Moderate	Significant heterogeneity among studies; low scientific quality of 1918 vaccine studies; inconsistent reporting of influenza incidence
Demicheli et al., 2014	Healthy adults and pregnant women during 1968 pandemic	90	6	33,768	1968 and 2009 pandemic vaccines	Influenza or ILI cases	High	Methodological quality was rated as good for 10%; high risk of bias for 20%; impact of bias could not be determined for 70%

Fielding et al., 2014	General population during 2009 pandemic	11	11	1,527	Oseltamivir	Duration of viral shedding	Moderate	Significant heterogeneity noted; prevented meta-analysis and limits scope
Jackson et al., 2013	General population during 1918, 1968, and 2009 pandemics	79	57	N/A	School closure	Cumulative and peak influenza attack rates	Moderate	Significant heterogeneity noted; prevented meta-analysis and limits scope
Jefferson et al., 2008	General population during 1968 pandemic	22	10	12,575	Amantadine prophylaxis	Influenza or ILI cases	High	Significant heterogeneity noted; little information on randomization procedures for studies reviewed
Jefferson et al., 2014	Healthy children (under 16) during 2009 pandemic	75	5	Not reported	2009 pandemic vaccine	Influenza infection	High	Generally poor methodological quality of studies included; poor reporting and high risk of bias

Li et al., 2016	General population during 2009 pandemic	30	12	1,469	Traditional Chinese medicine	Duration of viral shedding	High	Small sample size limits statistical power
Li et al., 2015	General population during 2009 pandemic	28	28	135,347	Seasonal influenza vaccine	Pandemic influenza infection	High	12 of 28 studies had high risk of bias; significant heterogeneity noted among case–control studies
Manzoli et al., 2011	General population during 2009 pandemic	33	18	18,444	2009 pandemic vaccine	Influenza seroconversion	Moderate	Most studies included were sponsored by companies developing the vaccine under study
Mizumoto et al., 2013	General population during 2009 pandemic	17	8	Not reported	Mass antiviral prophylaxis and contact tracing	Secondary infection risk	Moderate	Heterogeneous, arbitrary definitions of "contact", case ascertainment, study setting, and treatment duration

Mukerji et al., 2015	General population during 2009 pandemic	7	3	Not reported	N-95 masks	Economic benefit	High	Results are of limited utility; limited inclusion of clinical data to inform effectiveness estimates
Osterholm et al., 2012	Canadian and European general population during 2009 pandemic	5	5	Not reported	2009 pandemic vaccine	Laboratory-confirmed influenza	Moderate	All studies were observational and of low statistical power
Perez Velasco et al., 2012	General population during 2009 pandemic	44	44	Not reported	Any	Cost-effectiveness, utility, or benefit	High	Evidence is of low quality and generally inconclusive; variations in intervention implementation
Wong et al., 2014	General population during 2009 pandemic	10	1	149	Hand hygiene and facemask	Laboratory-confirmed influenza or ILI	High	Small sample size of included trial lead to significant imprecision and limited generalizability
Yin et al., 2012	General population during 2009 pandemic	27	27	3,011,641	Seasonal and pandemic influenza vaccines	Laboratory-confirmed influenza	High	Most studies included were of low or moderate quality; significant heterogeneity noted

Yin et al., 2011	General population during 2009 pandemic	16	16	17,921	Pandemic influenza vaccine	Influenza seroconversion	High	Nine of 16 studies were of low quality; significant heterogeneity noted

*Quality of studies is reported as indicated by the quality assessment of the original authors.

3.3.2 Quality assessment

Inter-reviewer agreement on the quality of the systematic reviews assessed was strong. Of the 17 reviews collected, ten were rated as being of high methodological quality, six were of moderate quality and one was of low quality (**Appendix 9**). It should be noted, however, that the quality of the systematic reviews alone does not suggest that the conclusions drawn can be viewed with a high degree of certainty. Rather, insufficient data, appreciable heterogeneity, and wide confidence intervals were noted across many of the reviews. Comments on the quality of evidence obtained from the review, as well as an independent assessment of the methodological rigor of that review, are also included in **Table 4**.

3.3.3 Pandemic influenza vaccine effectiveness

Of the eight reviews assessing the effectiveness of pandemic influenza vaccines, seven report on the effectiveness of the 2009 pH1N1 vaccine [199, 201-206], one reports on the 1968 pandemic vaccine [201] and one reports on the efficacy of killed bacterial vaccines used during the 1918 pandemic [200]. With few exceptions — notably the 1918 bacterial vaccines, used prior to identification of the influenza virus — there appears to be a general consensus that pandemic vaccines were effective across age groups in preventing pandemic influenza infection.

With regard to the 2009 H1N1 pandemic, Breteler *et al.* [199] report on a study of schoolchildren in China [216], where a vaccine effectiveness of 87% (95% CI: 75–93%) was found. The review by Demicheli *et al.* [201] included a single pandemic study [217], which estimated a risk ratio of 0.11 (95% CI 0.06–0.21) associated with the 2009 inactivated pandemic vaccine in pregnant Japanese women. A 2014 review by Jefferson *et al.* [202] did not pool the results of five pandemic vaccination studies [218-222], but reported a consensus across studies

that pandemic vaccines provided a significant protective effect against infection, with vaccine efficiency ranging from 71.9–96%. Similarly, Osterholm *et al.* [204] did not pool the results of five observational studies of the effectiveness of monovalent pandemic H1N1 vaccination, but reported a median effectiveness of 69% (range: 60–93%). Yin *et al.* [205] examined 11 case-control studies reporting on pandemic influenza vaccination and laboratory-confirmed influenza, calculating a combined odds ratio of 0.14 (95% CI 0.07–0.27).

Both Manzoli *et al.* [203] and Yin *et al.* [206] reviewed the seroprotective effect of different H1N1 pandemic vaccines. Manzoli *et al.* [203] found a significant impact of higher vaccine concentrations for single-dose vaccines (RR of seroconversion 1.05; 95% CI 1.03–1.07 per dose step increase), but no significant effects were associated with higher concentrations in two-dose vaccines, administration of a second dose (except in children), or addition of vaccine adjuvants such as aluminum. Yin *et al.* [206] did not report quantitative effects on infection, but concluded that pandemic vaccination significantly impacted seroconversion, regardless of administration of one or two doses or the addition of aluminum hydroxide as an adjuvant, neither of which significantly improved the immune response.

Demicheli *et al.* [201] reported that all forms of the 1968 inactivated vaccine were effective in preventing both confirmed influenza and ILI. While the effect was greater for influenza than ILI, it should be noted that all results for confirmed influenza derived from a single study [223]. The authors found no significant effect of live aerosol vaccines. Lastly, Chien *et al.* [200] evaluated the effectiveness of mixed killed bacterial vaccines in reducing influenza incidence during the 1918 pandemic, finding no significant protective effect; this is not surprising given that bacterial vaccines are likely to be ineffective against viral pathogens.

3.3.4 Antiviral effectiveness

Three systematic reviews evaluated studies on the role of antiviral prophylaxis and treatment in reducing pandemic influenza infection [207-209]. Fielding *et al*. [207] found that oseltamivir treatment received within 48 hours of symptom onset tended to reduce the duration of viral shedding (3–5 days) relative to no treatment (4–9 days) and to treatment received over 48 hours after onset (5–7 days). This contraction of the infectious period of the index case could reduce secondary infections [207]. Mizumoto *et al.* [209] reported that secondary infection rates generally decreased in situations where mass oseltamivir prophylaxis had been employed, with a median secondary infection risk of 2.1% (relative to 16.6% among those not receiving prophylaxis). In both cases differences in study design, exposure and treatment strategies precluded pooled estimates of effectiveness. Jefferson *et al*. [208] evaluated the effectiveness of amantadine prophylaxis during the 1968 influenza pandemic, reporting significant protective effects against confirmed influenza (RR 0.27; 95% CI 0.17–0.46) and ILI (RR: 0.78; 95% CI 0.74–0.83). However, the authors point out that amantadine significantly increased adverse gastrointestinal and nervous system effects, suggesting that they should only be used in emergency situations, and may not be appropriate for mass prophylaxis.

3.3.5 Seasonal influenza vaccine effectiveness

Two systematic reviews, both from the 2009 pandemic, report on the cross-protection of seasonal influenza vaccines against pandemic influenza infection for the three Northern hemisphere influenza seasons between 2007 and 2010 and the two Southern hemisphere influenza seasons between 2008 and 2009 [205, 210]. Li *et al.* [210] report a non-significant risk increase across four randomized control trials (RR: 1.13; 95% CI 0.56–2.29), though we argue that these

findings should be interpreted with caution, due to small sample size (n=1,515). They also report a non-significant protective effect across 16 case–control studies (n=40,868, OR: 0.80; 95% CI 0.61–1.05). Yin *et al.* [205] report a similar, non-significant protective effect across 11 case-control studies (n=31,699, OR: 0.81; 95% CI 0.58–1.13), but found a significant effect when five studies with a high risk of bias were excluded (n=28,292; OR: 0.66; 95% CI 0.48–0.91). Taken together, these two reviews suggest that seasonal influenza vaccination had a moderate, though non-significant effect in protecting from influenza infection during the 2009 pandemic.

3.3.6 Personal protective measure effectiveness

Of the two systematic reviews analyzing personal protective measures an influenza epidemic, one [212] reported on its effectiveness in preventing infection while the other [211] discussed its economic benefit. Wong *et al*. reviewed ten studies of hand hygiene and facemask use in developed countries, and obtained an insignificant estimate of risk reduction associated with hand hygiene alone (RR: 0.82; 95% CI 0.66–1.02) but a significant risk reduction when hand hygiene was practiced in conjunction with facemask use (RR: 0.73; 95% CI 0.53–0.99). However, only one of these ten studies [224] was performed in a pandemic setting, with the other nine dealing instead with seasonal influenza control. With small sample size limiting generalizability (n=149), insignificant risk reductions associated with hand hygiene and facemask use for laboratory-confirmed influenza (RR: 0.64; 95% CI 0.32–1.29) and influenza-like illness (RR: 0.52; 95% CI 0.21–1.29) were found in the pandemic study [224]. Mukerji *et al.* [211] do not report quantitative data on the effectiveness of interventions in preventing infection, but reviewed past cost-effectiveness studies of mask use. Noting important limitations in the studies reviewed, these authors suggest that masks and respirators may be cost-effective, though there is insufficient data to inform more specific interventions.

3.3.7 School closure effectiveness

A single systematic review [213] assessed the impact of school closure across 57 pandemic studies from the 1918, 1968, and 2009 pandemics. Despite reporting a contact rate reduction of 30–78% in school-aged children, statistical and methodological differences precluded the authors from pooling data for meta-analysis, comparing of optimal intervention strategies, or commenting on statistical significance.

3.3.8 Traditional Chinese medicine effectiveness

A review by Li *et al.* [214] examined the effect of Chinese medicines, herbs, extracts or other ingredients in reducing the duration of viral shedding in individuals infected with pandemic H1N1, both alone and in combination with oseltamivir treatment. In a meta-analysis of 12 studies (n=1,469), using oseltamivir treatment as a control, the mean duration of viral shedding did not differ significantly between the TCM and oseltamivir treatment groups (mean difference 0.07 days; 95% CI -0.07–0.21). However, a significant reduction in duration of viral shedding was noted in a comparison between a group receiving both TCM and oseltamivir and an oseltamivir control (mean difference -0.52 days; 95% CI -0.96–-0.09).

3.4 Discussion

The present systematic review is the first assess the state of knowledge regarding interventions to prevent pandemic influenza transmission as reported in existing systematic reviews and meta-analyses. This is an important information gap, as the high degree of uncertainty and heterogeneity regarding pandemic outbreaks and response suggests value in analyzing overarching trends in intervention effectiveness. Variability in pandemic environments — including the degree of infectiousness, population demographics and susceptibility and intervention strategies and timing

— inhibit the generalizability of effectiveness measures reported from a small number of studies to other settings and future pandemics.

Some authors [208, 225] have proposed that intervention effectiveness can be expected to mirror what is observed during seasonal influenza epidemics. This viewpoint is problematic for several reasons. First, seasonal influenza epidemics tend not to be considered as emergency situations, and extreme response measures are not employed [215]. This limits the ability to evaluate the effectiveness of interventions such as school closure, facemask use or quarantine of infected individuals, which would be inappropriate during standard seasonal influenza seasons. As a consequence, there is no conclusive evidence on the impact of these strategies: there was, in fact, substantial uncertainty about which measures to implement during the 2009 pandemic [224, 226]. Second, the assertion that seasonal influenza research remains relevant to pandemic influenza situations remains controversial [227]. Some suggest that intervention effectiveness may increase in pandemic situations, due to media attention and public anxiety increasing rates of adherence [228]; this was the case during the SARS epidemic [226, 229]. Additionally, the uncertain timing of pandemic influenza outbreaks, relative to usual influenza seasons, may alter non-pharmaceutical intervention effectiveness by impacting the relative importance of different modes of transmission, which have been suggested to vary with ambient temperature and relative humidity [212, 230]. Differences in background immunity and proportional age burdens may also result in differential intervention effectiveness in interrupting seasonal and pandemic influenza transmission. In short, there is a need for more targeted reviews examining the empirical data from past pandemic events, where high viral loads, transmission rates and public anxiety [227, 231] may have impacted the effectiveness of interventions that were implemented.

The results of this review were insufficient to draw concrete conclusions on the effectiveness of most interventions. Of the 17 reviews included, only seven specifically reviewed pandemic influenza situations, while the other ten conducted subgroup analyses: two of these [199, 212] found only a single pandemic study that met their inclusion criteria. The most commonly investigated intervention was pandemic influenza vaccination, which was found to be highly effective in preventing pandemic influenza infection and ILI. This is not surprising, as the 2009 pandemic vaccine was a very close match with the circulating strain [204]. Rather, the concern with pandemic vaccines is that they may not be available in time for the early stages of a pandemic, as vaccine production, development and distribution can take over six months [103, 232]. The few reviews of the interventions that may be employed in the interim reported mixed results. Where measures of statistical significance were reported, only antiviral prophylaxis with amantadine — a drug with known adverse side effects — demonstrated a significant protective effect. A lack of primary data precluded reporting of statistical significance for non-pharmaceutical measures such as hand hygiene, facemask use and school closure. It is likely that the most impactful and cost-effective approach to interrupting pandemic influenza transmission involves a layered approach combining multiple pharmaceutical and non-pharmaceutical intervention strategies, although this notion is not well explored in the quantitative analysis of included reviews. The overall lack of quantitative primary data on intervention effectiveness supports the crucial role of mathematical modelling in charting pandemic transmission dynamics and supporting the assessment of public health interventions under conditions of uncertainty.

Though not a focus of this article, several reviews were noted that dealt with the effectiveness of treatment options for pandemic influenza [233-241]. While these were beyond the scope of the present review, assessments of four major treatment strategies were found. Results suggest that

early treatment with neuraminidase inhibitors can reduce hospitalization [240], ventilator support [236] and death [234-236]. Two reviews [237, 239] — based on a single study — mention a benefit of convalescent plasma for treating severe pandemic influenza cases. Three reviews [233, 237, 239] conclude that there is insufficient evidence to comment on the potential benefit of extracorporeal membrane oxygenation to treat influenza-associated respiratory failure. Two reviews [237, 239] found no benefit of corticosteroid therapy to treat acute lung injury, while another [241] found that it significantly increases nosocomial infection and mortality.

The executed search strategy found no systematic reviews relating to either border control measures or hospital triage protocols. Additional searches of the primary literature suggested a low efficacy associated with border control measures. These include the use of non-contact infrared thermometers in airports to detect infected passengers, where studies from the 2009 pandemic found that the positive predictive value ranged from 0.9% to 76.0%, and was likely to be too low to effectively detect and contain pandemic infection [242, 243]. A study of entry screening for pandemic H1N1 at Auckland International Airport — which focused on encouraging infection reporting and did not use thermal scanning or active screening — reported a screening sensitivity of 5.8%, which the authors concluded to be insufficient to delay the spread of pandemic influenza [244]. The general consensus appears to be that even rigorous and expensive border control measures are unlikely to delay the spread of pandemic influenza by more than a few days [245, 246]. No empirical studies were found that quantified the effectiveness of alternate models of care — such as hospital triage protocols — in containing pandemic influenza.

This present systematic review is subject to certain limitations. First, a decision was made to review existing systematic reviews and meta-analyses, rather than primary literature. This was done in an effort to account for the clinical, methodological and statistical heterogeneity in this

field, while summarizing and assessing current, high-quality research regarding preventative interventions for pandemic influenza, and is consistent with past health intervention research methodologies [247]. While it is possible that this approach omits some primary research, this was deemed unlikely to substantially affect results, given the broad search and inclusion criteria and considering that the last pandemic occurred seven years ago, meaning that recent reviews are likely to have captured relevant primary literature. This approach provided an efficient means of summarizing and assessing the results of numerous reviews in a single study, allowing a more fulsome discussion of the quality of existing evidence on pandemic influenza interventions than would have been feasible from a review of the primary literature. Second, as high heterogeneity both within and between included studies prevented further meta-analysis, we were necessarily restricted to a narrative synthesis of current research and persisting knowledge gaps. The potential for publication biases was noted, as the marginally protective role of interventions such as hand hygiene and mask use may have been overestimated by the disproportionate publication of significant results (the association was still not found to be significant, however). Location bias was also present, as most results included in the reviews were from higher-income countries, and some interventions, such as mass antiviral prophylaxis, may not be feasible in low-resource settings. Another limitation of this review was that most of the available data were obtained from studies of the relatively mild 2009 H1N1 pandemic; this precluded analysis of the how intervention effectiveness is affected by disease characteristics, and may limit to generalizability of findings to future pandemics of unknown severity. Lastly, outcome reporting bias may have influenced the results, given the variability of influenza case definitions that were used in the primary studies, sometimes with little clinical basis.

3.5 Conclusion

This systematic review provides the first synthesis of existing systematic reviews and meta-analyses on interventions to prevent pandemic influenza infection, comparing findings to advance knowledge and understanding of optimal intervention strategies. Important knowledge gaps persist in this area, particularly with regard to the effect of non-pharmaceutical interventions in limiting transmission and infection. While pandemic vaccination appears to be effective in preventing influenza, it is crucial to prepare for the early phases of a pandemic where vaccines may be unavailable. Future work could focus on the impact of personal protective measures in reducing transmission rates; an important avenue for primary research is the prospective study of intervention effectiveness in infectious disease emergency situations. In the meantime, it is hoped the results of the present review will be of value in informing the development of future pandemic intervention strategies.

Chapter 4. Effectiveness of personal protective measures in reducing pandemic influenza transmission: a systematic review and meta-analysis

Authors Note

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Publication Status Information

This manuscript has been published in the journal *Epidemics* (Saunders-Hastings, P., Crispo, J., Sikora, L., & Krewski, D. (2017). Assessing the effectiveness of personal protective measures in reducing pandemic influenza transmission: a systematic review. *Epidemics*). A systematic review protocol was registered and published in *PROSPERO in* September, 2016 (Saunders-Hastings, P., Crispo, J., Sikora, L., & Krewski, D. (2016). Assessing the effectiveness of personal protective measures in reducing pandemic influenza transmission: a systematic review protocol. *PROSPERO (*registration number CRD42016039896*)*).

Abstract

The potential severity of influenza pandemics necessitates informed policy planning to direct early and efficient responses. The primary objective of this review was to examine the effectiveness of personal protective measures in preventing pandemic influenza transmission in human populations.

We conducted a systematic review of primary literature quantifying the effectiveness of selected interventions. Eligible studies were collected from five databases (Medline, Embase, PubMed, Cochrane Library and CINAHL) and grey literature searches. Where appropriate, random effects meta-analyses were conducted using inverse variance statistical calculations.

Meta-analyses suggest that regular hand hygiene provided a significant protective effect (N=3,930; OR=0.62; 95% CI 0.52–0.73; I^2=0%), and facemask use provided a non-significant protective effect (N=1,371; OR=0.53; 95% CI 0.16–1.71; I^2=48%) against 2009 pandemic influenza infection. These interventions may therefore be effective at limiting transmission during future pandemics.

PROSPERO Registration: 42016039896

4.1 Introduction

Influenza pandemics may arise from antigenic shifts, when reassortment between different viral strains results in the emergence of a novel influenza virus to which most individuals are immunologically naïve [61]. If this new pathogen causes clinical illness in humans and is able to transmit effectively between humans, a global pandemic may occur. This has happened four times in the past one hundred years: the 1918 Spanish flu, the 1957 Asian flu, the 1968 Hong Kong flu

and the 2009 Swine flu. Together these events have resulted in millions of cases of illness, hospitalization and death, as well as a significant social and economic burden [73, 112, 149, 248]. The Spanish flu demonstrates the catastrophic potential of such events, having caused between 20 and 50 million deaths globally [73-76]. Advances in medicine and public health render such dramatic consequences unlikely today [249]. The emergence of antivirals, vaccines and mechanical ventilators should help protect from such a catastrophic pandemic in the future, and pandemic-attributable mortality has decreased in the three influenza pandemics since the Spanish flu [249] . However, the unpredictable nature of influenza pandemics, coupled with increasing opportunities for viral reassortment, necessitate further studies of appropriate mechanisms to respond to such events and mitigate their impact.

The irregular cycle of influenza pandemics makes them difficult to study, with most of the available, scientifically rigorous data deriving from the recent 2009 pandemic. This is problematic given that the 2009 pandemic strain — A(H1N1)pdm09 — is known to have been quite mild, with hospitalization and death rates similar to recent seasonal influenza [112]. The disease characteristics of future pandemics may differ substantially from those in the past. Little is known about the effectiveness of a suite of potential interventions to interrupt pandemic influenza infection. This is especially true of non-pharmaceutical measures such as social distancing (school closure, patient quarantine) and personal protective measures (PPMs). Pharmaceutical measures such as pandemic vaccination are effective [199, 201, 203, 205, 250], but may not be available in the early stages of a pandemic influenza outbreak [103, 232]. Social distancing policies, meanwhile, are of uncertain effectiveness, and are often expensive, unpopular and difficult to implement [156, 168, 215]. Consequently, patient quarantine has not been broadly implemented since the 1918 pandemic [90], while uncertainty regarding the effectiveness of school closure has

limited its implementation over the course of the past three pandemics [116, 167]. However, PPMs such as respiratory etiquette, hand hygiene and the use of facemasks are inexpensive and easy to implement, and are commonly recommended and undertaken during influenza outbreaks [251-253].

The primary objective of this review and meta-analysis is to quantify the effectiveness of PPMs in reducing the risk of human-to-human pandemic influenza infection. A secondary objective is to assess the relative effectiveness of these interventions. This is currently an important knowledge gap: a search for existing systematic reviews evaluating pandemic influenza interventions found only a single systematic review [212] on the effectiveness of PPMs in preventing pandemic influenza infection; focusing specifically on hand hygiene in the community, the review found only one study that was conducted during an influenza pandemic [224]. However, the authors only included randomized control trials (RCTs) in their analysis, potentially missing important insights from observational studies. Given the important role PPMs may play in the early stages of a future pandemic, this review provides an important and timely assessment of the state of PPM literature and, where possible, quantification of pooled estimates of PPM effectiveness in interrupting pandemic influenza transmission.

4.2 Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to guide the development of the systematic review methodology (**Appendix 10**) [191]. A protocol was developed *a priori* and registered in the National Institute for Health Research International Prospective Register of Systematic Reviews (PROSPERO) [250].

4.2.1 Search strategy

The literature search was conducted by PSH on June 30, 2016, with no language or date restrictions. Searches were conducted across five databases: PubMed (all dates), Medline via Ovid (1946–June 30, 2016), Embase via Ovid (1947–June 30, 2016), Cochrane Library via Ovid (all dates) and the Cumulative Index to Nursing and Allied Health (CINAHL; all dates). **Table 5** illustrates the general search strategy, built in Medline, with database-specific variations included in **Appendix 11**. To supplement these searches, researchers conducted searches of the reference lists of included studies, and of the grey literature using Google Scholar.

Table 5. Systematic review search strategy, as executed in Medline

1. Influenza, Human/
2. Exp Influenza A virus A/
3. 1 or 2
4. Pandemics/
5. (pandemic* adj3 (influenza* of flu* or grippe)).tw.
6. 4 or 5
7. 3 and 6
8. Exp Hand Hygiene/
9. (handwashing or hand washing or hand-washing).tw.
10. ((hand*) adj3 (hygien* or disinfect* or sanitiz* or sanitis* or wash* or scrub* or cleans*)).tw.
11. Or/8–10
12. Cough/
13. (cough* and (influenza* or flu* or grippe)).tw.
14. ((respirat* or breath* or sneez* or cough*) adj3 (etiquette* or custom* or maneuver* or practic*)).tw.
15. Or/12–14
16. Masks/
17. (mask* and (influenza* or flu* or grippe)).tw.
18. (facemask* and (influenza* or flu* or grippe)).tw.
19. (N95* and (influenza* or flu* or grippe)).tw.
20. (N-95* and (influenza* or flu* or grippe)).tw.
21. Or/16–20
22. 11 or 15 or 21
23. 7 and 22

4.2.2 Eligibility criteria and study inclusion

In this review, investigators sought to assess the effectiveness of commonly recommended PPMs in reducing the risk of pandemic influenza infection in humans. Personal protective measures included any form of hand hygiene, use of facemasks or respiratory etiquette (covering mouth during coughing and sneezing). Interventions more commonly recommended for healthcare staff, and less likely to be implemented in community settings, were not considered. These interventions include the use of goggles, gowns and gloves to prevent influenza transmission. **Table 6** lists the relevant eligibility criteria developed *a priori* and applied throughout the screening process.

All citations were imported into the web-based systematic review software DistillerSR (Evidence Partners Incorporated, Ottawa, Canada). Following deduplication, two independent, blind reviewers conducted title and abstract screening using a pilot-tested DistillerSR screening form that reflected the eligibility criteria. An assenting response from at least one reviewer resulted in article inclusion for full review, where articles were again subjected to blind review by two independent reviewers using a piloted DistillerSR form. At this stage, disagreements were resolved by consensus; third-party arbitration was implemented as necessary.

Table 6. Eligibility criteria for assessed studies.

Category	Inclusion Criteria	Exclusion Criteria
Population	Humans exposed to a pandemic influenza	*In vivo* and *in vitro* laboratory studies, and non-human species
Intervention(s)	Any form of hand hygiene, respiratory etiquette, or the wearing of facemasks	No intervention or other interventions, including vaccination, antiviral use, school or work closure, or contact reduction
Comparison(s)	The impact or effectiveness of an intervention of interest compared to no intervention or other forms of intervention.	No comparisons made
Outcome(s)	Quantified change in risk of pandemic influenza transmission	No quantified impact
Study type	Randomized trials, case–control, cohort, and cross-sectional studies	Predictive mathematical modelling studies; case study and case series reports; case–crossover, crossover, before–after, and ecologic studies; expert opinion and editorials; systematic reviews and meta-analyses

4.2.3 Data extraction

Two independent reviewers (PSH, JC) extracted data from included studies using an adapted data collection form developed by The Cochrane Collaboration [254]. The form collected information on study population(s), methods, intervention(s), outcome measure(s) and results.

4.2.4 Quality assessment

Quality assessment was conducted for included studies during the data extraction process. Tables assessing the risk of bias for randomized trials, case–control and cohort studies were included in the data extraction form. Quality assessment of randomized trials adopted the Cochrane Collaboration's tool for assessing risk of bias [255]. Quality appraisal for case–control and cohort studies was done using the Newcastle–Ottawa scale [256]. Both tools have been externally

validated and are commonly used in reviews of public health interventions [255, 257]. Disagreements regarding potential sources of bias were discussed and resolved by consensus. The quality of cross-sectional studies was not assessed, as the risk of bias in these studies was deemed to be innately high, and cross-sectional studies were excluded from data pooling. Study quality was not used as an eligibility criterion; rather, potential sources of bias are noted in the discussion of the implications of review findings.

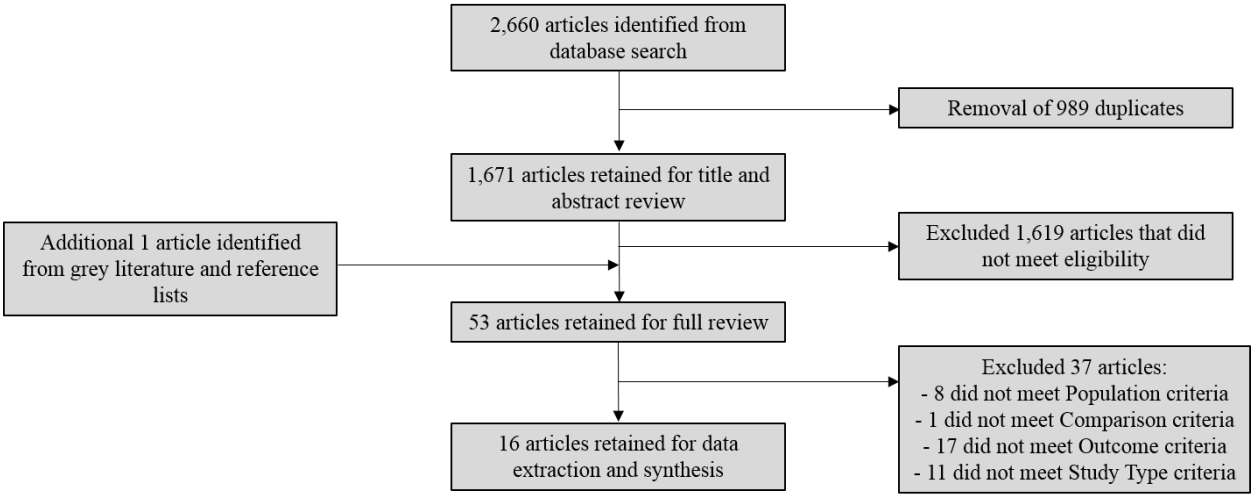
4.2.5 Data synthesis and analysis

Data from included studies were grouped based on categories of interventions and outcome measures. Synthesis proceeded in a two-stage process. Comparable data and risk estimates from studies with similar interventions and outcome measures were imported into Revman 5.3.5 (http://tech.cochrane.org/revman). Where possible, we used estimates of effect from models adjusted for the maximum number of covariates. Inverse variance weighting and random-effects modeling was used in all meta-analyses. The presence of significant data heterogeneity, as measured using the I^2 statistic (I^2>50% was considered to represent possible substantial uncertainty, as conveyed in the Cochrane Handbook [258]), did not preclude data pooling, but was noted in the discussion of results. In instances where only a single study was identified, intervention results were excluded from meta-analyses and were qualitatively described. Data permitting, subgroup analyses by age were conducted. Risk of publication bias was assessed via funnel plot inspection and Egger regression test.

4.3 Results

A total of 2,660 citations were retrieved from our search of the literature. Following elimination of duplicates, 1,671 citations were retained for title and abstract review. Of these, 52 were retained for full review, along with a single study identified through additional searches. Overall, 16 studies met the inclusion criteria for our study and were subject to data extraction. The study selection process is summarized in **Figure 3**, while a justification for articles excluded during full review is included in **Appendix 12**.

Figure 3. Data selection process



4.3.1 Included studies

Of the 16 studies included, 15 [226, 259-272] quantitatively described at least one measure of hand hygiene effectiveness, while eight [259, 260, 263, 265-268, 273] measured the effectiveness of facemask use; no studies evaluating the impact of any form of respiratory etiquette, such as covering one's mouth during coughing or sneezing, were identified. All studies derived from the A(H1N1)pdm09 pandemic. Six unique combinations of intervention group and outcome measures were pooled for meta-analysis; two of these had significant data heterogeneity. There were

insufficient data to conduct meta-analyses based on age group. The characteristics of individual studies are summarized in **Table 7,** organized by study and intervention types, while results from individual studies are included in **Appendix 13**.

Table 7. Summary of included studies.

Study	Type of Study	Population	Participants (N)	Intervention(s)	Outcome(s)
Azor-Martinez et al., 2014 [270]	RCT	Children aged 4–12 in Spain	1,616	Hand sanitizer	School absenteeism
Cheng et al., 2010 [259]	Case–control study	Healthcare workers in Hong Kong	836	Surgical mask use and hand hygiene	Laboratory-confirmed influenza infection
Deng et al., 2011 [260]	Case–control study	Healthcare workers in Beijing, China	280	Surgical masks and use of disposable tissues for hand hygiene	Laboratory-confirmed influenza infection
Godoy et al., 2012 [264]	Multicenter case–control study	Inpatients and individuals who received primary care at participating centers	3,087	Hand hygiene	Hospital admission with laboratory-confirmed influenza
Jaeger et al., 2011 [273]	Cohort study	Healthcare workers in Southern California	63	Surgical masks and N95 respirators	Laboratory-confirmed influenza infection
Kim et al., 2012 [265]	Cross-sectional survey	School-aged children in South Korea	15,945	Handwashing and facemask use	Laboratory-confirmed influenza infection

Kuster et al., 2013 [268]	Cohort study	Adult healthcare and non-healthcare workers in Toronto, Canada	732	Hand hygiene and facial protection	Laboratory-confirmed influenza infection
Li et al., 2011 [261]	Case–control study	Students 15–21 years old in Guangzhou, China	1,644	Handwashing	Laboratory-confirmed influenza infection
Liu et al., 2011 [262]	Case–control study	Individuals in Beijing, China	216	Handwashing	Secondary household infection (diagnosis)
Merck et al., 2014 [271]	Cohort study	Individuals 17–95 in Stockholm, Sweden	4,365	Handwashing	Influenza-like illness
Remschmidt et al., 2013 [269]	Cohort study	German households with an infected individual ≥2 years old	375	Handwashing	Secondary household infection (ILI)
Suess et al., 2012 [266]	Cluster RCT	Households in Berlin, Germany with an infected individual ≥2 years old	302	Facemasks and hand hygiene	Laboratory-confirmed secondary influenza infection
Torner et al., 2015 [226]	Multicenter case–control study	Outpatient children 6 months to 7 years old in Spain	478	Hand hygiene	Laboratory-confirmed influenza infection
Toyokawa et al., 2011 [263]	Cross-sectional survey	Healthcare workers in Kobe, Japan	269	Hand hygiene, surgical masks, and N95 respirators	Laboratory-confirmed influenza infection

Zhang et al., 2012 [267]	Case–control study	Healthcare workers in Beijing, China	255	Hand hygiene and mask use	Laboratory-confirmed influenza infection
Zhang et al., 2013 [272]	Case–control study	Households in China	162 (households)	Handwashing	Laboratory-confirmed secondary influenza infection

4.3.2 Quality assessment

Inter-rater agreement of the quality of included studies was strong. The results of this assessment are included in **Table 8**–**Table 10**, which highlights potential sources of bias across different study types. These are incorporated into the discussion of the implications of findings of our review. Funnel plots assessing the risk of publication bias are included in **Figure 4**. Visual inspection of plots was used, as the limited number of included studies and dichotomous nature of the outcome measures of interest make regression testing inappropriate [274].

Table 8. Risk of bias assessment of included RCTs.

	Risk of Bias (low, high, unclear)						
RCT	**Random Sequence Generation**	**Allocation Concealment**	**Performance Bias**	**Detection Bias**	**Attrition Bias**	**Reporting Bias**	**Other Bias**
Azor-Martinez et al., 2014	Low	Unclear	High	High	Low	Low	High
Suess et al., 2012	Unclear	Low	Low	Unclear	Low	High	None

Table 9. Risk of bias assessment of included cohort studies.

	Risk of Bias*								
Cohort Study	**Exposed Cohort Representativeness**	**Non-Exposed Cohort Selection**	**Ascertainment of Exposure**	**Absence of Outcome at Start**	**Comparability of Cohorts**	**Assessment of Outcome**	**Length of Follow Up**	**Adequacy of Follow up**	**Total Score**
Jaeger et al., 2011	0	1	0	0	0	1	1	1	4
Kuster et al., 2013	1	0	0	1	1	1	1	1	6
Merck et al., 2014	1	1	0	0	1	0	1	1	5
Remschmidt et al., 2013	0	1	1	0	0	0	1	0	3

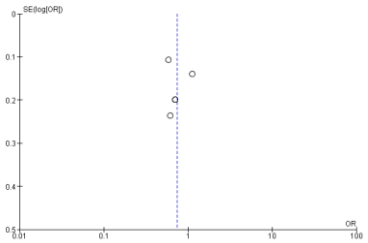
Table 10. Risk of bias assessment of included case–control studies.

	Risk of Bias*								
Case–Control Study	**Case Definition**	**Case Representativeness**	**Selection of Controls**	**Definition of Controls**	**Comparability of Cases and Controls**	**Ascertainment of Exposure**	**Method of Ascertainment**	**Non-Response Rate**	**Total Score**
Cheng et al., 2010	1	1	1	1	0	1	1	1	7
Deng et al., 2011	1	0	0	1	0	0	1	1	4
Godoy et al., 2011	1	0	1	1	0	0	1	0	4
Li et al., 2011	0	1	1	0	0	1	1	1	5
Liu et al., 2011	0	1	1	1	2	0	1	1	7
Torner et al., 2015	1	0	1	1	2	0	1	1	7
Zhang et al., 2013	1	1	1	1	1	0	1	1	7
Zhang et al., 2012	1	1	1	1	2	0	0	0	6

*Score of 0 indicates risk of bias; a score of 1 or 2 was awarded if the study took appropriate measures to limit the risk of bias. The forms and criteria used for quality assessment can be found at [255] for RCTs and [256] for case–control and cohort studies.

Figure 4. Funnel plots assessing publication bias in meta-analysis results for (a) hand-washing frequency and influenza; (b) subgroup analysis of hand-washing frequency and influenza; (c) hand-washing frequency and ILI; (d) hand sanitizer use and influenza; (e) hand hygiene after contact with an index case and influenza; (f) hand hygiene after contact with contaminated surfaces and influenza; and (g) facemask use and influenza.

(a)



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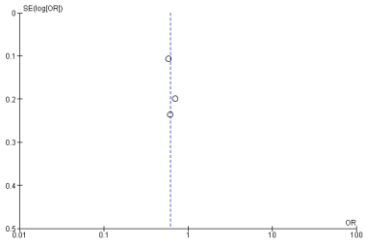

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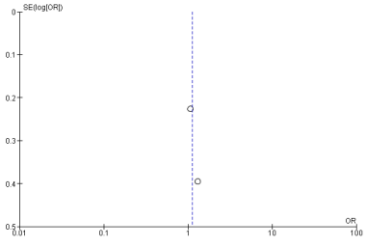

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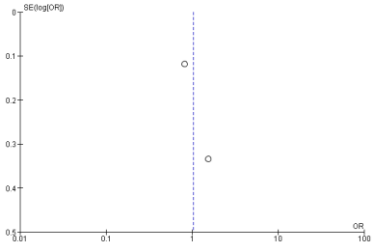
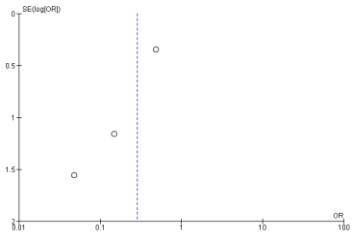
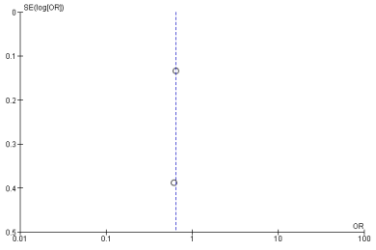


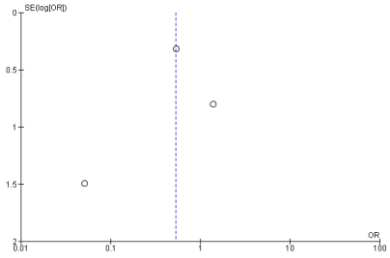
(e)



(f)



(g)



4.3.3 Hand hygiene

Fifteen studies were identified from our search that evaluated the effectiveness of some form of hand hygiene in preventing pandemic influenza infection; two were RCTs [266, 270], eight were case–control studies [226, 259-262, 264, 267, 272], three were cohort studies [268, 269, 271] and two were cross-sectional surveys [263, 265]. Of the studies that could not be pooled for meta-analysis, two RCTs reported a significant effect of hand hygiene. One reported that the incidence and proportion of school absence associated with pandemic influenza decreased in schools where a hand sanitizer intervention was implemented [270], while the other found that hand hygiene in conjunction with facemask use reduced risk of secondary influenza infection (OR=0.26; 95% confidence interval (CI) 0.07–0.93) [266]. These were not pooled because they did not have a comparable outcome measure or single intervention, respectively. A single cohort study reported that each 10% increase in healthcare worker adherence to hand hygiene recommendations resulted in a reduced risk of influenza infection (OR=0.84; 95% CI 0.73–0.98) [268], but was not pooled because it did not provide estimates of effect that compared an intervention to a control. Two cross-sectional surveys reported a non-significant protective effect of subjectively reported "frequent" hand-washing, with OR=0.99 (95% CI 0.96–1.02) [265] and OR=0.58 (95% CI 0.07–5.13) [263], but were excluded from meta-analysis due to the innately high bias in cross-sectional surveys.

The remaining studies were pooled to examine five intervention-outcome comparisons, included in **Figure 5**. Meta-analysis of five studies [226, 261, 262, 264, 272] comparing the frequency of hand-washing with laboratory-confirmed influenza found a significant protective effect, but also significant statistical heterogeneity (**Figure 5a**; N=5,789; OR=0.74; 95% CI 0.56–0.97; I^2=72%). However, this protective effect was even more pronounced in a subgroup analysis

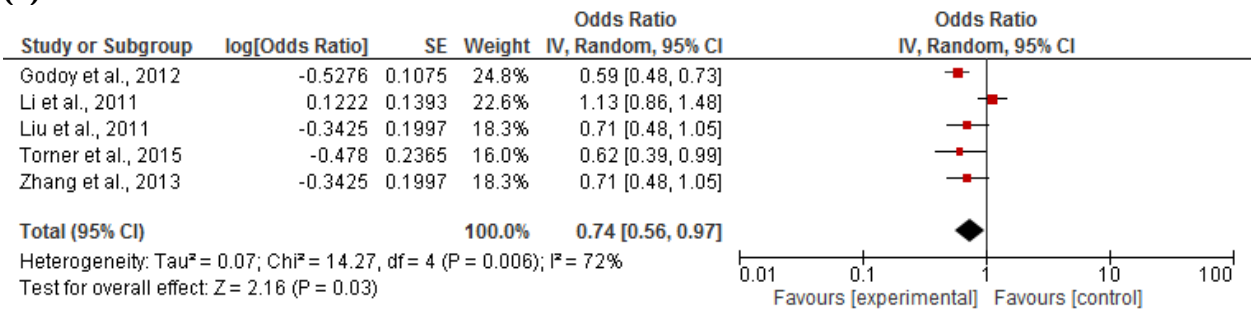
excluding studies where frequency was subjectively defined by the study participants, and retaining those that reported a minimum number of times study participants washed their hands daily (**Figure 5b**; N=3,930; OR=0.62; 95% CI 0.52–0.73; I^2=0%) [226, 264, 272].

A separate meta-analysis of two cohort studies [269, 271] comparing hand-washing frequency with self-reported influenza-like illness (ILI) found a non-significant increase in risk associated with hand-washing (**Figure 5c**; N=4,740; RR=1.12; 95% CI 0.76–1.64; I^2=0%). A meta-analysis of two case–control studies [226, 264] examining the subjectively defined "occasional" use of alcohol-based sanitizers also found a non-significant risk increase in the presence of significant statistical heterogeneity (**Figure 5d**; N=3,565; OR=1.04; 95% CI 0.57–1.89; I^2=68%).

Hand hygiene motivated by influenza exposure was found to be significantly protective in two cases. Occasional hand hygiene both following contact with an index case (**Figure 5e**; N=1,371; OR=0.29; 95% CI 0.09–0.93; I^2=31%) [259, 260, 267] and following contact with contaminated surfaces (**Figure 5f**; N=3,565; OR=0.65; 95% CI 0.50–0.83; I^2=0%) [226, 264] was found to protect against confirmed pandemic influenza infection.

Figure 5. Forest plots of meta-analysis results of for (a) hand-washing frequency and influenza; (b) subgroup analysis of hand-washing frequency and influenza; (c) hand-washing frequency and ILI; (d) hand sanitizer use and influenza; (e) hand hygiene after contact with an index case and influenza; (f) hand hygiene after contact with contaminated surfaces and influenza; and (g) facemask use and influenza

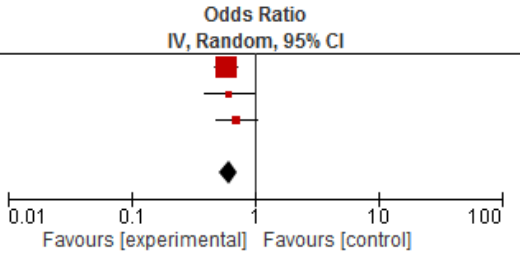
(a)



(b)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Godoy et al., 2012	-0.5276	0.1075	66.8%	0.59 [0.48, 0.73]
Torner et al., 2015	-0.478	0.2365	13.8%	0.62 [0.39, 0.99]
Zhang et al., 2013	-0.3425	0.1997	19.4%	0.71 [0.48, 1.05]
Total (95% CI)			**100.0%**	**0.62 [0.52, 0.73]**

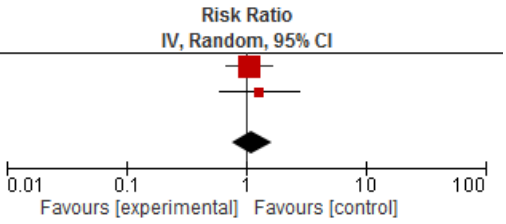
Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 5.52 (P < 0.00001)



(c)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Merck et al., 2014	0.0583	0.2265	75.2%	1.06 [0.68, 1.65]
Remschmidt et al., 2013	0.2624	0.3945	24.8%	1.30 [0.60, 2.82]
Total (95% CI)			**100.0%**	**1.12 [0.76, 1.64]**

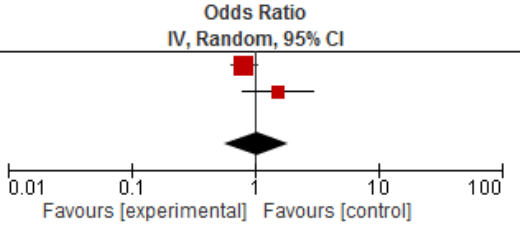
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.55 (P = 0.58)



(d)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Godoy et al., 2012	-0.1985	0.1185	62.3%	0.82 [0.65, 1.03]
Torner et al., 2015	0.4318	0.3342	37.7%	1.54 [0.80, 2.96]
Total (95% CI)			**100.0%**	**1.04 [0.57, 1.89]**

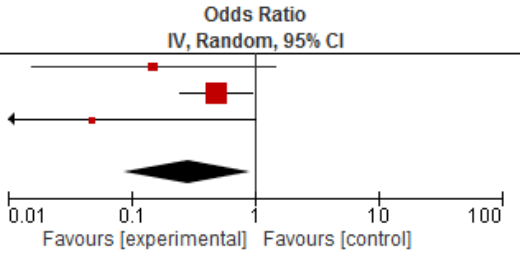
Heterogeneity: Tau² = 0.14; Chi² = 3.16, df = 1 (P = 0.08); I² = 68%
Test for overall effect: Z = 0.13 (P = 0.90)



(e)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Cheng et al., 2010	-1.8927	1.1571	20.5%	0.15 [0.02, 1.46]
Deng et al., 2011	-0.7161	0.3474	66.8%	0.49 [0.25, 0.97]
Zhang et al., 2012	-3.028	1.5573	12.7%	0.05 [0.00, 1.02]
Total (95% CI)			**100.0%**	**0.29 [0.09, 0.93]**

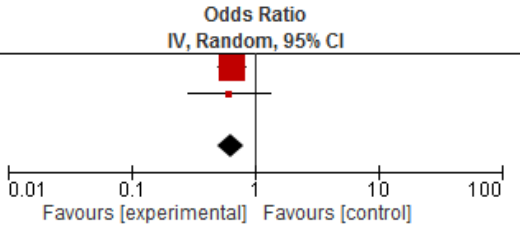
Heterogeneity: Tau² = 0.42; Chi² = 2.88, df = 2 (P = 0.24); I² = 31%
Test for overall effect: Z = 2.08 (P = 0.04)



(f)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Godoy et al., 2012	-0.4308	0.1339	89.3%	0.65 [0.50, 0.85]
Torner et al., 2015	-0.478	0.3877	10.7%	0.62 [0.29, 1.33]
Total (95% CI)			**100.0%**	**0.65 [0.50, 0.83]**

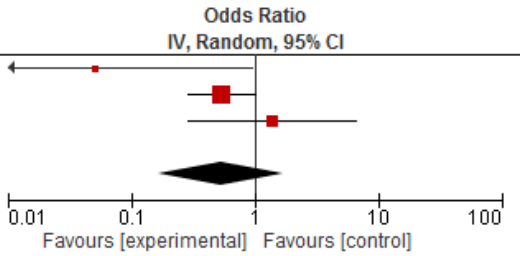
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 3.44 (P = 0.0006)



(g)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Cheng et al., 2010	-2.9624	1.4926	13.0%	0.05 [0.00, 0.96]
Deng et al., 2011	-0.6221	0.3199	56.4%	0.54 [0.29, 1.00]
Zhang et al., 2012	0.3268	0.7992	30.6%	1.39 [0.29, 6.64]
Total (95% CI)			**100.0%**	**0.53 [0.16, 1.71]**

Heterogeneity: Tau² = 0.54; Chi² = 3.85, df = 2 (P = 0.15); I² = 48%
Test for overall effect: Z = 1.06 (P = 0.29)



4.3.4 Facemask use

Eight studies evaluated the effectiveness of facemask use in preventing pandemic influenza infection [259, 260, 263, 265-268, 273]. One cohort study reported that the risk of influenza infection among healthcare workers decreases for each 10% increase in adherence to facial protection guidelines (OR=0.92; 95% CI 0.79–1.07) [268] was not pooled for meta-analysis because it did not provide estimates of effect comparing an intervention to a control. A cluster randomized control trial found a significantly protective effect of facemask use (OR=0.28; 95% CI 0.08–0.98) [266]. A cohort study found a non-significant protective effect (RR=0.09; 0.00–1.60) [273]. One cross-sectional survey reported a significant protective effect of continuous mask use in children, relative to non-users (OR=0.51; 95% CI 0.30–0.88), but a non-significant risk increase in irregular users relative to non-users (OR=1.02; 95% CI 0.83–1.25) [265]. Another cross-sectional survey reported a non-significant risk increase associated with frequent use of surgical masks (OR=6.59; 95% CI 0.55–78.3) and N95 respirators (OR=2.28; 95% CI 0.20–20.2) relative to infrequent use, but is based on a small sample size (N=87) [263]. Of the remaining three studies pooled for meta-analysis [259, 260, 266, 267, 273], all reported on the use of facemasks among healthcare workers dealing with infected patients. Meta-analysis found a non-significant protective effect of mask use in preventing influenza infection (**Figure 5g**; N=1,371; OR=0.53; 95% CI 0.16–0.1.71; I^2=48%). If the randomized control trial and cohort study were pooled with the case–control studies, heterogeneity decreased and a significant protective effect was found (not illustrated: N=1,736; OR=0.41 95% CI 0.18–0.92; I^2=35%).

4.4 Discussion

Analyses of hand hygiene found significant protective effects associated with frequent hand-washing and hand-washing after contact with an index patient or a contaminated surface. These results compare favourably to the results of a systematic review of RCTs evaluating hand hygiene effectiveness during seasonal influenza epidemics, which found a significant protective effect associated with a combination of hand hygiene and facemask use, but no significant effect of hand hygiene alone in preventing influenza infection [212]. Non-significant increases in risk were associated with hand-washing frequency and ILI and with the occasional use of hand sanitizer and influenza, although these results are based on small samples size and subjective definitions of intervention and outcome measures by primary study authors.

No studies were found that evaluated the effectiveness of respiratory etiquette. However, a recent study evaluated the effectiveness of cough etiquette maneuvers in blocking aerosol particles, finding that they did not block the release or dispersion of aerosol droplets, particularly those smaller than one micron in size [275]. As a virus, influenza particles are extremely small, measuring 0.08–0.12 microns in diameter [276], and could easily be carried in small droplets expelled during coughing or sneezing.

The present systematic review is the first to successfully quantify the effectiveness of PPMs in preventing pandemic influenza infection. Several past reviews have attempted to produce an estimate of effect by reviewing the impact of personal protective measures on transmission of multiple respiratory viruses [225, 251, 277, 278]. Jefferson and colleagues, for example, pooled case–control study data to calculate estimates of effect of handwashing eleven times a day and simple mask-wearing against SARS transmission, estimating OR of 0.54 (95% CI 0.44–0.67) and 0.32 (95% CI 0.26–0.39), respectively; these do not differ significantly from our own estimates.

However, as the authors of one of these reviews recognized, observational studies of SARS are "of limited use for guiding policy on influenza" [277]. This is because the epidemiology of SARS differs substantially from that of influenza: SARS transmission tends to occur predominantly in nosocomial settings and infection rarely affects children, involves a long incubation period and low infectiousness in the early stages [277]. It should also be noted that, across the reviews mentioned above, the latest search conducted was in January, 2011; all but one of our included studies were published after this date, demonstrating that primary research associated with the A(H1N1)pdm09 strain was still being published at the time these reviews were conducted.

It has been postulated that the effectiveness of PPMs during seasonal influenza epidemics may differ during an influenza pandemic [228, 279-282], as public anxiety may increase rates of intervention adherence. There is also uncertainty regarding the relative importance of contact, droplet and airborne routes of transmission in driving influenza infection [283, 284], which will impact the importance of PPMs targeting a particular route (hand hygiene for contact transmission, respiratory etiquette and facemask use for airborne and droplet transmission).

The role of different routes of transmission may shift during influenza pandemics, given their unpredictable seasonality relative to the usual Northern Hemisphere flu season, which tends to run from October through March but peaks between December and February [285]. Colder temperatures ($\leq 4^{o}C$) tend to prolong the environmental persistence of influenza A [286], which could increase the relative burden of contact transmission and the importance of hand hygiene after contact with contaminated surfaces.

Conversely, studies using guinea pigs have found that high temperatures ($\geq 30^{o}C$) prevent aerosol transmission of influenza, but do not affect contact transmission [287, 288]. Meanwhile, low relative humidity (20–30%) appears to promote influenza virus survival in air, increasing

aerosol and droplet transmission; these are inhibited at high relative humidity (≥80%) [287, 289]. Taken together, variability in adherence and transmission patterns may alter the effectiveness of PPMs during an influenza pandemic relative to a seasonal epidemic; this uncertainty has resulted in challenges for health policy and infection control efforts [289].

Enhancing knowledge in this area is crucial to informing recommendations on the use of individual protective measures during future influenza pandemics. We conducted a systematic review of the primary literature, pooling data where possible and appropriate to arrive at quantitative estimates of intervention effectiveness. The primary finding was that regular hand hygiene was significantly protective in protecting from pandemic influenza infection, while facemask use was not significantly protective.

The significant protective effect of hand hygiene following contact with infected individuals or contaminated cases, which were found to be comparable to general hand hygiene practices, supports the position that protective measures both during and immediately following viral exposure will drive intervention effectiveness. While this seems intuitively reasonable, an important implication is that the frequency of performing such maneuvers may need to increase in pandemic situations, where attack rates and viral loads are likely to be higher than during seasonal epidemics [231], increasing the frequency of exposure events.

Our systematic review is not without limitations. Out of a recognition that little non-pharmaceutical intervention research that has been conducted in pandemic settings, we took a broad approach to the search strategy, combining multiple intervention–outcome pairs. This did not restrict depth of analysis, however, as data were still limited. Second, most studies included in our review have a moderate-to-high risk of bias, which may limit the interpretability of their results. Inappropriate or unspecified ascertainment of exposure was the most common source of

potential bias [226, 260, 261, 264, 267, 268, 271-273], due to a lack of blinding and reliance of subject self-reporting. While more logistically complicated and resource-intensive, prospective studies that verify subject behaviour would enhance understanding of intervention effectiveness. The representativeness of cases [226, 260, 264] and exposed cohorts [261, 269, 273], along with their comparability to control groups [226, 260, 261, 264, 269, 273], present other sources of bias, as the potential for selection bias was often present, and studies often failed to account for important confounding factors, such as vaccination status.

The non-blinded, retrospective nature of most studies included in our review presents a risk of performance, detection, and reporting biases, which could over-estimate the true effectiveness of PPMs in preventing influenza infection, as cases and controls may misjudge their adoption of PPMs in order to rationalize their infection status. Given the overall lack of data on this subject, quality-based subgroup analyses were not conducted. A range of economical, logistical and ethical barriers present substantial challenges in the design of controlled, prospective pandemic influenza intervention trials; consequently, it was decided that the potential importance of non-pharmaceutical interventions justifies the decision to acquire as much data as possible, despite risks of biased results. Assessment of funnel plots (**Figure 4**) demonstrated some asymmetry and gaps; this may be indicative of publication bias, but is it impossible to conclude with certainty given the small number of studies included in each meta-analysis. It should also be noted that all available data were obtained from studies conducted within the context of the A(H1N1)pdm09 pandemic; this unavoidable constraint may limit the generalizability of our findings to future pandemics of unknown severity. It would be inappropriate to extrapolate this across all strains of past and future pandemics, which may differ in terms of pathogenicity, timing and public response.

Important knowledge gaps persist. It is unclear what constitutes an appropriate "threshold" for adequate, protective hand hygiene and facemask use; it is likely that this will vary depending on individual factors such as exposure, susceptibility and risk of adverse outcomes. This presents challenges in recommending appropriate behaviour during pandemic situations. Study questions using subjective terms to define frequency of PPM use, such as "rarely", "occasionally" or "sometimes", contribute to this problem. A study of facemask use [265], for example, found a significant protective effect of regular use relative to no use, but not of irregular use relative to no use; it is unclear how much time spent wearing a facemask is necessary to constitute "continuous". This self-reporting by study subjects of their own intervention status likely contributed to the observed heterogeneity, complicating interpretation of the findings. Studies based on the exact number of times an action was performed daily are likely to provide more reliable results, although such studies are also at risk of recall bias. Small sample sizes have limited the statistical power of our meta-analyses, and the relative merits of use different forms of PPMs are uncertain.

Given the questionable effectiveness of respiratory etiquette, mask use and hand hygiene should form the foundation of protective behavior. As compliance with good hand hygiene practices may be higher than that for facemasks, which have been poorly accepted in the past [290, 291], an optimal intervention strategy may combine broad recommendations for frequent hand hygiene, combined with targeted facemask use among high-risk populations (healthcare workers, schools-aged children, the elderly). Risk communication strategies should clarify locations and situations where viral contact is likely, emphasizing the value of engaging in protective behaviours during and immediately following exposure to these environments.

4.5 Conclusion

This review constitutes a contribution to pandemic influenza research, presenting the first systematic review and meta-analysis to quantify the effectiveness of PPMs in preventing pandemic influenza transmission. While data were not available on the effectiveness of respiratory etiquette, hand hygiene was found to be significantly effective in preventing infection. Facemask use demonstrated mixed results, but a randomized control trial suggests that it is effective. Future studies are needed to evaluate the relative impact of different routes of influenza transmission, and how this may shift between seasonal and pandemic settings. Despite persisting knowledge gaps in relative effectiveness between interventions and across population groups, results suggest that campaigns to increase the frequency of hand hygiene, alongside use of facemasks in situations with a high risk of exposure, are likely to contribute to preventing pandemic influenza infection.

Chapter 5. Modelling community-control strategies to protect hospital resources during a pandemic influenza in Ottawa, Canada

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Publication Status Information

An adapted version of this manuscript was published on June 14, 2017 in *PLoS ONE* (Saunders-Hastings, P.; Quinn Hayes, B.; Smith?, R.; Krewski, D. Modelling community-control strategies to protect hospital resources during an influenza pandemic in Ottawa, Canada. *PloS ONE* **2017**, *12*, e0179315).

Abstract

A novel influenza virus has emerged to produce a global pandemic four times in the past one hundred years, resulting in millions of infections, hospitalizations and deaths. There is substantial uncertainty about when, where and how the next influenza pandemic will occur.

We developed a novel mathematical model to chart the evolution of an influenza pandemic. We estimate the likely burden of future influenza pandemics through health and economic endpoints. An important component of this is the adequacy of existing hospital-resource capacity. Using a simulated population reflective of Ottawa, Canada, we model the potential impact of a future influenza pandemic under different combinations of pharmaceutical and non-pharmaceutical interventions.

There was substantial variation in projected pandemic impact and outcomes across intervention scenarios. In a population of 1.2 million, the illness attack rate ranged from 8.4% (all interventions) to 54.5% (no interventions); peak acute care hospital capacity ranged from 0.2% (all interventions) to 13.8% (no interventions); peak ICU capacity ranged from 1.1% (all interventions) to 90.2% (no interventions); and mortality ranged from 11 (all interventions) to 363 deaths (no interventions). Associated estimates of economic burden ranged from CAD $115 million to over $2 billion when extended mass school closure was implemented.

Children accounted for a disproportionate number of pandemic infections, particularly in household settings. Pharmaceutical interventions effectively reduced peak and total pandemic burden without affecting timing, while non-pharmaceutical measures delayed and attenuated pandemic wave progression. The timely implementation of a layered intervention bundle appeared likely to protect hospital resource adequacy in Ottawa. The adaptable nature of this model provides

value in informing pandemic preparedness policy planning in situations of uncertainty, as scenarios can be updated in real time as more data become available.

5.1 Introduction

Influenza is an infectious disease that transmits between humans via inhalation of viral particles expelled by infected individuals during coughing or sneezing and carried in aerosol, respiratory droplets and fomites [1]. Though individuals experience infection differently, it often involves a combination of respiratory and systemic symptoms [292]. While generally self-limiting, influenza-related hospitalization and death is commonly associated with lower respiratory tract and neurological complications; in fact, influenza is the most deadly vaccine-preventable disease in North America [13]. As an RNA virus with a high mutation rate, humans are unable to maintain adequate long term immunity to influenza infection, leading to annual outbreaks of seasonal influenza [78]. In the United States, seasonal influenza accounts for between 3,000 and 49,000 deaths each year [293]. In recent years, the average number of influenza-associated hospitalizations and deaths in Canada is estimated to be approximately 12,000 and 3,500, respectively [294, 295].

These figures do not, however, reflect the more catastrophic potential of a pandemic influenza outbreak. Triggered by an antigenic shift — a reassortment of viral segments creating a new influenza strain — that creates a novel influenza virus to which humans possess little to no immunity, an influenza pandemic has the potential to transmit and spread rapidly across the globe [61]. This has happened on four occasions over the past one hundred years, leading to tens of millions of infections, hospitalizations and deaths [73, 77, 112, 149, 249]. While most of this burden was driven by the 1918 Spanish flu pandemic, even the most recent 2009 Swine flu pandemic is estimated to have resulted in as many as 575,400 deaths globally [148, 149], even

though it is considered to be a mild strain compared to past pandemics [296]. Were a pandemic strain of a pathogenicity comparable to that of the 1918 outbreak to emerge today, projections suggest it could result in 21–31 million deaths worldwide [103].

Influenza pandemics emerge at uneven and unpredictable intervals [1, 63, 64]. The current global landscape, however, is one that is supportive of pandemic emergence. Unprecedented levels of human–animal interaction, viral diversity and extensive international travel collectively increase the threat of viral reassortment, crossover to humans and global spread [172-177]. The threat of a global pandemic and its potential consequences present major challenges for public health and emergency preparedness policy efforts.

Given that the epidemiological features of a pandemic cannot be known until after its emergence, there is significant uncertainty regarding best practices in resource- and control-strategy planning [297, 298]. This is problematic, as pandemic planning is crucial to limiting illness, death and essential-service disruption, thereby mitigating the health, social and economic burden of pandemics. Mathematical models of disease transmission, accounting for the uncertainty and randomness inherent in pandemic emergence and spread, have become valuable tools in pandemic planning and management [299, 300]. Given that empirical field studies in pandemic situations are generally infeasible or unethical, they are of vital importance. Unfortunately, important gaps persist in the field of pandemic modelling, particularly with respect to accessibility, assessment of resource capacity and economic evaluation [32]. The model presented herein seeks to address these gaps.

This paper presents initial findings generated by InFluNet, a new, discrete-time simulation model that combines ordinary differential equations (ODEs) with stochastic approaches. Designed to capture the range of factors influencing pandemic transmission — while remaining accessible

to public-health practitioners lacking formal modelling training — InFluNet combines epidemiological and demographic data to allow prediction of the health and economic burdens associated with future pandemics. Emphasizing the adequacy of hospital-resource capacity, the model allows evaluation of the potential for community intervention strategies to contain pandemic spread and ensure hospital resource adequacy. Results should inform policy-planning for interventions targeting specific stages of the disease life-cycle, and specific settings (household, school, workplace, and community), supporting more efficient and cost-effective control strategies.

5.2 Methods

InFluNet is a population-level, discrete-time simulation model that builds on previous deterministic and stochastic influenza models [157, 232, 301-306]. The model combines differential equations estimating the rate of transmission contacts and disease progression with stochastic methods of estimating social mixing behaviour and transmission probability. This dual approach effectively describes the average behaviour of larger urban populations, while incorporating the uncertainty associated with transmissibility and pathogenicity of a new influenza strain. This section describes the InFluNet simulation model, as well as the data inputs and outputs associated with the model.

5.2.1 Social contact network

The model is structured to represent three independent transmission time–location–steps over the course of the day: household, school/work and community. Although it is common for models to combine location-specific estimates of transmission dynamics [307-309], this risks obscuring the setting within which the outbreak is being propelled forward, as well as analyses of how

specific interventions will influence outbreak development and severity. InFluNet models a transmission cycle composed of the average time spent in the household (12 hours), at school or work (8 hours) and in the community (4 hours). These baseline time-location divisions are derived from an empirical study of a representative North American municipality [310] and Statistics Canada [311] national estimates of average time spent per day in various locations. They are subject to change under certain interventions, including voluntary isolation, quarantine and school closure.

The simulation model was developed to predict the behaviour of a pandemic outbreak in a developed, urban setting. Demographic parameters — such as age-stratified population, average earnings and local unemployment rates — mirror those of the Ottawa–Gatineau Census metropolitan area (CMA) from the 2011 census [312]. The household contact group size ranged from one to six and was determined stochastically, reflecting the variation that dominates such small-scale transmission processes. School and work group sizes were estimated to constitute thirty and twenty people, respectively, choices that were informed by similar modelling approaches [7, 157]. The community group size was fixed at 100 people, reflecting the number of random contacts an individual is likely to have in their home and work neighbourhoods [232, 302].

InFluNet uses ODEs to estimate age-specific contact rates between various age groups. Five age groups are identified: infant (0–4), child (5–18), young adult (19–29), adult (30–64) and senior (65+). This reflects age groupings of past studies [301, 305, 306, 313], based on previously observed patterns of pandemic influenza transmission and outcomes. Because the expected duration of a pandemic outbreak is short, we assumed a closed population, with no birth or death rate included, as these are unlikely to meaningfully affect results [314]. While past modelling

studies have incorporated assumptions of heterogeneous mixing, few base these assumptions on empirical data, as is the case with InFluNet [314].

Individuals will interact with others at different rates, both within and outside their age groups. The age-specific numbers of daily contacts in **Table 11** have been estimated from past empirical studies in the United States [310, 314]. These studies reported the total number of contacts within and between age groups. We calculate per-capita contact rates by dividing the total contacts by the total population of each age group, calibrating estimates to reflect the empirical data of overall contacts to within 0.5 contacts per day. Between-group contact rates are asymmetrical as a result of differences in the population size of each age-group. For example, every infant is likely to interact with an adult on a daily basis, but not every adult is likely to have daily interaction with an infant.

Table 11. Average number of daily contacts by age group per person per day [310].

	Infant	**Child**	**Young adult**	**Adult**	**Senior**	**Total**
Infant	0.9511	3.5509	1.6740	4.8698	0.6594	11.7052
Child	1.2237	7.3670	1.6153	3.5244	0.6363	14.3668
Young adult	0.6096	1.7070	6.7059	12.1926	1.3209	22.5359
Adult	0.6195	1.3010	4.2591	12.6380	1.4094	20.2271
Senior	0.3498	0.9794	1.9239	5.8766	2.1827	11.3124

These daily totals are further divided into location-specific and age-stratified contact tables, through estimation of how the location-specific frequency and intimacy of interaction will vary between age groups (**Table 12**–**Table 14**). These estimates are used to generate hourly contact rates, which determine the number of effective contacts that will in turn influence risk of disease exposure and contraction [315]. Contact rates are subject to change under various interventions, including community-contact reduction and personal protective measures.

Table 12. Number of contacts by age group per day (household).

	Infant	Child	Young adult	Adult	Senior	Total
Infant	0.6658	2.4856	1.1718	3.4088	0.5276	8.2596
Child	0.8566	1.8417	1.1307	2.4671	0.5091	6.8053
Young adult	0.4267	1.1949	1.3412	1.8289	0.5283	5.3200
Adult	0.4337	0.9107	0.6389	3.7914	0.7047	6.4793
Senior	0.2798	0.7835	0.7695	2.9383	1.3096	6.0808

Table 13. Number of contacts by age group per day (school and workplace)

	Infant	Child	Young adult	Adult	Senior	Total
Infant	0.1427	0.5326	0.2511	0.7305	0.0659	1.7228
Child	0.1836	4.4202	0.2423	0.5287	0.0636	5.4383
Young adult	0.0914	0.2560	3.3530	7.9252	0.3302	11.9558
Adult	0.0929	0.1951	2.7684	5.0552	0.3523	8.4641
Senior	0.0350	0.0979	0.4810	1.4691	0.3274	2.4104

Table 14. Number of contacts by age group per day (community).

	Infant	Child	Young adult	Adult	Senior	Total
Infant	0.1427	0.5326	0.2511	0.7305	0.0659	1.7228
Child	0.1836	1.1050	0.2423	0.5287	0.0636	2.1232
Young adult	0.0914	0.2560	2.0118	2.4385	0.4623	5.2601
Adult	0.0929	0.1951	0.8518	3.7914	0.3523	5.2837
Senior	0.0350	0.0979	0.6734	1.4691	0.5457	2.8211

More sophisticated interactions such as concurrent relationships and social biases in mixing were excluded, as the main focus of the model is to assess the cumulative and peak burden of an influenza pandemic, with particular emphasis on the adequacy of hospital surge capacity during times of peak patient demand; the above assumptions are more important in the early stages of an outbreak and have been rarely incorporated in past disease-transmission models [314]. InFluNet should adequately reflect the heterogeneity of social mixing to estimate trends in disease-transmission patterns.

5.2.2 Transmissibility

Realistic modelling of the rate of disease transmission is critical to obtaining useful results and insights. A problematic assumption in infectious disease modelling is to chart disease transmission as driven by the basic reproduction number (R_0) or the effective contact rate (β). R_0 represents the number of secondary infections that an average index case would produce in a completely susceptible population. Typically, if $R_0<1$, an outbreak does not occur, whereas if $R_0>1$, an outbreak will occur. In simple infectious disease models with no background death rate, the equation for the reproduction number is as follows:

$$R_0 = \gamma\beta T,$$

where γ is the number of "effective" contacts per unit time, β is the per-contact probability of infection transmission and T is the average duration of the infectious period.

This method of modelling disease transmission introduces error in several ways [316]. First, as soon as the first infection occurs, the population is not entirely susceptible, so R_0 no longer applies, and a related variable, the effective reproduction number (R_e) becomes relevant. The same is true once interventions are implemented. Second, an estimated R_0 has been found to vary depending on the method of calculation [317], and the same model can give notably different estimates depending on the method of calculation used [318]. One study, for example, used four methods to estimate the R_0 of the 1918 Spanish flu pandemic: estimates ranged from 2.1 to 2.98 (95% CI 0.5–3.5) [319].

The effective contact rate, a combination of the number of contacts and the per-contact transmission probability, is also problematic for model analysis. It is a simplification of transmission dynamics that incorporates numerous factors, and grouping them into a single rate

precludes analysis of how these factors, and interventions acting upon them, can affect the timing and scale of an outbreak. Instead, InFluNet uses a "next-generation operator" approach described previously in a model of smallpox [314] and reflective of a heterogeneous population [320]. In this approach, transmissibility can be described as follows:

$$\beta = \beta_C + \beta_A + \beta_{AV}$$

where

$$\beta_C = \gamma \cdot \alpha_C \cdot \eta_C \cdot (1 - e^{-\sigma \cdot \tau}) \cdot \frac{I_C}{N},$$

$$\beta_A = \gamma \cdot \alpha_A \cdot \eta_A \cdot (1 - e^{-\sigma \cdot \tau}) \cdot \frac{I_A}{N} \quad \text{and}$$

$$\beta_{AV} = \gamma \cdot \alpha_{AV} \cdot \eta_{AV} \cdot (1 - e^{-\sigma \cdot \tau}) \cdot \frac{I_{AV}}{N}.$$

As above, the rate of disease transmission from symptomatic (β_C), asymptomatic (β_A) and symptomatic treated (β_{AV}) depends on the six parameters [310, 314] described in **Table 15**.

Table 15. Transmissibility function parameters.

Symbol	Definition	Sample value	References	Range
γ	Number of effective contacts	As per contact tables	[314]	$1e^{-2–10}$ (contacts/day)
α	Susceptibility	1.0 for infants, children, and young adults; 0.95 for adults; 0.65 for seniors	[321]	0–1
η	Infectivity	1.0	Assumed	0–1
σ	Duration of contacts	As per contact tables	[314]	1/2–1/6 (days/contact)
τ	Mean number of transmission events per unit time	0.275	[103, 298, 322, 323]	0.17–0.42
$\frac{I_C}{N}, \frac{I_A}{N}$	Proportion of population that symptomatically and asymptomatically infected	Model-generated	NA	0–10%

The number of contacts per unit time (γ) among individuals within and across different age groups is defined by the population contact model, reflecting preferential mixing between certain age groups, and is influenced by mixing group size and location. The probability of transmission given a contact is the result of the susceptibility of the susceptible group (α), infectivity of the infected group (η) and duration of contact between the two (σ). The baseline assumption is that 5% of adults and 35% of seniors will not be susceptible to pandemic infection due to prior exposure, a rate of pre-existing immunity observed in the United States in a study of the 2009 H1N1 pandemic [321]. In the absence of reliable data, we assume that all infected individuals will be fully infectious; both parameters can change according to vaccination and treatment status. An important value of pharmaceutical interventions is that only they can alter the susceptibility and infectivity profile of a population, whereas non-pharmaceutical interventions act instead on the social–contact patterns of a population [324]. The mean number of transmission events per unit time (τ) is a parameter reflecting the intrinsic transmissibility of the disease in question; in the case of InFluNet, this has been assumed to range between 0. 17 and 0.42, which would mirror an R_0 value between 1.5 and 2.5, reflecting historical estimates of pandemic influenza [103, 298, 322, 323]. This approach incorporates sophisticated techniques to model realistic disease-transmission assumptions and allows assessment of how interventions are likely to affect pandemic transmission and burden. In this study, we modelled a transmissibility parameter of 0.275, equivalent to the transmissibility reported from the 1957 pandemic [33]. This pandemic was chosen as it demonstrated a moderate transmissibility, relative to the more severe 1918 pandemic and milder 1968 and 2009 pandemics. Lastly, the proportion of infected individuals (I_C/N, I_A/N) accounts for varying levels of infection within a community. With parameters varying according to the evolution and dissipation of a pandemic wave — in addition to the implementation of interventions

— this approach allows the sophisticated calculation of a β which is not constant but which changes over the course of a pandemic.

5.2.3 Model structure

InFluNet combines demographic, hospital and intervention data, allowing simulation of a pandemic influenza outbreak under millions of possible scenarios. A simulation is run five times, with the output value being averaged across simulations and reported with 95% confidence intervals calculated via the standard deviation approach. The loop structure was determined by calculating the variance between model simulations, and running continuous simulations until the average value had a standard error below 5%.

The InFluNet model follows the general structure of an age-dependent SEIR (susceptible–exposed–infected–recovered) model, a structure that has predicted outbreaks with relative accuracy in the past [325-328]. The transmission model flow diagram is illustrated in **Figure 6**. Susceptible individuals (S) can be vaccinated, moving either to an immune, "vaccinated" group (V) or remaining in a susceptible, "failed vaccination" (S_V) group; the proportion of individuals moving into these will depend on the estimated vaccine coverage (N_C) and vaccine efficacy (V_E). A failed vaccination group was included to reflect the fact that those who get vaccinated but still become infected may experience reduced infectiousness or disease severity than infected individuals who did not receive vaccination [313, 329]. Susceptible individuals can also receive antiviral prophylaxis (AVP), moving to a less susceptible group that, if still infected, will experience a less severe infection. Infection can occur among "susceptible", "failed vaccination" and "antiviral prophylaxis" individuals, though the severity of influenza infection, both with respect to infectivity and likelihood of complications, may be reduced among the S_V and AVP groups.

The simulation begins with 50 infected cases being seeded in the population across the five age groups at a rate proportional to the population size of each group. When subsequent infections occur, infected individuals move immediately to the latent, or "exposed" (E) group, where they remain for the duration of the influenza latent period €, which is distributed between one and three days (30% one-day; 50% two-day; 20% three-day latent periods), reflecting the assumptions of past models [157, 330] and empirical Canadian data from the 2009 H1N1 pandemic (pH1N1) [331]. Following completion of the latent period, infected individuals pass into an infectious period until they recover (r) after four to seven days (40% four-day; 30% five-day; 15% six-day; and 15% seven-day infectious period), again reflecting the assumptions of past models [157, 305, 313] and empirical Canadian data from the 2009 H1N1 pandemic [332]. Of those who have been infected, two thirds experience symptomatic, "clinical" infection (I_C), while one third develop asymptomatic infections (I_A) and are half as infectious as symptomatic individuals [232, 299, 302, 333, 334]. It should be noted that, in a study of the infectious period of pH1N1 [332], 8% of the infected study subjects were still shedding replicating virus after eight days, so our estimates may underestimate the infectious period for a small proportion of individuals. However, it was decided that this broad distribution — alongside longer durations of infection for complicated, hospitalized cases — was likely to capture what could reasonably be expected during a future pandemic.

Of those who are symptomatic, a proportion can seek treatment with antivirals, reducing their infectivity and hospitalization rate by a certain percentage and shortening their duration of infection by one day [232, 324, 335, 336]. The movement of populations through the healthcare system is derived from approximations of the empirical data from the North American experience of the 2009 pH1N1. A small proportion (0.4–4.0%) [337-339] will require hospitalization in an acute bed for an average of four days, as reported by Canadian Institute of Health Information

[152] during pH1N1. Age-specific hospitalization rates are modeled with children as the baseline group and other age groups scaled to the childhood hospitalization rate according to predefined ratios. Infants are expected to have a five-fold higher hospitalization rate, young adults twice as high, adults four times as high, and seniors ten times as high. While it is impossible to know the age-specific hospital burden prior to pandemic emergence, these ratios reflect the empirical hospitalization data gathered in the United States during the 2009 pandemic [340].

The mortality rate for those in an acute bed is 3.125% [341, 342]. Of those hospitalized, 16% will also require ICU care and mechanical ventilation, approximating empirical data from the Canadian experience of pandemic influenza [339]. It also assumes that all those who are admitted to the ICU have a sufficiently critical illness to also warrant ventilation; in the study of the 2009 pandemic in Canada, 93.2% of those who received ICU care also received ventilation [339]. Of those requiring ICU and ventilator care, there is an associated mortality rate of 50% [342]. As with age-specific hospitalization rates, we model age-specific mortality rates given hospitalization, approximating the assumptions of past studies modelling Canadian contexts: using infants as the baseline group, mortality in children is twice as likely; mortality in young adults and adults is ten times as likely; and mortality in seniors is twenty times as likely [161]. We assume that 100% of deaths in those under 65 years old occur in hospital, while 75% of deaths among seniors occur in hospital, with the remaining 25% in other settings such as retirement and long-term care facilities [343, 344]. The average duration of hospital stay for those requiring ICU care and ventilator support is estimated to be ten days, approximating empirical observations from Canadian experience of pH1N1 [339]. No interventions are modelled that affect the rate of ICU admission, ventilator support, or death given hospitalization. Rather, we model the impact of community interventions in reducing initial infection and clinical disease severity. In addition, natural birth

and death rates were excluded from the transmission model, as incorporation of natural birth and death rates had no effect on model predictions and considerations regarding long-term equilibrium were irrelevant given the short-term nature of the planning horizon.

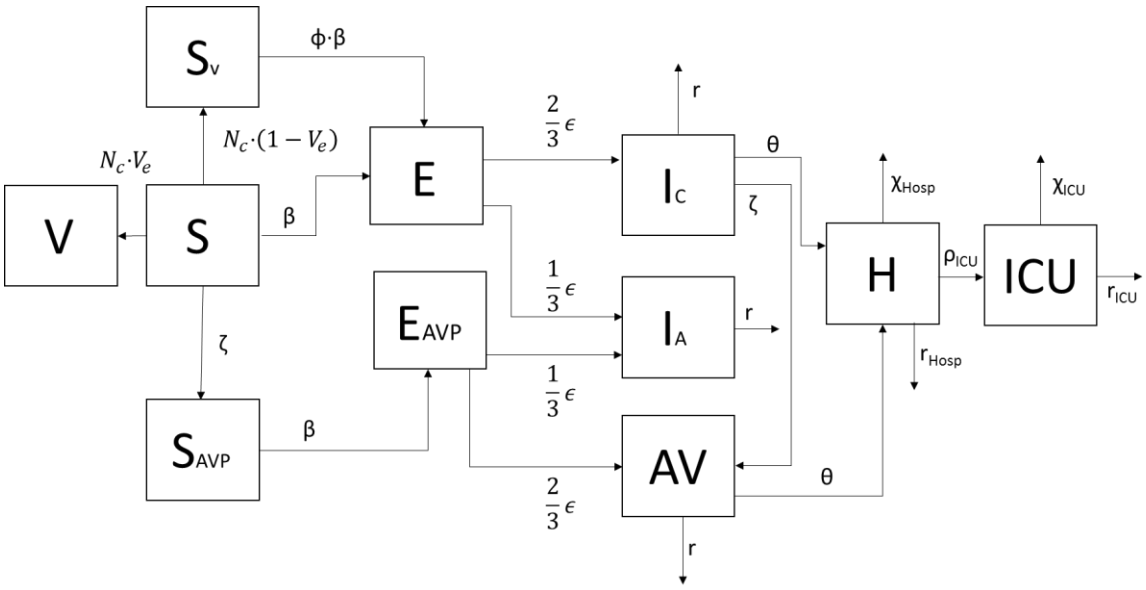

Figure 6. Transmission model flow diagram.

From **Figure 6**, we arrive at the system of ODEs presented on the following page. Descriptions, ranges, and sample values for model parameters are provided in **Table 16**. Please note that the six parameters used to calculate β — which will vary over the course of a pandemic — are discussed in **Section 5.2.2.** Intervention parameters are discussed in **Section 5.2.5**.

$\frac{dS}{dt} = -(N_C + \zeta + \beta) \cdot S$	Susceptible
$\frac{dE}{dt} = \beta \cdot (S + \phi \cdot S_V) - E \cdot \epsilon$	Latent Infected
$\frac{dS_V}{dt} = (1 - V_e) \cdot N_C \cdot S - \phi \cdot S_V \cdot \beta$	Susceptible with failed vaccination
$\frac{dV}{dt} = V_e \cdot N_C \cdot S$	Vaccinated
$\frac{dS_{AVP}}{dt} = \zeta \cdot S - \beta \cdot S_{AVP}$	Antiviral prophylaxis
$\frac{dE_{AVP}}{dt} = \beta \cdot S_{AVP} - E_{AVP} \cdot \epsilon$	Latent infected treated with prophylaxis
$\frac{dI_C}{dt} = \frac{2}{3} \cdot E \cdot \epsilon - I_C(\theta + r + \zeta)$	Infected Symptomatic
$\frac{dI_A}{dt} = \frac{1}{3} \cdot (E + E_{AVP}) \cdot \epsilon - I_A \cdot r$	Infected Asymptomatic
$\frac{dAV}{dt} = I_C \cdot \zeta + \frac{2}{3} \cdot E_{AVP} \cdot \epsilon - AV(\theta + r)$	Treated with Antivirals
$\frac{dH}{dt} = (I_C + AV) \cdot \theta - \left(r_{Hosp} + \chi_{Hosp} + \rho_{ICU}\right) \cdot H$	Hospitalized
$\frac{dICU}{dt} = \rho_{ICU} \cdot H - (r_{ICU} + \chi_{ICU}) \cdot ICU$	Intensive Care Unit

Table 16. Model parameters

Symbol	Definition	Sample value	References	Range
N_C	Rate of vaccination	$8.5e^{-4}$ (1/days)	[161]	$8.5e^{-4}$ (1/days)
V_e	Vaccine efficiency	65%	[202, 204, 205, 313, 329]	40–90%
φ	Reduction in infectivity due to vaccination	35%	[313, 329]	20–50%
ε	Rate of disease progression	1/1.6 days	[157, 330, 331]	1/3–1/7 (1/days)
θ	Rate of hospitalization	Age-dependent	[152, 337-340]	$1e^{-3}$–$1e^{-1}$ (1/days)
r	Rate of recovery	r = 1/4.8 Hosp = 1/3.35 ICU = 1/10.25	[157, 305, 313, 332]	1/4–1/7 (1/days)
ζ	Rate of treatment/prophylaxis with antivirals	$1e^{-3}$	Assumed	$1e^{-3}$ (1/days)
ω	Reduction in recovery time	1 day	[331, 334, 345]	0–2 days
χ	Death rate in hospital setting	Hosp = $1e^{-3}$ ICU = 0.1	[341, 342]	$1e^{-3}$–$1e^{-1}$ (1/days)
ρ	Progression through hospital	ICU = 0.05	[339]	0.05–0.5

5.2.4 Resources

Hospital resources are aggregated and estimated at the level of the CMA. Data regarding hospital bed capacity — categorized as “acute”, “ICU” and “other” — were obtained from the most recent data from the Canadian Institute for Health Information, reported on January 28, 2016 [346]. These data report on hospital bed capacity by function for all hospitals in Canada, except those in Quebec. Investigators first calculated the number of acute beds in each CMA, followed by the number of ICU beds. The number of “other” beds — including long-term care, psychiatric, and rehabilitative beds — was also calculated to inform a discussion of the potential for bed repurposing in emergency situations, though this type of service disruption would be better

avoided through community intervention. As Quebec does not contribute to CIHI information collection, hospital data for this province was sought separately. Data were publicly available through the Ministry of Health and Social Services website, last updated on October 4, 2016 [347], and hospitals were logged into a database individually. Some records contained no in-patient beds and were instead designed for delivery of other social services. These were excluded from the analysis, as it was decided that their inclusion would overestimate in-patient hospital capacity during a pandemic event. Because Quebec hospitals did not report their number of ICU beds, we calculated the proportion of hospital beds outside of Quebec that were designated for the ICU (6.2%) and extrapolated this to Quebec hospitals.

No provincial or national data were available on ventilator capacity. Instead, we assumed that each available ICU bed would have a ventilator available; this assumption is supported by similar per-capita availability of ventilators [348] and ICU beds [349]. Combining these hospital-resource data with the Census demographic data, we generated individual profiles for each Canadian CMA; the Ottawa–Gatineau profile included in **Appendix 14** was used for the following analysis.

5.2.5 Intervention approaches

InFluNet allows the evaluation of eight different interventions (vaccination, antiviral treatment, antiviral prophylaxis, school closure, community-contact reduction, personal protective measures, voluntary isolation and quarantine), with coverage, intensity and effectiveness measures determined by user inputs. Interventions can be categorized as either pharmaceutical or non-pharmaceutical, with every iteration presented in a single matrix. Pharmaceutical interventions can affect individual susceptibility, infectivity and hospitalization, while non-pharmaceutical interventions can change where and how individuals are interacting. This method allows

consideration of 192 different intervention combinations and millions of unique strategy profiles, providing sophisticated insights into optimal control strategies. In this study, we provide a "Best Guess" (BG), "Worst Case" (WC), and "Best Case" (BC) for each parameter, to generate a range of estimated intervention impacts. Each intervention is discussed separately below.

5.2.5.1 Vaccination

Vaccination interventions (V) vary according to the time to vaccine delivery, population coverage and effectiveness with regard to individual susceptibility, infectivity and disease severity (reduction in hospitalization rate). The impact of vaccination occurs two weeks after receipt of the vaccine. The maximum weekly vaccination rate is set as 7.5% of the population [161]. Total coverage is estimated to be 35% (range 25–45%). The BG value approximates the average Canadian influenza vaccine coverage between 2001 and 2012 (34.2%) [350]; the WC value represents the lower bound of the 95% confidence interval from the lowest vaccine coverage reported between 2001 and 2012 (2010: 26.5%) [350]; the BC value is the influenza vaccine coverage reported in Ontario following the first wave of the 2009 H1N1 pandemic [161].

In these simulations, we are modelling the protective effect of a strongly matched pandemic vaccine. We are not modelling the potential impact of seasonal influenza vaccination, as two independent systematic reviews found no evidence of a significant effect of seasonal flu vaccination in preventing a pandemic flu outbreak [205, 210]; in fact, there has been some suggestion that seasonal vaccination may actually increase pandemic infection, as it precludes seasonal infection and temporary immunity [351-354]. Instead, we model the impact of pandemic vaccination under situations where it is available in time to be effective in controlling the outbreak. Vaccine efficacy for susceptibility (VE_S) is estimated to be 65% (range 40–90%), reflecting the

findings of four independent systematic reviews [202, 204, 205, 355]; vaccine efficacy for infectiousness (VE_I) is assumed to be 35% (range 20–50%), reflecting past modelling assumptions in the absence of reliable empirical data [313, 329]; reduction in hospitalization rate is estimated to be 60% (range 25–90%), as reported in a systematic review of seasonal vaccine impact on seasonal influenza hospitalization, which was viewed as the most reliable estimate available [356]. These changes are incorporated by scaling the susceptibility (α), infectivity (η) and hospitalization rate (θ) of those vaccinated by the estimated impact. Taken together, these three parameters allow us to include the assumption that vaccinated individuals will be less susceptible to infection and experience less severe and infectious illness if infected.

5.2.5.2 Antiviral treatment

Antiviral treatment (AVT) scenarios vary by the coverage and effectiveness in reducing infectivity and disease severity (with respect to hospitalization). Antiviral treatment also reduces the duration of the infectious period by one day [331, 334, 345]. The rate of antiviral distribution was set to be sufficiently high so as to not impede receipt of antivirals by infected individuals, reflecting the assumption that easy access to antivirals through local pharmacies would prevent demand from exceeding distribution capacity. It is also possible to model the impact of antivirals on a resistant viral strain, which is assumed to reduce drug effectiveness by 50% [232, 324, 335, 336]. In our simulations, we assume a non-resistant pandemic strain, with a reduction in infectivity (η) of 75% (range 57–82%), as reported in past systematic reviews and modelling studies [232, 324, 335, 336, 357]. The reduction in the hospitalization rate (θ) is 10% (0–40%), as reported in a systematic review [231].

5.2.5.3 Antiviral prophylaxis

Antiviral prophylaxis (AVP) refers to the preventive — rather than therapeutic — use of antivirals among those who are at high risk of viral exposure or severe disease, due to their relationship or proximity to an infectious case or health status, respectively. As InFluNet does not model preferential care for individuals at high risk of severe infection, we assume that prophylaxis — if implemented — would proceed in a targeted manner, with the distribution of drugs among household, school and work contacts, but not throughout the broader community.

We assume that individuals who receive prophylaxis will have a reduced susceptibility to infection (α) of 30% (range 10–50%), approximating conclusions from a systematic review [204]. Of those who are infected despite prophylaxis, we assume that they will have a reduced infectivity and hospitalization rate equal to that among those who received antiviral treatment.

5.2.5.4 School closure

School closure (SC) is considered as an emergency measure that will only take effect when the proportion of the population that is currently symptomatically infected surpasses a predefined threshold. We use the threshold of 0.2%, as informed by a previous study modelling school closure [341]. When SC takes effect, all children (5–18 years old) are removed from the school setting, and their contact rate is set to zero for that eight-hour period [358, 359]; we assumed no increase in household- or community-contact rate [360]. A certain percentage of adults (30–64 years old) are also redistributed, as some parents will be forced to stay home with their children. We assume that 20% (range 8–33%) of adults would be forced to stay home as a result of school closure,

approximating empirical data from school closures in New York City as a result of the 2009 pandemic [156].

5.2.5.5 Community-contact reduction

For community-contact reduction (CCR), the contact rate (γ) in the community setting is scaled by a certain percentage across all age groups, reflecting social distancing in the community but not the household, school or work environment. We assume a reduction of 50% (range 25–75%), reflecting assumptions made in past modelling studies, as empirical data were unavailable [7, 232, 333, 334].

5.2.5.6 Personal protective measures

Personal protective measures (PPM) include hand hygiene and facemask use, which are modelled as changes in the duration of contacts between individuals (σ). Respiratory etiquette (covering mouth during cough or sneeze) was not included, as studies suggest that it is ineffective in preventing viral transmission [275, 361-363]. Each of these behaviours has an effectiveness measure informed by past research. Hand hygiene is estimated to be 26% (3–44%) effective [226, 261, 262, 264, 267] and mask use 60% (8–82%) effective [259, 260, 266, 269, 273]. The actual impact of these interventions will depend on the population adherence, which is set by the user. We assume adherence rates of 38% (20–55%) and 3% (1–5%) for hand hygiene and mask use, respectively [264, 265, 271, 291, 364, 365].

5.2.5.7 Voluntary isolation

Voluntary isolation (VI) defines a percentage of symptomatically infected individuals who will withdraw from school or work settings while ill. Isolated individuals have no contact in the school/work location, though their household and community contacts are assumed to be unchanged [366, 367]. Adherence to voluntary isolation recommendations is estimated to be 30% (range 10–50%), approximating empirical data from the 2009 pandemic [367].

5.2.5.8 Quarantine

We present quarantine (Q) as a voluntary withdrawal to the household for the entire duration of infection and view mandatory or hospital quarantine as infeasible in mass-infection scenarios such as pandemic influenza. Quarantined individuals have no contact in the school/work or community setting, though their household contact rate is assumed to be unchanged. In this study, when quarantine is being simulated, it is as a proportion of voluntarily isolated individuals that adhere to more stringent isolation recommendations. However, it can either be modelled in conjunction with voluntary isolation or on its own. The adherence is estimated from reports of the 2003 SARS outbreak in Ontario to be 15% (range 5–25%) [368].

Table 17 and **Table 18** summarize the parameter definitions and user input ranges for each intervention parameter. The tables also gives the parameter values we used in this modelling study, as well as the sources that informed these values. Where possible, empirical values from the 2009 pandemic were used; where these were unavailable, we used assumptions employed in past modelling studies.

Table 17. Pharmaceutical intervention parameters. Best-guess scenarios reflect pooled estimates as available. Worst- and best-case scenarios (in terms of disease transmission but not necessarily resource allocation) reflect 95% confidence intervals where available; otherwise, they reflect ranges of estimates reported.

Intervention	Parameter[τ]	Theoretical Range	Worst Case Scenario	Best Guess	Best Case Scenario	Citation
Pandemic vaccination	Time delay (weeks)	0–4	4	0	Pre-vaccination	[103, 232]
	Coverage (%)*	0–100	25	35	45	[161, 350]
	Effectiveness (susceptibility) (%) */**	0–100	40	65	90	[202, 204, 205, 313, 329]
	Effectiveness (infectivity) (%)**	0–100	20	35	50	[313, 329]
	Reduction in hospitalization rate (%)*	0–100	25	60	90	[356]
Antiviral treatment	Coverage (% infected that seek treatment)**	0–100	30	50	70	[369]
	Effectiveness (infectivity) (%)*	0–100	57	75	82	[232, 324, 335, 336, 357]
	Reduction in hospitalization rate (%)*	0–100	0	10	40	[231]
	Resistant strain	Yes/No	Yes	No	No	None
Antiviral prophylaxis	Coverage (% of households, workplaces, and schools receiving prophylaxis)**	0–100	10	35	60	[301]
	Effectiveness (susceptibility) (%)*	0–100	10	30	50	[231, 302]
	Effectiveness (infectivity) (%)*/**	0–100	57	75	82	[232, 324, 335, 336, 357]
	Reduction in hospitalization rate (%)*	0–100	0	10	40	[231]
	Resistant strain	Yes/No	Yes	No	No	None

[τ] * approximated from empirical studies; ** approximated from modelling studies; *** approximated from qualitative studies

Table 18. Non-pharmaceutical intervention parameters. Best-guess scenarios reflect pooled estimates as available. Worst- and best-case scenarios (in terms of disease transmission but not necessarily resource allocation) reflect 95% confidence intervals where available; otherwise they reflect ranges of estimates reported.

Intervention	Parameter[τ]	Theoretical Range	Worst Case Scenario	Best Guess	Best Case Scenario	Citation
School closure	Adults that will be redistributed (%)*	0–100	8	20	33	[156]
Community-contact reduction	Reduction in community-contact rate (%)**	0–100	25	50	75	[7, 232, 333, 334]
Hand hygiene	Effectiveness (%)*	0–100	3	26	44	[226, 261, 262, 264, 267]
	Adherence (%)*	0–100	20	38	55	[264, 271, 291, 364]
Mask use	Effectiveness (%)*	0–100	8	60	82	[259, 260, 266, 269, 273]
	Adherence (%)*	0–100	1	3	5	[265, 365]
Voluntary isolation	Adherence (%)**	0–100	10	30	50	[367, 370]
Quarantine (subtracted from VI adherence	Adherence (%)***	0–100	5	15	25	[368]

[τ] * approximated from empirical studies; ** approximated from modelling studies; *** approximated from qualitative studies

5.2.6 Outcomes

The model generates results relating to health and economic outcomes. Health outcomes summarize consequences in terms of the number of symptomatic cases, hospitalizations, ICU admissions, ventilator demand and deaths by age, location and as a percentage of existing capacity. These data are reported on a daily basis and summarized over the course of the entire outbreak.

Economic outcomes aggregate the influenza- and intervention-associated costs to provide a cost–benefit analysis of intervention strategies of interest. Economic estimates are generated by

scaling health and intervention endpoints (as generated by the model) by a per-case economic cost, as given in **Table 19**.

The economic cost associated with mortality was calculated by assigning a value of $50,000 for each life-year lost (LYL), calculated using the difference between the midpoint of each age group and the national life expectancy. A 1.5% per year discounting rate was used, reflecting current views in health economics [371]. The $50,000 valuation per quality-adjusted life-year gained or saved represents the commonly accepted threshold below which health interventions are considered to be cost-effective in Canada [372]. This valuation was chosen as a middle-ground between present earning value and the subjective valuation of life; recent government estimates of the latter have ranged between six and nine million dollars (USD) [373]. Subjective valuations are inconsistent, do not recognize the economic value of protecting health among younger individuals and may overestimate the value of life to the extent that it renders measured policy recommendations infeasible. A sole focus on present earning value, meanwhile, may underestimate the value of life — particularly among seniors — by focusing only on economic productivity and potential.

The number of lost school days is calculated by combining results from school-closure days, symptomatic cases and hospitalizations. If school closure is one of the interventions being modelled, the number of school-closure days is multiplied by the number of school-aged children. This is added to the number of children that are likely to miss school due to voluntary withdrawal or quarantine, represented mathematically as the product of the number of symptomatic cases, adherence to isolation recommendations and an estimated five-day withdrawal period (as described in **Section 2.3**). Lastly, each childhood hospitalization is estimated to result in an additional four lost school days, and each ICU admission an additional ten lost school days [152].

Each lost school day, whether due to school closure or childhood illness, is estimated to cost $91.85, as informed by past North American modelling studies which assume that lost school days would be made up during summer break [157, 374].

The number of lost adult work days is calculated as the sum of young adults, adults and seniors who will miss work due to illness, hospitalization or school closure. As with children, symptomatic young adults and adults that voluntary isolate or quarantine themselves are expected to miss five days of work, while those hospitalized are expected to miss an additional four, and those requiring ICU care an additional ten [152, 332]. Meanwhile, 10% of symptomatic seniors — reflecting the Canadian employment rate of those over 65 [375]— that voluntarily withdraw are expected to miss five days of work due to illness, four days if requiring hospitalization, and ten days if requiring ICU care. If school closure is being modelled, a certain percentage of adults will also be forced to stay home to care for their children. The economic cost of lost work days is calculated as the product of the number of lost work days and the average daily earnings of an employee (in the case of the Ottawa CMA, this is $192.55 [376]).

There are three intervention-specific resource requirements that are also incorporated into economic calculations. The number of vaccinations needed is calculated as the product of the total population and the vaccination coverage, reflecting the assumption that only one vaccine dose will be needed. An empirical systematic review previously reported no significant difference in immunity between individuals who received one or two vaccine doses [206]. Vaccines are assumed to cost $20/dose, reflecting calculations from the 2009 pandemic in Ontario [161]. The total number of antiviral courses required is the sum of individuals who receive antiviral treatment and prophylaxis; the cost of antivirals is estimated to be $25/course, as informed by past Canadian influenza studies [7, 161, 377]. The number of masks required is calculated as the product of the

total population and adherence to mask recommendations; we assume that each adhering individual will require five masks and estimate a cost of $4/mask from a survey of local prices.

Table 19. Economic cost ($CAD) for outcomes of interest.

Economic consequences		
Category	**Unit Cost**	**Citation**
Total hospital bed days	$1,042/day	[161, 377]
Total ICU + ventilator days	$2,084/day	[161]
Total deaths	0–4: $2,355,172 5–18: $2,207,744 19–29: $1,956,694 30–64: $1,374,086 65+: $424,296	[371, 372]
Total lost school days	$91.85/day	[157, 374]
Total lost work days	192.55/day	[376]
Total vaccinations	$20.00/vaccination	[161]
Total courses of antivirals	$25.00	[7, 161, 377]
Total masks	$4.00/mask	Estimated

5.2.7 Analysis

We present summary values for six key outcome measures —cases of illness, hospitalization, ICU admission, peak acute care demand as a percentage of capacity, peak ICU demand as a percentage of capacity and death — across all 192 simulations conducted. The effect of the worst-case and best-case scenarios are evaluated through sensitivity analysis. We also present the results of a complete analysis for seven key intervention bundles of interest. The scenarios and reasons

for their emphasis are indicated below. Taken together, this two-tiered analysis should provide the breadth and depth of analysis needed to inform future pandemic planning.

1. No intervention: establish a baseline prediction.
2. Vaccination and antiviral treatment: assess the impact of commonly implemented pharmaceutical interventions in the absence of any non-pharmaceutical measures.
3. Vaccination, antiviral treatment and antiviral prophylaxis: assess the impact of the full range of pharmaceutical interventions that could be employed.
4. Community-contact reduction, personal protective measures and voluntary isolation: assess the impact of minimally invasive non-pharmaceutical interventions in cases where pharmaceutical measures may be unavailable.
5. School closure, community-contact reduction, personal protective measures, voluntary isolation and quarantine: assess the impact of the full scope of non-pharmaceutical measures in cases where pharmaceutical measures may be unavailable.
6. Community-contact reduction, personal protective measures, voluntary isolation and antiviral treatment: assess the impact of minimally disruptive non-pharmaceutical measures and antiviral treatment in cases where vaccination may not yet be available.
7. All interventions: assess the impact of implementing the full range of available interventions.

5.2.8 Validation

The InFluNet model was validated using four approaches, as informed by a recent review of mathematical modelling validation protocols [32]: parameterization, sensitivity analysis, structural validation and predictive validation. Parameterization involves the selection of values from empirical data; this was done wherever possible, prioritizing Canadian contexts where data were

available. Multivariate sensitivity analyses were conducted to evaluate the impact of change in certain disease and intervention parameters, as described in Section 2.9. Structural validity refers to the extent to which the model is consistent with current theory and practices, reflecting the way in which the real-world system works: InFluNet is based in epidemic theory and builds on the work of previously published transmission [310, 314] and intervention [157, 161, 324, 378] modelling research. Lastly, predictive validation assesses the extent to which the model will produce accurate data: this is the most difficult element of mathematical modelling validation, particularly in the case of pandemic influenza, where there is such heterogeneity in the disease, population and intervention parameters, and the majority of disease transmission processes are unreported and invisible to health-surveillance agencies. In an effort to overcome this challenge, we assess the predictive validity of our model by comparing its predicted attack rate in a pandemic scenario with a transmissibility parameter representative of the 2009 H1N1 to the results of a previously published pandemic study that calibrated its inputs to the 2009 H1N1 pandemic. Taking Hamilton, Ontario, as a simulated study population, Andradottir *et al* [157] constructed a simulation model that predicted an illness attack rate of 36.8%; taking the Ottawa–Gatineau CMA as a study population under similar assumptions, InFluNet predicted an illness attack rate of 41.0% (95% CI: 40.9–41.2%), though it was noted that Andradottir *et al* assumed a higher rate of pre-existing immunity. Given this, the small differences were interpreted as supportive of the predictive validity of our model. In this way, we calibrated our transmissibility parameter estimates to the basic reproduction number of previous models [157] and to empirical Canadian pandemic H1N1 attack rates [297, 331]. This was essential to anchoring a representative transmissibility parameter, as it is not enough to assume that reproductive rates will be identical across differential equation models with different transmission assumptions.

5.2.9 Sensitivity analysis

Multivariate sensitivity analyses were conducted to evaluate how changes in disease and intervention characteristics might affect the evolution, progression and control of the pandemic. The effect of disease parameters was evaluated by conducting simulations under different transmissibility and pathogenicity assumptions. The effect of intervention parameters was evaluated by comparing BC and WC intervention scenarios to the BG scenario.

5.3 Results

The subsections below present results related to symptomatic influenza infection, hospitalization, ICU admission, hospital resource demand, mortality and economic burden. **Table 20** summarizes the basic findings of the seven key intervention scenarios of interest. Results from all 192 simulations are discussed in their respective subsections, with summary tables included in the supplementary material.

Table 20. Summary of health-outcome measures from simulations of seven key intervention scenarios.

Intervention*	Outcome			
	Symptomatic Cases	Hospitalizations	ICU	Deaths
None	677,546	2,472	580	363
V+AVT	622,681	815	192	118
V+AVT+AVP	600,394	765	180	109
CCR+PPM+VI	203,771	634	151	65
CCR+PPM+VI+AVT	200,537	560	133	58
SC+CCR+PPM+Q	189,015	550	132	56
SC+CCR+PPM+Q+ V+AVT+AVP	104,051	108	26	11

*V = vaccination; AVT = antiviral treatment; AVP = antiviral prophylaxis; CCR = community-contact reduction; PPM = personal protective measures; VI = voluntary isolation; Q = voluntary isolation and quarantine; SC = school closure

5.3.1 Symptomatic infection

Under assumptions reflective of an influenza pandemic of transmissibility similar to the 1957 H2N2 pandemic, the InFluNet model projected that, in the absence of any intervention, about 677,546 symptomatic influenza infections would occur in the Ottawa–Gatineau CMA. This amounts to an illness attack rate of 53.4%. No single intervention implemented in isolation successfully brought the attack rate under 30%. Of the eight interventions, vaccination, personal protective measures and combined voluntary isolation and quarantine procedures resulted in the greatest reductions, producing attack rates of 50.0%, 45.5% and 33.9%, respectively. Antiviral treatment, antiviral prophylaxis, school closure and community-contact reduction produced only small reductions in illness attack rate, whether implemented alone or in combination with other interventions.

The timely initiation of multiple pandemic control measures resulted in significant reductions in symptomatic case numbers. This was particularly true when vaccination was combined with personal protective measures and isolation of infected individuals. Even in the absence of any pharmaceutical intervention, adherence to rigorous non-pharmaceutical protocols — school closure, community-contact reduction, personal protective measures, voluntary isolation and quarantine — resulted in a reduction of the illness attack rate to 15.2%, by delaying peak pandemic transmission beyond the 100-day simulation interval. Modelling of all eight interventions implemented in conjunction reduced the illness attack rate to 8.4%. Results of all 192 simulations are included in **Appendix 15**.

With no intervention, the relative proportions of symptomatic infection approximately mirrored the age-stratified population distribution. **Table 21** presents cases of symptomatic

infection by age group, along with a calculation of the percentage of all cases represented by each age group.

Table 21. Predicted number of cases of symptomatic infection by intervention type, and percentage of total infections accounted for by each group.

Intervention	Age group					
	Infant	**Child**	**Young adult**	**Adult**	**Senior**	**Total**
None	39,628	111,066	103,976	344,858	78,018	677,546
	5.8%	16.4%	15.3%	50.9%	11.5%	100.0%
V+AVT	36508	101985	95567	317617	71004	622681
	5.9%	16.4%	15.3%	51.0%	11.4%	100.0%
V+AVT+AVP	35270	98279	92158	306757	67930	600394
	5.9%	16.4%	15.3%	51.1%	11.3%	100.0%
CCR+PPM+VI	17427	36467	24842	105413	19622	203771
	8.6%	17.9%	12.2%	51.7%	9.6%	100.0%
CCR+PPM+VI+AVT	17183	35893	24427	103747	19287	200537
	8.6%	17.9%	12.2%	51.7%	9.6%	100.0%
SC+CCR+PPM+Q	17998	53368	25040	72406	20204	189016
	9.5%	28.2%	13.2%	38.3%	10.7%	100.0%
SC+CCR+PPM+Q+V+AVT+AVP	10102	28481	13196	41842	10430	104051
	9.7%	27.4%	12.7%	40.2%	10.0%	100.0%

While pharmaceutical interventions did little to redistribute the age-specific burden of influenza infection, non-pharmaceutical interventions appear to shift the burden towards younger age groups. This may be because measures like school closure and community-contact reduction redistribute more infections to the household, where children tend to be more prone to infection than adults. **Table 22** presents the distribution of transmission events by location, along with a calculation of the percentage of all cases represented by each location. Results suggest that pharmaceutical measures have little impact on the role of different locations in influenza transmission, but that non-pharmaceutical measures — school closures in particular — redistribute infection events to the household and community.

Table 22. Transmission events by location, and percentage of total infections accounted for by each location.

Intervention	Location			
	Household	School/work	Community	Total
None	337,135	233,370	107,040	677,546
	49.8%	34.4%	15.8%	100.0%
V+AVT	309,759	214,515	98,407	622,681
	49.7%	34.5%	15.8%	100.0%
V+AVT+AVP	298,522	206,797	95,075	600,394
	49.7%	34.4%	15.8%	100.0%
CCR+PPM+VI	101,447	71,084	31,240	203,771
	49.8%	34.9%	15.3%	100.0%
CCR+PPM+VI+AVT	99,827	69,962	30,748	200,537
	49.8%	34.9%	15.3%	100.0%
SC+CCR+PPM+Q	105,416	42,435	41,165	189,016
	55.8%	22.5%	21.8%	100.0%
SC+CCR+PPM+Q+V+AVT+AVP	57,076	24,453	22,522	104,051
	54.9%	23.5%	21.6%	100.0%

Figure 7 presents the number of new infections by day over the first 100 days of a pandemic influenza outbreak. Of interest is that pharmaceutical interventions alone (orange and grey lines) appear to result in a contraction of the pandemic peak without affecting its shape; under cases of pharmaceutical intervention — as with no intervention — transmission begins to accelerate about a month after infected individuals were added to the simulation, and there is only a small delay in the pandemic peak. Conversely, aggressive non-pharmaceutical interventions, which implement multiple containment measures in parallel, can delay the pandemic beyond the assumed window for the pandemic wave. Personal protective measures and voluntary isolation seem to account for the majority of this effect, with only small changes resulting from the further addition of community-contact reduction, school closure, quarantine or pharmaceutical measures.

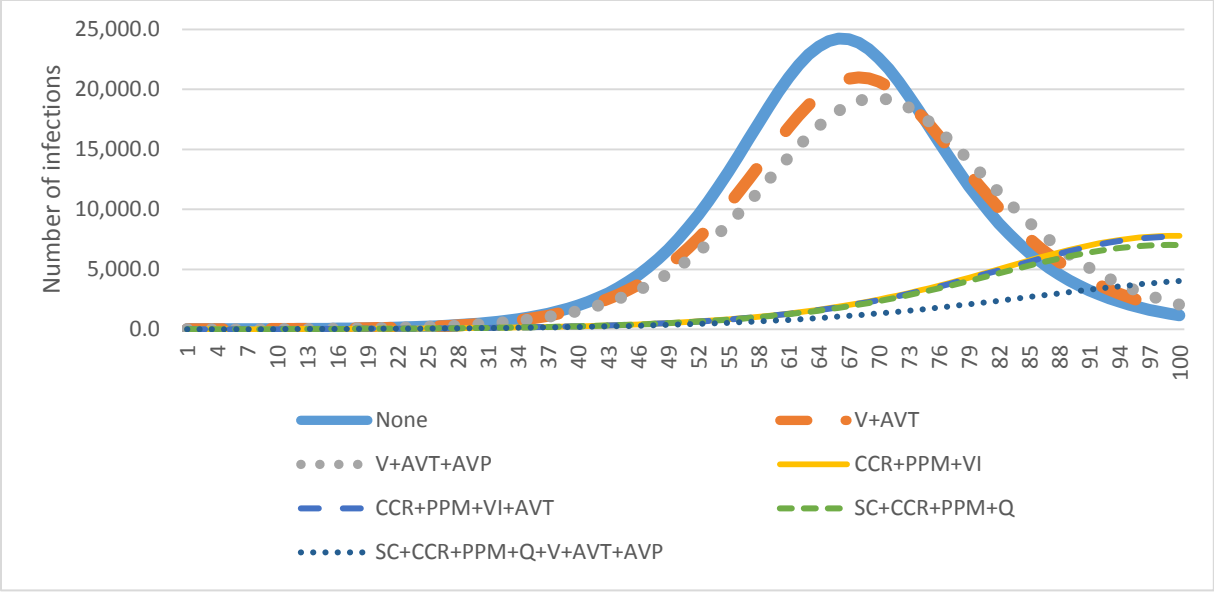

Figure 7. New infections by day under seven key intervention scenarios.

5.3.2 Hospitalization

A total of 2,472 pandemic-associated hospitalizations were projected under a "no intervention" scenario. As seen in **Table 20**, both pharmaceutical and non-pharmaceutical interventions were effective in reducing the number and rate of hospitalizations. As a result, there was substantial variation in the number of hospitalizations that could arise under different intervention scenarios, ranging from 2,472 (no intervention) to 108 (all eight interventions). Hospitalization projections for all 192 intervention scenarios are presented in **Appendix 16.**

Table 23 presents the age-stratified hospitalization totals across the seven intervention bundles of interest. Infants and seniors experienced a disproportionate number of hospitalizations given their population sizes, accounting for 7.4% and 28.8% of hospitalizations despite representing 5.7% and 12.6% of the total population, respectively. Children and adults had disproportionately low hospitalization rates, accounting for 4.2% and 7.8% of hospitalizations, despite representing 16.4% and 15.3% of the population, respectively. While pharmaceutical interventions did little to

redistribute the hospitalization burden — as they were not modelled to target particular age groups — non-pharmaceutical measures resulted in higher relative burdens among infants, children and adults, though total hospitalizations decreased across all age groups.

Table 23. Predicted number of hospitalizations, and percentage of total hospitalizations accounted for by each group.

Intervention	Age group					
	Infant	**Child**	**Young adult**	**Adult**	**Senior**	**Total**
None	184	104	193	1279	712	2472
	7.4%	4.2%	7.8%	51.7%	28.8%	100.0%
V+AVT	61	34	64	423	234	816
	7.5%	4.2%	7.8%	51.8%	28.7%	100.0%
V+AVT+AVP	58	32	60	398	218	766
	7.6%	4.2%	7.8%	52.0%	28.5%	100.0%
CCR+PPM+VI	71	30	40	339	154	634
	11.2%	4.7%	6.3%	53.5%	24.3%	100.0%
CCR+PPM+VI+AVT	63	26	35	300	136	560
	11.3%	4.7%	6.2%	53.6%	24.3%	100.0%
SC+CCR+PPM+Q	74	45	40	234	158	550
	13.4%	8.2%	7.2%	42.5%	28.7%	100.0%
SC+CCR+PPM+Q+V+AVT+AVP	15	8	7	48	30	108
	13.4%	7.5%	6.9%	44.4%	27.8%	100.0%

Figure 8 presents findings relating to the demand for acute-care hospital beds over the first 100 days of a pandemic influenza outbreak. Similar to the observed effects on symptomatic infections, pharmaceutical interventions resulted in a contraction of peak demand, while layered non-pharmaceutical interventions resulted in its delay and attenuation. Peak acute care demand ranged from 13.8% (no intervention) to 0.2% (all eight interventions). The peak hospitalization demand for all 192 intervention scenarios is summarized in **Appendix 17.**

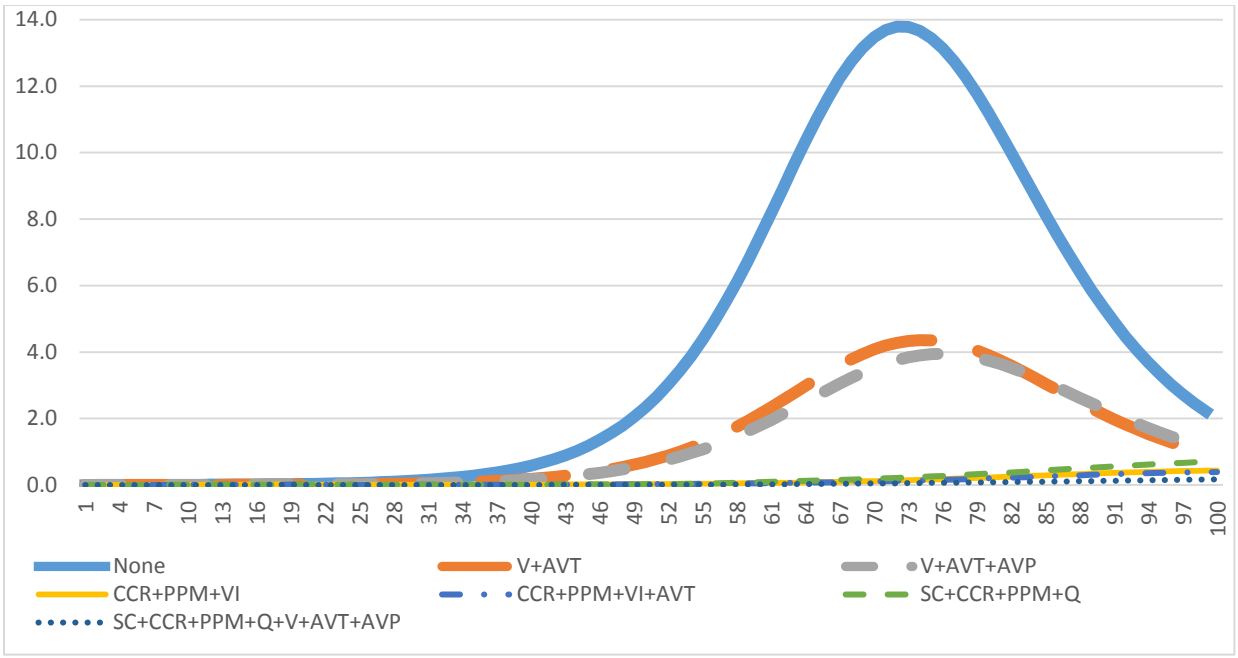

Figure 8. Daily acute-care hospital demand, charted as the percentage of all acute-care hospital beds in the Ottawa–Gatineau CMA, under seven key intervention scenarios.

5.3.3 Intensive care unit admission

In a pandemic where no intervention measures are implemented, InFluNet simulations projected approximately 580 ICU admissions over the first 100 days of the outbreak. As with acute-care hospitalization, there is a broad range of ICU demand scenarios, dependent on the intervention scenario being simulated; total ICU admissions ranged from 580 to 26 (all eight interventions). Many moderate intervention scenarios combining a pharmaceutical and non-pharmaceutical intervention resulted in a range of 100 to 400 ICU admissions. The ICU admission estimates for all 192 intervention scenarios are presented in **Appendix 18**.

Table 24 presents estimates of age-stratified ICU admission, alongside a calculation of the proportion of total admissions accounted for by each age group. As with acute-care hospitalization, infants and seniors represented a disproportionately high share of the ICU

admissions, reflective of our assumption that infants and seniors were more likely to experience critical illness as a result of complicated influenza infection. This distinction was even more pronounced in infants, which represented 11.9% of ICU admissions under a "no intervention" scenario, despite representing only 5.7% of the total population. Similar to acute-care hospitalization, pharmaceutical measures were not found to significantly affect the distribution of age-specific ICU admission; non-pharmaceutical measures redistributed admissions towards younger age groups, while reducing the total number of admissions.

Table 24. Predicted number of ICU admissions, and percentage of total admissions accounted for by each group.

Intervention	Age group					
	Infant	**Child**	**Young adult**	**Adult**	**Senior**	**Total**
None	69	37	47	309	119	581
	11.9%	6.4%	8.1%	53.2%	20.5%	100.0%
V+AVT	23	12	15	102	39	191
	12.0%	6.3%	7.9%	53.4%	20.4%	100.0%
V+AVT+AVP	21	11	15	96	37	180
	11.7%	6.1%	8.3%	53.3%	20.6%	100.0%
CCR+PPM+VI	24	10	9	81	27	151
	15.9%	6.6%	6.0%	53.6%	17.9%	100.0%
CCR+PPM+VI+AVT	21	8	8	71	24	132
	16.0%	5.7%	6.1%	54.0%	18.3%	100.0%
SC+CCR+PPM+Q	33	18	9	52	20	132
	25.0%	13.6%	6.8%	39.4%	15.2%	100.0%
SC+CCR+PPM+Q+V+AVT+AVP	7	3	2	11	4	27
	25.9%	11.1%	7.4%	40.7%	14.8%	100.0%

Figure 9 presents the findings relating to daily demand for ICU beds, as a percentage of the Ottawa–Gatineau CMA ICU capacity. Again, pharmaceutical measures resulted in a contraction of the pandemic peak, while layered non-pharmaceutical measures produced a dramatic attenuation of the wave itself. Peak ICU demand ranged from 90.2% (no interventions)

to 1.1% (all eight interventions). The peak ICU demand for all 192 intervention scenarios is summarized in **Appendix 19**.

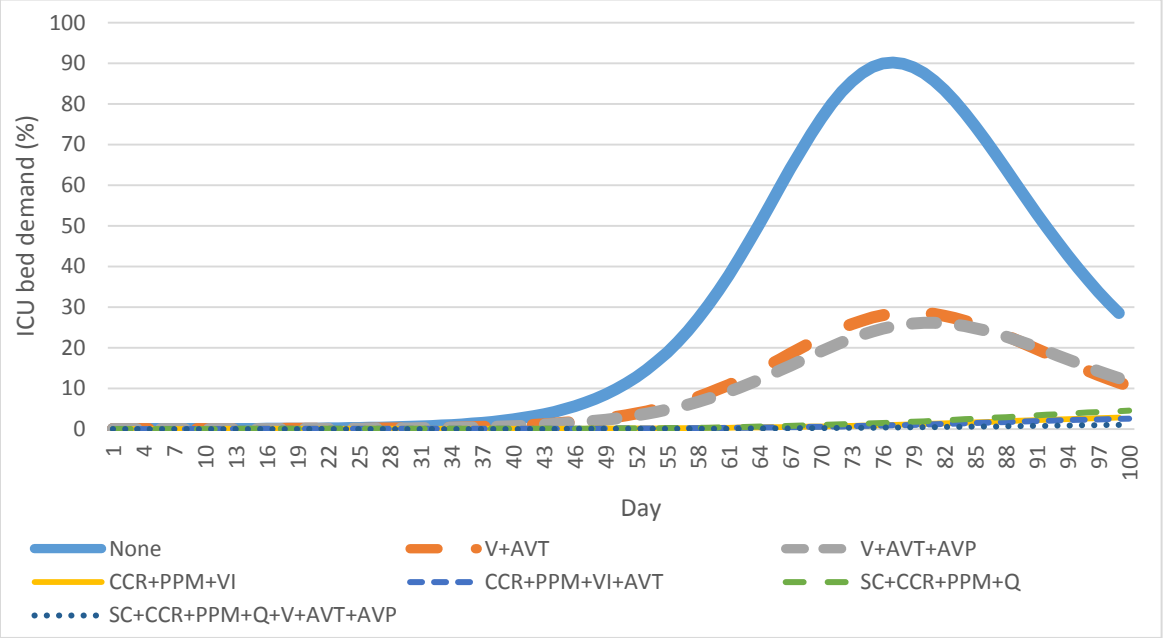

Figure 9. Daily ICU demand, charted as the percentage of all ICU beds in the Ottawa–Gatineau CMA, across seven interventions of interest.

5.3.4 Mortality

The InFluNet model projected 363 pandemic-related deaths under a "no intervention" scenario. Rigorous non-pharmaceutical interventions and most intervention scenarios incorporating vaccination reduced this figure to below 100, while scenarios modelling antiviral treatment, prophylaxis and more moderate non-pharmaceutical interventions tended to predict between 100 and 300 deaths. The mortality estimates for all 192 intervention scenarios are presented in **Appendix 20**.

Age-specific mortality rates are presented in **Table 25**, alongside the proportion of the total mortality estimate for each age group. Seniors are over-represented with regard to mortality,

accounting for 41.2% of deaths in the "no intervention" scenario. This was due in part to the assumption that additional mortality would occur in seniors outside of the hospital setting and reflects the assumption that many influenza deaths will occur among those with weaker immune systems. Interventions had relatively little effect on the age-specific distribution of mortality, suggesting that age-specific mortality rates dominate mortality distribution, rather than rates of symptomatic infection. Because influenza-related mortality is such a rare occurrence, even significant shifts in age-specific infection rates had relatively little effect on mortality distributions.

Table 25. Predicted number of deaths, and percentage of total mortality accounted for by each age group.

Intervention	Age group					
	Infant	**Child**	**Young adult**	**Adult**	**Senior**	**Total**
None	4	4	27	179	150	364
	1.1%	1.1%	7.4%	49.2%	41.2%	100.0%
V+AVT	1	1	9	58	49	118
	0.8%	0.8%	7.6%	49.2%	41.5%	100.0%
V+AVT+AVP	1	1	8	54	45	109
	0.9%	0.9%	7.3%	49.5%	41.3%	100.0%
CCR+PPM+VI	1	1	4	35	25	66
	1.5%	1.5%	6.1%	53.0%	37.9%	100.0%
CCR+PPM+VI+AVT	1	1	4	31	22	59
	1.7%	2.4%	6.7%	52.2%	37.0%	100.0%
SC+CCR+PPM+Q	1	1	4	24	25	55
	1.8%	1.8%	7.3%	43.6%	45.5%	100.0%
SC+CCR+PPM+Q+V+AVT+AVP	0	0	1	5	5	11
	0.0%	0.0%	9.1%	45.5%	45.5%	100.0%

Figure 10 presents the cumulative number of deaths projected to occur in the first 100 days of a pandemic outbreak across the seven interventions of interest. Deaths begin accumulating almost two months after initial seeding of infected individuals. While mortality totals in "no intervention" and pharmaceutical intervention scenarios appeared to be levelling off after 100

days, non-pharmaceutical interventions did not demonstrate similar rate reductions, suggesting a threat of a prolonged first wave or more severe second wave.

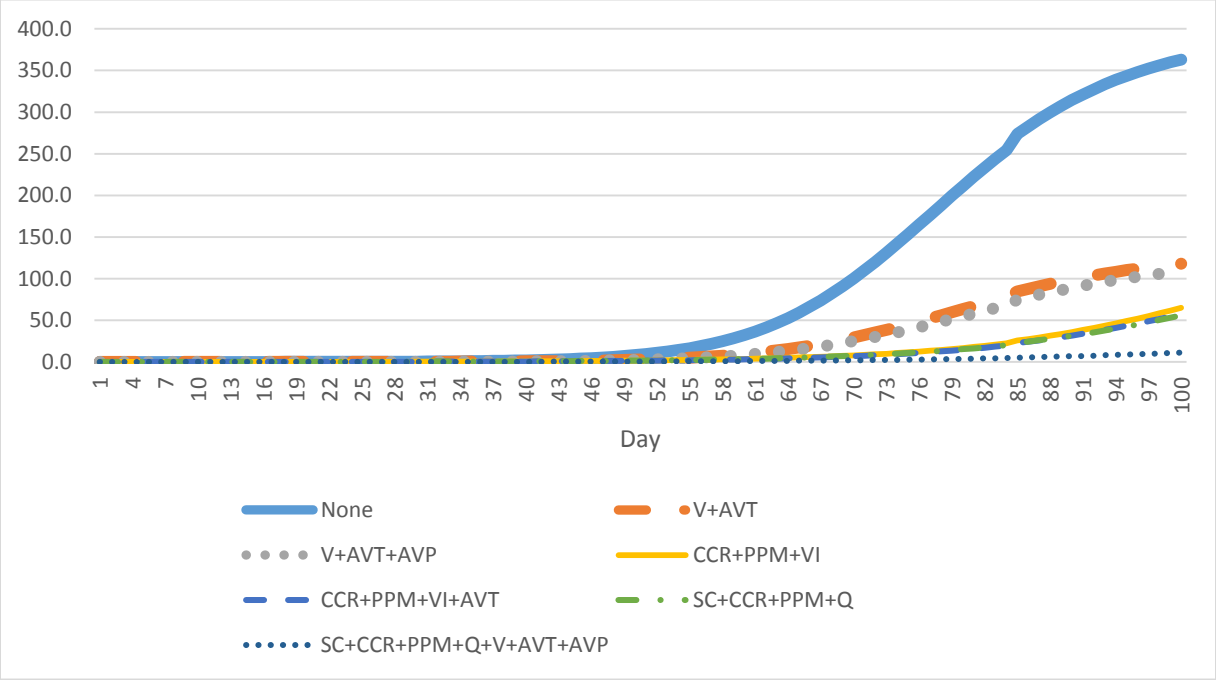

Figure 10. Cumulative mortality over the first 100 days of a pandemic influenza outbreak across seven interventions of interest.

5.3.5 Economic analysis

Estimates of the economic burden for an influenza pandemic — for the seven intervention scenarios of interest — ranged from CAD $115 million to $2.15 billion in the Ottawa–Gatineau CMA alone. The cost breakdown for each intervention scenario is presented in **Table 26**, with more detailed, intervention-specific summaries available in **Appendix 21**. Of the interventions that were subject to economic evaluation, a layered non-pharmaceutical approach, in combination with antiviral therapy, seemed to be the most cost-effective approach. The least cost-effective approaches incorporated school closures, which resulted in massive costs associated with lost school and work days, with relatively little additional benefit.

Table 26. Predicted costs (CAD) of pandemic-associated morbidity and mortality, as well as key intervention inputs.

Cost category	Intervention						
	None	**V+AVT**	**V+AVT+AVP**	**CCR+PPM+VI**	**CCR+PPM+ VI+AVT**	**SC+CCR+ PPM+Q**	**All**
Hospital bed days	10,303,296	3,396,920	3,188,520	2,642,512	2,334,080	2,292,400	450,144
ICU bed days	12,087,200	4,001,280	3,751,200	3,146,840	2,771,720	2,750,880	541,840
Deaths (infant)	9,420,688	2,355,172	2,355,172	2,355,172	2,355,172	2,355,172	0
Deaths (child)	8,830,976	2,207,744	2,207,744	2,207,744	2,207,744	2,207,744	0
Deaths (young adult)	52,830,738	17,610,246	15,653,552	7,826,776	7,826,776	7,826,776	1,956,694
Deaths (adult)	245,961,394	79,696,988	74,200,644	48,093,010	42,596,666	32,978,064	6,870,430
Deaths (seniors)	63,644,400	20,790,504	19,093,320	10,607,400	9,334,512	10,607,400	2,121,480
Lost school days	72,194	23,514	21,860	5,044,494	4,962,104	910,837,138	794,463,188
Lost work days (YA + adults)	1,819,212	600,371	566,482	38,086,197	37,429,987	1,179,410,918	1,023,034,132
Lost work days (seniors)	83,759	25,609	23,876	583,812	572,259	599,601	314,242
Vaccinations	0	8,724,240	8,724,240	0	0	0	8,724,240
Antivirals	0	7,783,530	9,048,375	0	2,506,608	0	2,593,125
Masks	0	0	0	747,792	747,792	747,792	747,792
Total	405,053,858	147,216,118	138,834,986	121,341,749	115,645,420	2,152,613,885	1,841,817,306

5.3.6 Sensitivity analysis

The sensitivity analyses detailed in **Appendix 22** produced three main findings. First, personal protective measures, voluntary isolation, quarantine and vaccination all demonstrated a wide range of potential outcomes, depending on parameter assumptions. School closures, community-contact reduction, antiviral therapy and antiviral prophylaxis exhibited relatively little change between BG, WC and BC scenarios. Vaccination and personal protective measures showed particularly high sensitivity to shifting assumptions, with all six health outcome counts shifting over 100% between BC and WC scenarios.

Second, interventions to interrupt community transmission became less effective as transmissibility increased. As shown in **Table 27**, all interventions produced a smaller reduction in the number of symptomatic cases relative to no intervention under a higher transmissibility parameter, though the order of interventions in terms of effectiveness did not change. The differential impact between BG, BC and WC intervention scenarios was also smaller at higher disease transmissibility, though a similar effect was not observed at a higher hospitalization rate.

Table 27. Percent (%) reduction in number of symptomatic cases, given influenza transmissibility parameter equivalent to R_o of 1.65 or 1.80.

Intervention	Transmissibility parameter (τ)	
	τ = 0.275	τ = 0.3
SC	-1.1	-0.8
CCR	-0.6	-0.4
PPM	-16.4	-8.8
VI	-36.5	-27.5
Q	-37.7	-28.2
V	-7.9	-6.1
AVT	-0.2	-0.1
AVP	-2.8	-0.9

Third, increasing the hospitalization rate had a much more dramatic effect on health outcomes than did increasing disease transmissibility. **Table 28** presents the "no intervention" findings for the four scenarios. The higher transmissibility in Scenario 2 led to more infections, but only relatively small increases in mortality and hospital-resource use. The higher hospitalization rate in Scenario 3, however, led to large increases in predicted hospital resource demand and mortality relative to Scenario 1, despite having the same transmissibility and fewer symptomatic cases.

Table 28. Health outcome summaries for four pandemic scenarios. Scenario 1: $\tau = 0.275$; hospitalization rate = 0.4%; Scenario 2: $\tau = 0.3$; hospitalization rate = 0.4%; Scenario 3: $\tau = 0.275$; hospitalization rate = 1.0%; Scenario 4: $\tau = 0.3$; hospitalization rate = 1.0%.

Outcome	Scenario			
	1	2	3	4
Symptomatic cases	677,546	713,920	675,699	712,553
Hospitalizations	2,472	2,633	4,893	5,217
ICU	580	612	1,149	1,200
Peak hospital demand (%)	14	16	27	32
Peak ICU demand (%)	90	103	179	204
Deaths	363	400	717	791

5.4 Discussion

The objective of this study was to assess the threat posed by the emergence of a novel, transmissible pandemic influenza strain, with respect to potential health and economic burdens. A key area of focus was the assessment of the adequacy of hospital-resource capacity to accommodate expected increases in patient demand, both in acute and intensive-care settings. To accomplish this, we developed and validated InFluNet, a novel mathematical model, which incorporates stochastic elements to account for uncertainty in disease transmission dynamics.

Using a simulated population representative of the Ottawa–Gatineau CMA, we suggest that the timely implementation of a layered, multi-pronged intervention strategy will effectively control

pandemic transmission and protect hospital resource adequacy. However, even aggressive intervention simulations produced illness attack rates over 10% and over 100 deaths. The economic burden is expected to be high, estimated between CAD $115 and $405 million, with costs rising into the billions when extended school closure is implemented. Our model suggests that the most cost-effective approach to pandemic control involves a combination of community-contact reduction, personal protective measures, voluntary isolation and antiviral therapy. The associated cost of $115 million may be lower, as this estimate assumes that individuals who miss work due to voluntary isolation are unable to work from home. However, our estimates did not account for the potential costs of community-contact reduction, which may include shifts in consumer behaviour.

Vaccination, personal protective measures and isolation of infected individuals were found to be the most effective interventions, whereas school closure, community-contact reduction, antiviral therapy and antiviral prophylaxis had less effect on pandemic burden. Sensitivity analysis suggested that the most effective interventions were also those most susceptible to change under shifting assumptions of effectiveness, adherence and timing. All interventions became less effective in limiting transmission as disease transmissibility increased. In all cases, delayed interventions were significantly less effective than cases in which the intervention was implemented from the start of the simulation, suggesting the need for strong and proactive preparedness planning. Sensitivity analysis also suggested that a more virulent strain, with a higher hospitalization rate, is of greater concern than a more transmissible one, with a hospitalization rate of 1% threatening to overwhelm hospital resource capacity even under moderate transmissibility assumptions.

Pharmaceutical and non-pharmaceutical interventions resulted in different effects on the evolution and progression of the pandemic. While pharmaceutical interventions did little to alter the location of transmission events or age-specific burden, non-pharmaceutical interventions tended to redistribute more transmission events to the household and community, as well as to younger age groups. This may be because we did not model age-specific targeting of pharmaceutical interventions and assumed that young adults and adults had a higher community-contact rate than did other age groups; as a result, community-contact reduction and voluntary isolation seemed to disproportionately benefit these age groups.

A common simplification in modelling studies is the assumption of homogenous mixing, wherein individuals are assumed to interact equally across age and geographic groups [379]. This is problematic, as it can overestimate the final pandemic size, leading to unrealistic predictions of hospital-resource strain and the scale of intervention required for transmission containment [314, 380]. Further, it precludes analysis of particular interventions targeted towards specific age groups, such as vaccination campaigns prioritizing children or the elderly. To avoid this, InFluNet models a two-layered system of heterogeneous mixing, wherein individuals in different age groups interact at different rates depending on their location, reflecting the age- and location-dependent forces that will influence disease transmission rates.

Our vaccination simulations assumed that a well-matched pandemic vaccine would be available at the onset of the pandemic; this may represent an unlikely scenario, as vaccine production, development and distribution can take over six months [103, 232]. However, we included this intervention as a means of evaluating the impact of the intervention were it to be available. The effectiveness of timely vaccination suggests value in strengthening international collaboration with regard to surveillance and sharing of circulating influenza strains. Also, by

assuming that older age groups maintain some immunity to the pandemic strain, we are modelling the emergence of a pandemic strain that is not entirely novel: this reflects the experience of the past four pandemics but could underestimate population susceptibility to an entirely novel strain, such as an avian influenza. It should also be noted that antiviral prophylaxis may only be available in the early stages of an outbreak, after which contract tracing may become infeasible [301]; we do not account for this in our model.

Pharmaceutical interventions tended to reduce the overall burden of the pandemic without affecting its timing. Non-pharmaceutical interventions, by contrast, tended to delay the development of the pandemic to an extent that the pandemic was not completed after 100 days. We used 100 days as the upper limit of pandemic-wave duration, but such containment of transmission could lead to either a prolonged wave or more severe second wave. This is because pharmaceutical measures contribute to shifting the susceptibility profile of a population, whereas non-pharmaceutical measures contain transmission without affecting the population profile. As a result, if non-pharmaceutical measures are retracted prematurely, there is the risk of disease re-emergence.

The present study is subject to certain limitations. First, we do not account for possible adverse side effects from pharmaceutical interventions, which may marginally reduce the health benefit of mass vaccination [157] and antiviral prophylaxis [208]. We assumed that these associated risks would be insignificant in the context of other unavoidable uncertainties in model assumptions.

Second, we treat the entire CMA as a single homogenous area. While individuals are likely to mix preferentially in neighbourhood and workplace pockets, we decided that the most effective method of evaluating macro-level threats to the community and health system would be to treat the CMA as a single unit.

Third, we have excluded analysis of preferential targeting of at-risk individuals —and associated ethical considerations — as outside the scope of this analysis, prioritizing instead an assessment of community-level practices to control pandemic burden.

Fourth, we do not include every conceivable intervention, excluding for example hospital triage protocols and influenza helplines. Hospital triage and influenza helplines were excluded because we view their main benefit as being a reduction in unnecessary hospital visitation, and our hospitalization rate already assumed that only those needing hospitalization would be admitted. However, we note that triage protocols could increase the proportion of individuals — especially seniors — that die outside of hospital settings. We also did not model nosocomial infection and therefore did not examine the value of hospital-infection control practices.

Fifth, we chose to model social-contact behaviour based upon empirical data from the United States, as none were available in Canadian contexts. While this may skew our estimates slightly, similar contact-rate assumptions in previous modelling studies of the mid-sized Ontario cities London [324] and Hamilton [157] suggest that the same contact structure would apply in Ottawa.

Sixth, while agent-models (ABMs) are more effective at modelling the stochasticity inherent in disease transmission, the decision was made to pursue a differential equation models (DEMs). ABM models require a large computational burden and, given the number of InFluNet compartments alongside the age-specific and location-specific transmission dynamics, an ABM would have obstructed the depth of analysis, limited sensitivity analysis and impeded its uptake among public-health practitioners with limited modelling training [381]. As a secondary objective of this project was to construct a model that was scalable to different populations and accessible to policy audiences, and considering the output differences between DEMs and ABMs are small within the larger scope of parameter uncertainty, we chose to construct a DEM.

Lastly, as with all prospective mathematical models, InFluNet is subject to a high degree of uncertainty; this is particularly true in our case, where a high level of analytical complexity necessitates numerous assumptions relating to disease and intervention characteristics. We therefore emphasize that the results of our model are best interpreted as general patterns of intervention effectiveness rather than specific predictions of the number of likely cases, hospitalizations and deaths. Future research can add to this analysis through in-depth assessment of targeted interventions, based on age or risk profile and evaluation of other communities to assess community characteristics that may lead to higher pandemic burdens and strain on health system capacity.

The strength of InFluNet is its incorporation of empirical social contact, disease and intervention data to chart pandemic progression against real-world hospital-capacity data. It also allows the most complex analysis of mitigation strategies, helping to inform pandemic preparedness planning in both community and hospital settings. We are aware of no other mathematical models that incorporated such diverse intervention bundles alongside our broad range of health and economic endpoints. The results of this initial analysis suggest that the hospital capacity of the Ottawa–Gatineau region will be adequate to accommodate a transmissible but mild pandemic influenza under most intervention strategies but that it could quickly become overwhelmed by a more virulent strain.

5.5 Conclusion

This study provides valuable new insights in pandemic preparedness, presenting a novel model of pandemic transmission as it relates to health and economic outcomes and hospital-surge capacity. Our analysis suggests that personal protective measures, isolation of infected individuals and vaccination are most effective at containing pandemic transmission. A layered approach

incorporating the timely implementation of multiple non-pharmaceutical interventions is likely to effectively contain pandemic transmission and maintain the adequacy of hospital resource capacity in the Ottawa–Gatineau area. However, we found that even small increases in disease transmissibility or virulence constitute a significant threat, both in terms of surges in patient demand and overall burden. Given the need for timely interventions, future studies are needed to assess optimal intervention strategies under a broad range of disease, intervention, population and resource assumptions.

Chapter 6. National assessment of Canadian pandemic preparedness: employing InFluNet to identify high-risk areas for inter-wave vaccine distribution

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Publication Status Information

This manuscript has been published in the journal *Infectious Disease Modelling* (Saunders-Hastings, P. Hayes, B., Smith?, R., Krewski, D. (2017). National assessment of Canadian pandemic preparedness: Employing InFluNet to identify high-risk areas for inter-wave vaccine distribution. *Infectious Disease Modelling*.

Abstract

Influenza pandemics emerge at irregular and unpredictable intervals to cause substantial health, economic and social burdens. Optimizing health-system response is vital to mitigating the consequences of future pandemics.

We used a mathematical model to assess the preparedness of Canadian health systems to accommodate pandemic-related increases in patient demand. We identify vulnerable areas, assess the potential of inter-wave vaccination to mitigate impacts and evaluate the association between demographic and health-system characteristics in order to identify predictors of pandemic consequences.

Modelled average attack rates were 23.7–37.2% with no intervention and 2.5–6.4% with pre-vaccination. Peak acute-care demand was 7.5–19.5% of capacity with no intervention and 0.6–2.6% with pre-vaccination. The peak ICU demand was 39.3–101.8% with no intervention and 2.9–13.3% with pre-vaccination. Total mortality was 2,258–7,944 with no intervention and 88–472 with pre-vaccination. Regions of Southwestern Ontario were identified as most vulnerable to surges in patient demand. The strongest predictors of peak acute-care demand and ICU demand were acute-care bed capacity ($R = -0.8697$; $r^2 = 0.7564$) and ICU bed capacity ($R = -0.8151$; $r^2 = 0.6644$), respectively. Demographic characteristics had mild associations with predicted pandemic consequences.

Inter-wave vaccination provided adequate acute-care resource protection under all scenarios; ICU resource adequacy was protected under mild disease assumptions, but moderate and severe diseases caused demand to exceed expected availability in 21% and 49% of study areas,

respectively. Our study informs priority vaccine distribution strategies for pandemic planning, emphasizing the need for targeted early vaccine distribution to high-risk individuals and areas.

6.1 Introduction

In response to widespread global transmission of the A(H1N1) influenza virus, the World Health Organization declared a pandemic on June 11, 2009; this marked the fourth time in one hundred years that a novel influenza virus had emerged to cause significant social, economic and health burdens [249]. Influenza is an RNA virus that causes annual outbreaks of acute respiratory infections [13]. With a high mutation rate preventing the accumulation of natural immunity, influenza is the most deadly vaccine-preventable disease in North America [13].

Influenza pandemics result from the emergence of new viral strains to which humans possess no appreciable immunity. This tends to be the result of a process called *antigenic shift*, wherein viral components from different sources interact and combine to form a new viral genotype; if this strain can transmit easily between human hosts and results in illness, a pandemic may emerge. The combined burden of the past four occurrences — the Spanish flu (1918), Asian flu (1957), Hong Kong flu (1968) and Swine flu (2009) — amount to tens of millions of infections, hospitalizations and deaths [249]. In each case, the pandemic evolved in multiple successive waves, with the second often being more severe than the first [249].

Of particular concern in pandemic situations is the expected surge in patient demand, and the resulting strain on hospital-resource capacity. Hospitals tend to rely on just-in-time resource supply, and have limited surge capacity [355]. Sudden increases in patient demand could quickly overwhelm hospital capacity, leading to dangerous disruptions in service delivery [382]. A key

component of pandemic planning must therefore be the identification and support of vulnerable health systems in order to protect hospital-resource adequacy.

Influenza vaccination has been identified as the most cost-effective method of containing transmission and mitigating associated burdens [304]. However, the production, development and distribution of a new pandemic vaccine could take up to six months, which could make it unavailable to affect the first wave of a pandemic [232]. However, strategic allocation of a limited pandemic vaccine supply during the inter-wave period could help mitigate the threat of a problematic second wave. While an important component of this effort will be the targeting of high-risk individuals, strategic allocation should also involve the targeting of individuals within health systems at greatest risk of being overwhelmed by surges in patient demand.

In this article, we present the findings of modelling simulations for each Canadian Census Metropolitan Area (CMA). Using InFluNet — a mathematical model developed to predict the evolution and impacts of a pandemic influenza outbreak — we project the possible second-wave pandemic burden for each location under various vaccination and disease severity assumptions. Across six health outcomes, we identify areas at greatest risk from an influenza pandemic and identify high-priority areas for inter-wave vaccine allocation. While of particular relevance to Canadian contexts, this research also provides valuable insights for international pandemic preparedness by evaluating on the characteristics of demographic and health-system profiles that underlie regional pandemic influenza vulnerability.

6.2 Methods

The present study relied on InFluNet — a validated differential equation model developed by the authors — to conduct its model simulations. Below, we provide a brief summary of its

underlying assumptions and how it was employed to identify vulnerable Canadian hospital systems.

6.2.1 Social contact

InFluNet stratifies the population by age according to the following five groups: infant (0–4), child (5–18), young adult (19–29), adult (30–64) and senior (65 and over). Individuals interact in the household, school or workplace (depending on age) and community, for twelve, eight, and four hours each day, respectively. Individuals will interact preferentially within and across age groups, depending on their age and location. Estimates of location-based contact rates rely on previously published, empirical age-specific data from the United States [310], combined with time-location divisions as reported by Statistics Canada [311]. Contact rates by age and location are identical to those presented in **Table 11**–**Table 14** in **Chapter 5**.

6.2.2 Transmissibility

The model uses a next-generation operator approach to disease transmission, which has been described in detail in previous publications modelling disease in heterogeneous populations [314, 320]. This method assumes that the disease-transmission rate (β) depends on six parameters: number of effective contacts (γ), susceptibility (α), infectivity (η), duration of contacts (σ), mean number of transmission events per unit time (τ) and the proportion of the population that is infected (I_A/N). Equations are presented below, with specific transmissibility function parameters included in

Table 29. The transmission rate is

$$\beta = \beta_C + \beta_A,$$

where

$$\beta_C = \gamma \cdot \alpha_C \cdot \eta_C \cdot (1 - e^{-\sigma \cdot \tau}) \cdot \frac{I_C}{N} \quad \text{and}$$

$$\beta_A = \gamma \cdot \alpha_A \cdot \eta_A \cdot (1 - e^{-\sigma \cdot \tau}) \cdot \frac{I_A}{N}.$$

Table 29. Transmissibility function parameters

Symbol	Definition	Sample value	References	Range
γ	Number of effective contacts	As per contact tables	[314]	$1e^{-2–10}$ (contacts/day)
α	Susceptibility	0.66 for infants 0.47 for children 0.74 for young adults 0.89 for adults; 0.98 for seniors	[383, 384]	0–1
η	Infectivity	1.0	Assumed	0–1
σ	Duration of contacts	As per contact tables	[314]	1/2–1/6 (days/contact)
τ	Mean number of transmission events per unit time	0.275; 0.3	[33]	0.17–0.42
$\frac{I_C}{N}$, $\frac{I_A}{N}$	Proportion of population that symptomatically and asymptomatically infected	Model-generated	NA	0–10%

The contact parameters were drawn from empirical studies. Susceptibility has been reduced to reflect the pre-existing natural immunity that could reasonably be expected in an inter-wave period; estimates are based on empirical data on infection-driven immunity following the first wave of the A(H1N1) pandemic in the United States [383] and Canada [384]. We assume that unvaccinated infected individuals will be maximally infectious, as we found no reliable data to support recalibration. The number of transmission events were adjusted to estimate a pandemic

strain of transmissibility equivalent to the moderately transmissible 1957 pandemic (0.275) and highly transmissible 1918 pandemic (0.3) [33].

6.2.3 Model structure

InFluNet is a deterministic SEIR (susceptible–exposed–infected–recovered) model described by a system of ordinary differential equations. However, the model predictions vary according to the month in which the outbreak starts; the timing of the outbreak is randomly determined, and school attendance is eliminated for July and August. Each scenario is run over the course of five simulations, with the results being averaged and 95% confidence intervals being calculated via the standard deviation approach. The loop structure was determined by calculating the variance between model simulations, and running continuous simulations until the average value had a standard error below 5%. The model flow diagram is illustrated in **Figure 11**.

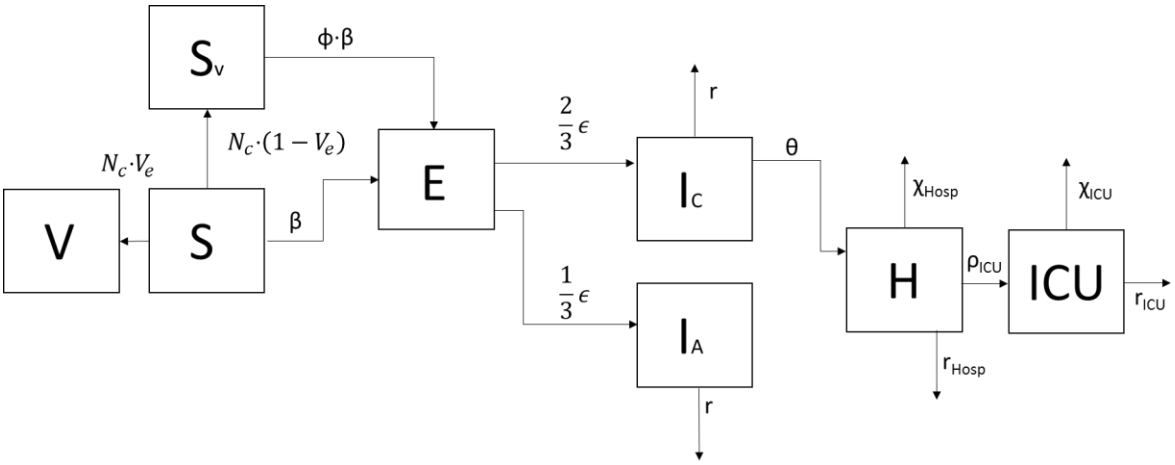

Figure 11. InFluNet transmission model flow diagram.

From **Figure 11**, we arrive at the system of ODEs presented below. Descriptions, ranges, and sample values for model parameters are provided in **Table 30**. The relevant ODEs and model parameters — described previously in **Chapter 5** — are repeated here for clarity.

$\frac{dS}{dt} = -(N_C + \beta) \cdot S$	Susceptible
$\frac{dE}{dt} = \beta \cdot (S + \phi \cdot S_V) - E \cdot \epsilon$	Latent Infected
$\frac{dS_V}{dt} = (1 - V_e) \cdot N_C \cdot S - \phi \cdot S_V \cdot \beta$	Susceptible with Failed Vaccination
$\frac{dV}{dt} = V_e \cdot N_C \cdot S$	Vaccinated
$\frac{dI_C}{dt} = \frac{2}{3} \cdot E \cdot \epsilon - I_C(\theta + r + \zeta)$	Infected Symptomatic
$\frac{dI_A}{dt} = \frac{1}{3} \cdot (E) \cdot \epsilon - I_A \cdot r$	Infected Asymptomatic
$\frac{dH}{dt} = (I_C) \cdot \theta - \left(r_{Hosp} + \chi_{Hosp} + \rho_{ICU}\right) \cdot H$	Hospitalized
$\frac{dICU}{dt} = \rho_{ICU} \cdot H - (r_{ICU} + \chi_{ICU}) \cdot ICU$	Intensive Care Unit

Each simulation begins with 50 infected cases being seeded across the five age groups in proportion to their relative size. A certain proportion (N_C) of susceptible individuals can receive vaccination, moving either to an immune "vaccinated" group (V) or a less susceptible — relative to the unvaccinated group — "failed vaccinated" group (S_V). Upon infection, individuals move to a latent, "exposed" group for a period of one to three days, followed by an infectious period of four to seven days [331, 332]. Two thirds will be symptomatic (I_C), while the remaining third will be asymptomatic (I_A) and half as infectious [232].

Of those who are symptomatic, a small proportion (0.4–1.0%) will require hospitalization for an average of four days [152]. Age-specific hospitalization rates were calibrated to reflect empirical data from the A(H1N1) pandemic [340]. Acute-care patients will experience a 3.125% mortality rate, while an additional 16% will require ICU care and ventilation for an average of ten days, with an associated mortality rate of 50% [339, 342]. Age-specific mortality rates given

hospitalization are drawn from previously published Canadian studies [161]. We assume that all deaths in those under 65 will occur in hospital, while 25% of deaths among seniors will occur in other settings, such as retirement homes and long-term care facilities. These estimates reflect empirical data from past pandemics in Canada. Model parameters are listed in **Table 30**.

Table 30. Model parameters

Symbol	Definition	Sample value	References	Range
N_C	Rate of vaccination	$8.5e^{-4}$ (1/days)	[161]	$8.5e^{-4}$ (1/days)
V_e	Vaccine efficiency	65%	[202]	40–90%
φ	Reduction in infectivity due to vaccination	35%	[313]	20–50%
ε	Rate of disease progression	1/1.6 days	[157]	1/3–1/7 (1/days)
θ	Rate of hospitalization	Age-dependent	[152, 339]	$1e^{-3}$–$1e^{-1}$ (1/days)
r	Rate of recovery	r = 1/4.8 Hosp = 1/3.35 ICU = 1/10.25	[157, 313, 332]	1/4–1/7 (1/days)
χ	Death rate in hospital setting	Hosp = $1e^{-3}$ ICU = 0.1	[342]	$1e^{-3}$–$1e^{-1}$ (1/days)
ρ	Progression through hospital	ICU = 0.05	[339]	0.05–0.5

6.2.4 Resources

Hospital-resource capacity was estimated using data from the Canadian Institute of Health Information [346]. Counts of "acute", "ICU" and "other" beds were obtained for each hospital. Since Quebec hospitals do not report to CIHI, this information was obtained separately through the Quebec Ministry of Health and Social Services [347]. As these hospitals did not report the number of ICU beds, we calculated the proportion of hospital beds outside of Quebec that were designated for the ICU (6.2%) and extrapolated this to Quebec hospitals. Hospitals were then mapped geographically using ArcGIS (ESRI, Ottawa, Canada), and hospitals within the borders of each CMA were combined for the purposes of the present analysis. Hospital-resource data were combined with Census demographic data to generated profiles for the 33 Canadian CMAs, included in **Appendix 23** [385].

6.2.5 Vaccination

The vaccination strategy being modelled involves inter-wave vaccination — or "prevaccination" — of 25% of the general population. In other words, a quarter of the population will have received vaccination prior to the onset of the second pandemic wave. We use a low coverage level to reflect a situation in which vaccine supply is limited, prioritizing high-risk populations. While recognizing that the first step of vaccine distribution could prioritize high-risk individuals, our interest is in identifying geographical areas where the hospital system is less able to accommodate surges in patient demand, and would therefore benefit from early vaccination to protect hospital-resource adequacy.

As informed by past empirical and modelling studies, we estimate vaccine efficacy for susceptibility (VE_S) to be 65% [202, 355]. We also assume that vaccinated individuals who still become infected will be 35% less infectious [313] and 60% less likely to require hospitalization [386, 387]. These efficacy estimates model a well-matched vaccine, but recognize that a high virus mutation rate, technological constraints, and variable individual responses will prevent the development of a perfectly matched vaccine. Effectiveness ranges were not incorporated in this study, as we seek to inform optimal vaccination strategies given a vaccine of a specified effectiveness.

6.2.6 Outcomes

Simulation results were calculated across six health outcomes of interest: cases of symptomatic infection, cases of hospitalization, cases of ICU admission, peak demand as a percentage of acute-care hospital capacity, peak ICU demand as a percentage of capacity and total deaths.

6.2.7 Analysis

Simulations for each of the 33 CMAs were run across eight vaccination–transmissibility–pathogenicity combinations. Summary measures for the six outcomes of interest are presented across all 264 scenarios. In this way, we conducted a univariate sensitivity analysis of the impact of shifting disease severity and population demographics.

We also associated the threat to health-system capacity with key demographic and hospital system characteristics, by plotting our results against the following CMA characteristics: proportion of total population that are seniors, adults, young adults, children and infants, as well as acute-care and ICU beds per 10,000 population. We assessed strength of linear relationships using the Pearson correlation coefficient (R), reported alongside the coefficient of determination (r^2) in order to present both the strength and direction of relationships and the proportion of health outcome variance accounted for by these relationships. We used previously reported thresholds to qualify the strength of correlations, presented in **Table 31**.

Table 31. Interpretation of the size and strength of Pearson correlation coefficient [388].

Correlation (R)	Interpretation
(+/-) 0.7–1.0	Strong correlation
(+/-) 0.5–0.69	Moderate correlation
(+/-) 0.3–0.49	Weak correlation
(+/-) 0–0.29	Negligible correlation

Sensitivity analyses for strength of association was undertaken using the five scenarios presented in **Table 32.** We evaluated the effect of increases in disease transmissibility and pathogenicity, vaccination and population susceptibility.

Table 32. Summary of five scenarios used for sensitivity analysis.

Scenario	Parameter			
	Transmissibility	**Hospitalization rate (%)**	**Vaccination**	**Pre-existing immunity**
1	0.275	0.4	No	Yes
2	0.3	0.4	No	Yes
3	0.275	1.0	No	Yes
4	0.275	0.4	Yes	Yes
5	0.275	0.4	No	No

This model has been previously validated through data parameterization, assessment of the structural validity and predictive validation. REB approval was not required for this study, as all data are publically available and do not involve individual health information.

6.3 Results

The following subsections describe model findings as they relate to symptomatic cases, acute-care hospital admissions, ICU admissions, and mortality associated with a second pandemic wave. Each includes an analysis of how the predicted burden of the pandemic varies by disease characteristics and vaccination distribution, as well as an additional analysis of the demographic and health-system predictors of hospital-resource inadequacy. These subsections discuss major findings, while full summary tables of all simulations (**Appendix 24**–**Appendix 29**) and sensitivity analyses (**Appendix 30**–**Appendix 31**) are included in the supplementary material**.**

6.3.1 Symptomatic cases

As presented in **Table 33**, the average illness attack rate across the 33 CMAs was 23.7–37.2% for simulations with no vaccination; it varied between 2.4% and 6.5% for simulations with vaccination.

Table 33. Illness attack rate according to disease profile and vaccination status, averaged across 33 CMAs.

Disease profile	Vaccination status	Average illness attack rate (%)
R_0 = 1.65; Hospitalization rate = 0.4%	No vaccination	23.7
	25% pre-vaccination	2.5
R_0 = 1.80; Hospitalization rate = 0.4%	No vaccination	37.8
	25% pre-vaccination	6.5
R_0 = 1.65; Hospitalization rate = 1.0%	No vaccination	23.2
	25% pre-vaccination	2.4
R_0 = 1.80; Hospitalization rate = 1.0%	No vaccination	37.2
	25% pre-vaccination	6.4

Vaccination of 25% of the population prior to onset of the second pandemic wave reduced symptomatic cases by an average of 83.8%, with a minimum reduction of 73.0% (Peterborough, Ontario) and a maximum reduction of 96.6% (Toronto, Ontario). Vaccination became less effective in preventing symptomatic infection under scenarios with higher transmissibility (mean reduction of 70.0%, range 55.1–95.0%) but still resulted in a marked reduction in infection. A higher hospitalization rate did not affect the impact of vaccination on illness attack rates.

The relative representation of different age groups did not have a strong impact on the number of symptomatic cases across CMAs. Two mild predictors were the percentage of adults (R = 0.3185; r^2 = 0.1014) and the percentage of seniors (R = -0.3774; r^2 = 0.1424), which had opposite effects on cases of symptomatic infection. Increased disease transmissibility, vaccination and the removal of pre-existing immunity reduced this correlation, while increasing the hospitalization rate had no effect.

6.3.2 Hospitalizations

The total number of all acute-care hospital admissions across the 33 CMAs ranged from 18,884 to 62,168 in scenarios of no vaccination and from 790 to 4,671 under scenarios where 25% of the

population had been vaccinated. The CMA with the highest number of hospitalizations was Toronto, Ontario (2,074–10,788 with no vaccination); the CMA with the lowest number of hospitalizations was Peterborough, Ontario (184–430 with no vaccination). However, the CMA with the highest proportion of hospitalizations was Brantford, Ontario (16.9–39.8 per 10,000 population with no vaccination); the lowest proportion was in Toronto, Ontario (3.7–19.3 per 10,000 population with no vaccination). The average number of hospitalizations across all CMAs ranged from 572 to 1,884 (12.9–33.5 per 10,000 population) in scenarios with no intervention and from 24 to 142 (0.9–4.0 per 10,000) under scenarios when 25% of the population had been pre-vaccinated. Vaccination reduced the number of hospitalizations by an average of 88.6–93.8%, with lower impacts associated with higher disease transmissibility and not elevated pathogenicity.

The peak acute-care hospital demand — presented as a percentage of acute-care capacity — ranged from 7.5% to 19.5% in situations with no vaccination and from 0.6% to 2.6% in situations with 25% pre-vaccination. Vaccination reduced peak acute-care demand by an average of 86.3%–91.9%, with the greatest reductions in effectiveness seen in scenarios with higher assumed disease transmissibility. The eight CMAs at elevated risk of acute-care resource constraints — where baseline model assumptions resulted in peak acute-care demand in excess of 10% of capacity — are identified in **Table 34.** Seven of the eight are located in the Southwestern Ontario region and one was in British Columbia.

Table 34. CMAs at elevated risk of acute-care hospital-resource inadequacy. Figures represent a range of results from model simulations of a virus with an R_0 of 1.65 and a hospitalization rate of 0.4% and a virus with an R_0 of 1.80 and a hospitalization rate of 1.0%.

CMA	Peak range with no vaccination (%)	Peak range with 25% vaccination (%)
Brantford, Ontario	15.3–38.4	1.9–6.4
Oshawa, Ontario	15.2–38.2	1.1–5.7
Kitchener–Cambridge–Waterloo, Ontario	14.8–37.1	0.9–5.0
Guelph, Ontario	12.2–32.8	1.6–5.1
Saint Catharine's–Niagara, Ontario	12.8–32.1	0.9–4.6
Barrie, Ontario	12.2–30.5	1.3–5.1
Windsor, Ontario	11.5–29.0	0.9–4.5
Abbotsford–Mission, British Columbia	10.1–25.4	1.1–4.2

The proportion of the population comprised of children was a moderately strong demographic predictor examined in our assessment of peak acute-care demand ($R = 0.6761$; $r^2 = 0.4572$). Increasing the hospitalization rate, vaccination coverage or population susceptibility weakened this correlation, while increasing disease transmissibility had no effect. A strong predictor was the number of acute-care beds per 10,000 population in each CMA ($R = -0.8697$; $r^2 = 0.7564$). Increasing transmissibility or population susceptibility resulted in a stronger correlation; vaccination weakened the correlation and increased hospitalization rate had no effect. The association between acute-care hospital bed capacity and peak acute-care demand across the five scenarios is presented in **Figure 12**.

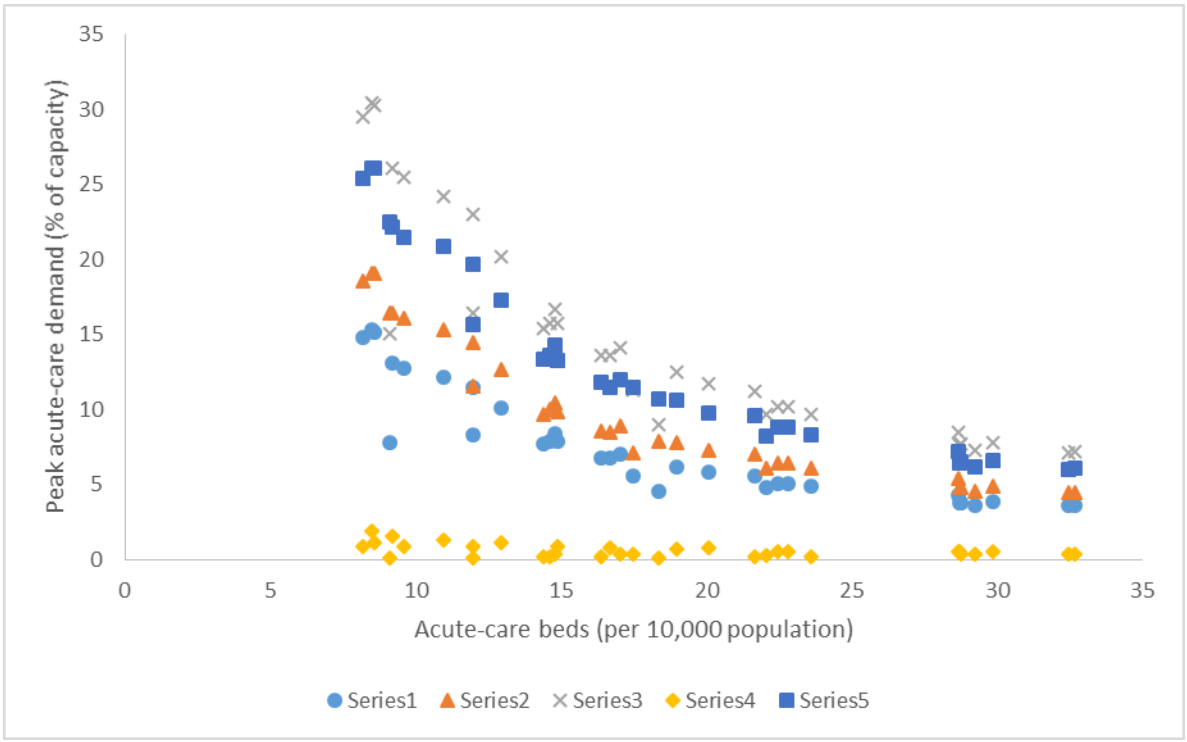

Figure 12. Peak acute-care demand as a function of acute-care beds staffed and in operation per 10,000 population across 33 CMAs and five sensitivity analysis scenarios. Scenario 1: R0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2: R0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

6.3.3 ICU admissions

The total number of all ICU admissions across the 33 CMAs ranged from 4,295 to 14,279 under scenarios of no vaccination and from 179 to 923 under scenarios with 25% pre-vaccination. As with hospitalizations, Toronto, Ontario, had the highest number of predicted ICU admissions (456–2,437 with no vaccination) and Peterborough, Ontario, had the lowest (43–101 with no vaccination). However, the CMA with the highest proportion of ICU admission was Brantford, Ontario (3.8–8.9 per 10,000 population with no vaccination); the lowest proportion was in Toronto, Ontario (0.8–4.4 per 10,000 population with no vaccination). The average number of ICU

admissions across all CMAs ranged from 130 to 433 (2.9–7.7 per 10,000 population) in scenarios with no vaccination and from 5 to 28 (0.2–0.9 per 10,000) when assuming 25% pre-vaccination. Vaccination reduced the number of ICU admissions by an average of 93.5–95.8%; increased disease transmissibility resulted in a small decrease in effectiveness, while increased pathogenicity had no effect.

The average peak ICU demand as a percentage of capacity ranged from 39.3% to 101.8% in situations with no vaccination and from 2.9% to 13.3% in situations with 25% pre-vaccination coverage. Vaccination reduced peak ICU demand by an average of 86.9–92.6%, with a small reduction in impact when disease transmissibility was increased. Of the 33 CMAs, 32 experienced a peak ICU demand above 10% of capacity under baseline assumption, while 18 experienced a peak ICU demand above 30%. These were identified as at elevated risk and are presented in **Table 35**: twelve CMAs are located in Ontario, four in British Columbia and two in Saskatchewan.

Table 35. CMAs at elevated risk of ICU-resource inadequacy. Figures presented are from model simulations reflecting a virus with an R_0 of 1.65 and a hospitalization rate of 0.4%.

CMA	Peak range no vaccination (%)	Peak range 25% vaccination (%)
Saint Catharine's–Niagara, Ontario	97.9–243.4	5.8–32.0
Oshawa, Ontario	82.7–205.3	5.3–28.2
Abbotsford–Mission, British Columbia	79.1–205.3	8.1–33.0
Barrie, Ontario	70.1–174.0	6.8–28.9
Kitchener–Cambridge–Waterloo, Ontario	68.4–170.2	3.5–20.3
Brantford, Ontario	67.8–168.5	7.8–28.9
Victoria, British Columbia	62.0–154.5	4.0–21.2
Windsor, Ontario	54.6–135.5	3.8–19.4
Vancouver, British Columbia	52.7–170.9	0.9–6.5
Greater Sudbury, Ontario	50.0–124.4	5.3–21.1
Ottawa–Gatineau, Ontario–Quebec	49.8–131.3	1.2–8.3
Guelph, Ontario	45.2–112.3	5.1–19.2
Kelowna, British Columbia	41.7–103.8	4.2–17.3
Saskatoon, Saskatchewan	37.8–94.2	3.0–14.4
Peterborough, Ontario	35.2–87.6	4.3–15.1
Regina, Saskatchewan	35.1–87.2	3.2–14.1
Hamilton, Ontario	33.2–82.6	1.2–7.7
Thunder Bay, Ontario	31.3–77.7	3.8–13.4

The proportion of the total population comprised of children was weakly correlated with peak ICU demand ($R = 0.4955$; $r^2 = 0.2456$). Increased vaccination and population susceptibility were the only two parameters that affected correlation strength, with both parameters weakening the correlation. The strongest predictor was the number of ICU beds per 10,000 population ($R = -0.8151$; $r^2 = 0.6644$). Increased disease transmissibility strengthened this correlation, while vaccination weakened it. Hospitalization rate and pre-existing immunity had no effect. The association between ICU bed capacity and peak ICU care demand across the five scenarios is presented in **Figure 13**.

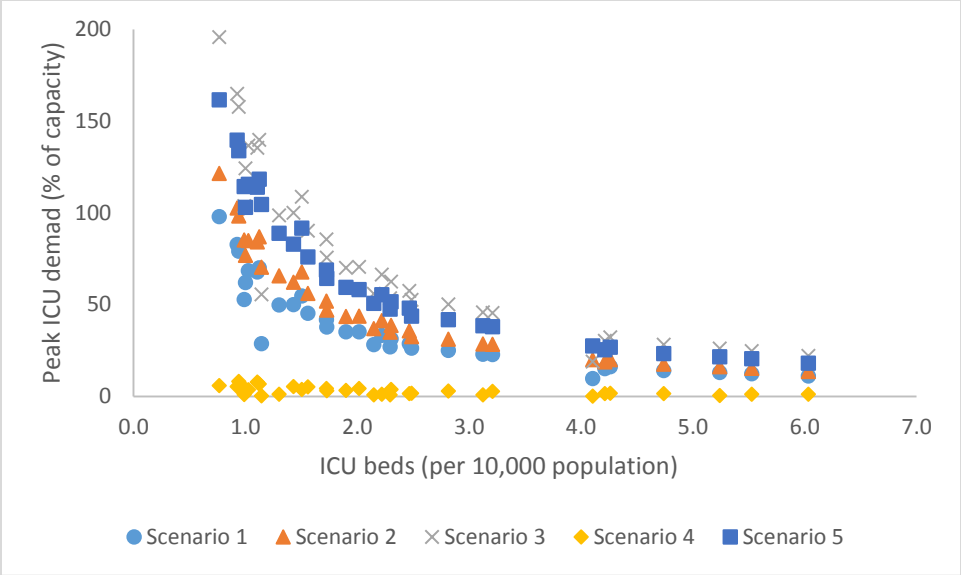

Figure 13. Peak ICU demand as a function of ICU beds staffed and in operation per 10,000 population across 33 CMAs and five sensitivity analysis scenarios. Scenario 1: R0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

6.3.4 Mortality

Total mortality across the 33 CMAs ranged from 2,258 to 7,944 fatalities in scenarios with no intervention, and from 88 to 472 in scenarios with 25% pre-vaccination. Toronto, Ontario, had the highest estimated mortality (199–1,130 with no vaccination) while Thunder Bay, Ontario, had the lowest (25–62 with no vaccination). Total and average mortality estimates are presented in **Table 36**.

Table 36. Total and average mortality, according to disease profile and vaccination status, across 33 CMAs.

Disease profile	Vaccination status	Mortality	
		Total	Average mortality per CMA
R_0 = 1.65; Hospitalization rate = 0.4%	No vaccination	2,258	68
	25% pre-vaccination	88	3
R_0 = 1.80; Hospitalization rate = 0.4%	No vaccination	4,003	121
	25% pre-vaccination	238	7
R_0 = 1.65; Hospitalization rate = 1.0%	No vaccination	4,423	134
	25% pre-vaccination	186	6
R_0 = 1.80; Hospitalization rate = 1.0%	No vaccination	7,944	241
	25% pre-vaccination	472	14

Pre-vaccination of 25% of the population reduced mortality by an average of 90.6–94.8%, with increased transmissibility resulting in a slight reduction in effect and increased pathogenicity having no effect. While there were no strong correlations between demographic profiles and mortality estimates, the two most notable correlations were mild associations with the population represented by infants ($R = 0.3558$; $r^2 = 0.1266$) and by seniors ($R = -0.4475$; $r^2 = 0.2002$). Both demonstrated stronger correlations under vaccination scenarios, weaker correlations under higher transmissibility and population susceptibility and were unaffected by increasing pathogenicity.

6.4 Discussion

To our knowledge, this is the first assessment of the preparedness of Canadian CMAs to accommodate surges in patient demand during a second pandemic influenza wave with the help of inter-wave vaccination. The primary objective of this study was to evaluate the relative threat of a second-wave influenza pandemic across 33 Canadian CMAs. There were two secondary objectives: to evaluate the potential of inter-wave vaccination to contain a second pandemic wave, and to assess the strength of correlation of various demographic and health system characteristics in predicting pandemic burden and hospital-capacity adequacy. In this way, we sought to inform

pandemic influenza vaccination planning in Canada and advance the identification of areas at high risk during influenza pandemics.

Canadian acute-care and ICU bed occupancy has been reported to routinely hover around 90% of total capacity [339, 389]. Across 264 unique CMA–disease–intervention combinations, we found that, under scenarios of no intervention, eight of the 33 CMAs experienced a peak acute-care hospitalization rate above 10% under the most mild disease scenarios ($R_0 = 1.65$; HR = 0.4%); seven of these were located in Southwestern Ontario. With respect to ICU demand, peak demand exceeded expected bed availability in all no-intervention scenarios except Montreal, Quebec, regardless of disease severity; the greatest strain is expected in Southwestern Ontario and British Columbia, while the Maritime, Prairie and Quebec CMAs appear to be at lower risk. From **Figure 12** and **Figure 13**, we suggest that the ability to accommodate surges in patient demand, even in the absence of vaccination, can be predicted by an acute-care and ICU-bed capacity threshold of 15/10,000 and 3/10,000, respectively. In summary, though patient demand for hospital beds may rarely exceed *total capacity*, in many cases likely bed *availability* was exceeded, suggesting that additional surge planning measures — such as triage and repurposing of beds — may be required

Inter-wave vaccination was found to be very effective, suggesting that a combination of natural immunity from first-wave infection and conferred immunity from receipt of an effective vaccine may contribute to a substantial protective herd effect. Under scenarios with 25% pre-vaccination, no CMA experienced a peak acute-care hospital demand above 6.4% of capacity (Brantford, Ontario) under the most severe disease assumptions ($R_0 = 1.80$; HR = 1.0%). While pre-vaccination was able to protect ICU-resource adequacy under mild disease assumptions, 7–8 CMAs experienced peak demand above 10% of capacity under moderate disease assumptions, and 16 exceeded 10% of capacity under severe disease assumptions. This points to the need for the early

identification of novel viral strains, the rapid development and distribution of pandemic vaccines and targeting critical care surge planning, particularly in areas less able to accommodate surges in patient demand.

Demographic characteristics had some weak associations with predicted pandemic burden. These included risk increases associated with the proportion of adults and symptomatic cases ($R = 0.3185$, $r^2 = 0.1014$), the proportion of infants and number of deaths ($R = 0.3558$, $r^2 = 0.1266$) and the overall protective effect of a higher proportion of seniors. We found much stronger correlations between overall acute-care and ICU bed capacity and peak demand. This suggests that the supply-side, health system factors will be much more important in determining the ability to accommodate surges in patient demand than will characteristics of the community itself.

Our findings suggest that vaccine distribution strategies could benefit from prioritization of metropolitan areas with reduced acute-care and ICU-bed capacity. This research builds upon the existing research base in a coherent manner. A modelling study of Hamilton, Ontario, predicted an illness attack rate of 34.1% in the absence of any interventions [157]; we predicted a similar rate of 31.5%. An assessment of pandemic vaccination in the United States mirrored our findings of a significantly protective effect of vaccination that decreased with increasing influenza transmissibility [313]. Finally, another modelling study predicted Canadian ICU and ventilator shortages for attack rates above 20–25%, concluding that vaccination could significantly reduce ventilator demand [339]. We extend this analysis by broadening the range of health-outcome measures, conducting metropolitan rather than provincial analyses and examining a second-wave pandemic when pandemic vaccination is realistically going to be available.

The present study is subject to certain limitations. First, we do not account for the protective effect of other interventions that could be implemented, including antiviral treatment and

prophylaxis, voluntary isolation and personal protective measures. As a result, we have likely overestimated the actual burden that would arise from a second-wave pandemic; this was done in an effort to identify high-risk areas that would most benefit from early vaccine distribution, with all else being equal.

Second, we do not consider the ethical implications of targeted resource allocation, as this was considered to be outside the scope of a paper focusing on the practical implications of vaccine distribution decisions. It must, however, be considered as planning for the next pandemic proceeds.

Third, our approach to estimating ICU capacity in Quebec as a proportion of total bed capacity may have overestimated critical-care capacity in the province. Indeed, peak acute-care demand was disproportionately higher in Quebec CMAs, relative to ICU demand, and more reliable estimates of capacity are needed. We also base our modelling assumptions related to movement through the hospital system on data from the mild 2009 H1N1; while lack of available data from earlier pandemics made this a necessary limitation, it may underestimate rates of critical illness and death given hospitalization.

Lastly, we treat each CMA as an independent unit, with no movement between areas; this may have overestimated the burden in smaller CMAs where infected individuals may seek care outside of their region. This possibility is particularly likely in the high-risk areas surrounding Toronto, where a higher density of critical care skills and resources results in referrals of complicated cases from surrounding areas. While this approach ignores the potential value of Local Health Integration Networks, it was chosen to allow assessment of individual CMA vulnerability. We also did not scale social contact rates according to variance in population density across CMAs, as this relationship is still poorly understood and difficult to quantify reliably [390]. In addition, contact rates saturate at higher population densities, and our focus on urban areas should prevent undue

bias from low population density [390]. Instead, we included a transmission parameter based upon the proportion of infected individuals across the entire population; this would decrease transmission risk in high-population city centers similar to scaling contact rates.

Despite these limitations, the present study constitutes an informative evaluation of the differential preparedness of Canadian hospital systems to accommodate surges in patient demand during a second-wave influenza pandemic. We highlight high-risk areas in need of priority vaccine distribution, and suggest that supply-side health system profiles are the strongest determinant of pandemic vulnerability.

6.5 Conclusion

This study provides important insights into Canadian pandemic preparedness, employing the InFluNet model to evaluate potential burdens, assess preparedness, and identify predictive factors across the 33 Canadian Census Metropolitan Areas. Our analysis suggests that health systems in Southwestern Ontario and British Columbia are at greatest risk of being stressed by surges in patient demand, while areas in the Quebec, the Maritimes and Prairie provinces are better able to accommodate these increases. Inter-wave vaccination was very effective in mitigating these threats, even under severe disease assumptions. Hospital capacity was a strong predictor of pandemic-associated pressures, while demographic characteristics had only mild correlations. Our study emphasizes the need for targeted early vaccine distribution to high-risk individuals and areas and points to the need for continued pandemic preparedness and surge capacity planning.

Chapter 7: Applying principles of risk decision-making to inform pandemic influenza preparedness and response policy

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Publication Status Information

This manuscript has been submitted to *Microbial Risk Analysis*, where it is currently under review.

Abstract

Influenza pandemics have occurred four times in the past one hundred years, resulting in severe illness, hospitalizations and death amongst millions of people. Pandemics can also have serious socioeconomic consequences that disproportionately affect certain population groups. As there is likely to be little time between pandemic virus emergence and global transmission, effective and ethical pandemic preparedness is crucial.

We critically review the most recent Canadian and Ontario pandemic influenza plans, acknowledging that both are currently under revision. Using the principles of public health ethics and risk management, we assess potential avenues for improved pandemic preparedness. In particular, we consider the tensions and trade-offs between different ethical and risk management approaches. Drawing on a taxonomy of regulatory, economic, advisory, community and technological risk management options, we propose intervention strategies at the intersection of ethical and effective risk management practice.

7.1 Introduction

Influenza infection is caused by an RNA virus which is easily transmitted, leading to annual epidemics of seasonal influenza around the globe [249]. The clinical spectrum of infection ranges from mild respiratory and systemic symptoms to severe lower respiratory, neurological or systemic illness resulting in hospitalization and death. In otherwise healthy people, typical infection is self-limiting and mild in nature [292]. However, influenza is currently the most deadly vaccine-preventable disease in North America [13].

Annually, influenza undergoes *antigenic* drift, resulting in a slightly modified virus to which there is residual immunity within the population. Rarely, influenza viruses can undergo an

antigenic shift, forming a new viral genotype to which humans possess little or no immunity. If this *shifted* virus is efficiently able to transmit between humans and cause significant disease, a global influenza pandemic may occur. This has occurred four times in the past one hundred years. The combined health burden of the 1918 (H1N1) Spanish flu, 1957 (H2N2) Asian flu, 1968 (H3N2) Hong Kong flu and 2009 (H1N1) Swine flu amounts to tens of millions of infections, hospitalizations and deaths [249]. Even the most recent pandemic in 2009 — recognized now as a mild one — is estimated to have resulted in as many as 575,400 global deaths in the first twelve months alone [148]. Increasing population density, international travel and viral diversity raise concerns of the possible outbreak of a new influenza pandemic in the near future [249].

Pandemic influenza can also have serious economic and social consequences. In Canada, worker absenteeism during the 2009 pandemic reached a peak of 9% during the month of November, although this was lower than the peak worker absenteeism of 20–25% expected by Public Health Agency of Canada [391, 392]. Total costs associated with the Canadian 2009 pandemic experience have been estimated at approximately CAD $2 billion; direct healthcare costs only accounted for approximately $200 million of this [152].

There is a well-documented social gradient of risk with respect to influenza exposure and the experience of adverse outcomes. A literature review of the social determinants of influenza risk reported increased vulnerability among those who were low-income, housing insecure, racial or ethnic minorities, illiterate or of lower educational status, employment insecure or pregnant, as well as those who had limited access to healthcare [393]. In Canada, the need for enhanced targeting of Indigenous groups, migrant workers and immigrants — all of whom tend to be over-represented in terms of influenza hospitalization — has been noted [28, 394]. In developing policy

recommendations, it is essential to consider these high-risk groups, in order to avoid an unequal and unfair allocation of resources for protection and treatment.

Age is an important risk factor, with the elderly and the very young tending to be at greater risk from seasonal influenza [395, 396]. Pandemic strains, however, typically result in a proportional shift of the health burden towards younger age groups [249]. During the Canadian 2009 H1N1 pandemic, for example, 70% of deaths were in those under 65 years old [397]. This can complicate assessment of high-risk age groups for prioritization in intervention design.

The need for effective pandemic preparedness policy has been noted by federal and provincial governments alike, in light of the fact that that there will be little response time between the emergence of a new pandemic strain and its spread into Canada [398, 399]. Current policies recognize the need for an inter-sectoral, "whole-of-society" approach to pandemic preparedness and response [398]. Identified areas of concern regarding pandemic response capability in Canada include the ability of health systems to accommodate increases in patient demand and maintain adequate supplies of consumables such as vaccines, antivirals and protective equipment [182, 183, 400]. Failure to meet these challenges could lead to the disruption of essential health and other services, which in turn could have a wide range of negative health, economic and social consequences [355].

Given these challenges, it is important that policy planning be based on best practices, as informed by the related fields of public health ethics (PHE) and risk decision-making (RDM). While national and provincial plans assert that they are anchored in these fields, there is little explicit discussion of how the principles of PHE and RDM inform specific intervention strategies,

and even less of the tensions and trade-offs that arise from the differential valuation of particular principles. This research aims to fill this knowledge gap.

In subsequent sections, we review existing national and provincial pandemic response plans, examining how PHE and RDM principles might reinforce or alter current practice and leveraging this discussion to inform the proposal of specific intervention strategies. Specifically, we review the national *Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector* and the provincial *Ontario Health Plan for an Influenza Pandemic* [398, 399]. The Ontario provincial plan was chosen for three reasons: Ontario is the most populated province in Canada; the plan is in its final iteration, and is currently undergoing revision to become the Ontario Influenza Response Plan; and a recent modelling study identified Ontario as the province most vulnerable to influenza-associated surges in patient demand [401].

We draw on the ethical framework of principlism, which promotes principles of justice, autonomy, beneficence and non-malfeasance, to examine collective rights as they relate to utility, equity, proportionality and reciprocity. This is complemented by an analysis of how the ten principles of RDM — elaborated in past publications [402, 403] and summarized in **Table 37** — provide insight for effective pandemic preparedness and response strategy development. We identify areas of agreement and of tensions in order to propose ways in which future plans may better incorporate these principles to advance ethical and efficient pandemic policy. We propose specific recommendations across the taxonomy of risk management interventions proposed in previous publications, including regulatory, economic, advisory, community and technological measures [404, 405].

Table 37. Ten principles of risk decision-making [402, 403].

Principle	Definition
1. Risk-based	Allocate resources to optimize return on investment
2. Precautionary principle	In presence of serious threat, act even under situations of substantial uncertainty
3. Balance benefits and risks	In evaluating risk management decisions, evaluate trade-offs in benefits and risks
4. Cost-effectiveness	Seek least cost solution to reduce risk by a given amount
5. Acceptable risk	Accept some level of risk remaining after appropriate management response
6. Zero risk	Seek to entirely eliminate risk
7. Equity	Ensure fair outcomes through an equal distribution of benefits and burdens
8. Stakeholder engagement	Foster opportunities for autonomous participation in decision-making
9. Transparency	Provide full and honest information disclosure to support informed decisions
10. Flexibility	Policies should be flexible to incorporation of new evidence as it becomes available

7.2 Current policies

7.2.1 Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector (CPIP)

CPIP has two primary objectives: to minimize morbidity and mortality and to avoid social disruption resulting from an influenza pandemic [398]. Designed as a guidance document to inform and support response activities of provincial and territorial governments, CPIP recognizes that much of the scope of pandemic response is outside of federal jurisdiction. However, it outlines an inter-sectoral risk management approach to inform provincial and territorial pandemic response. CPIP has been in place since 2004 and is reviewed and updated periodically. This emphasis on RDM was added in the most recent iteration of the plan, with the introduction of impact assessment, pandemic severity scenarios and response triggers [398].

The plan identifies the need for ethical, equitable and fair decision-making as it relates to the allocation of limited resources such as pandemic vaccine, antiviral medications and hospital resources [398]. Asserting that the determination of equitable allocation will be context-dependent, it clarifies that a focus on collective well-being should take precedence over a narrower clinical focus on individual interests. Other important ethical principles discussed are those of reciprocity and proportionality, discussed in detail in **Section 3.1**, though there is little discussion of the practical implications of adhering to these principles.

CPIP mentions several important principles of RDM, including transparency, inclusivity and accountability [398]. It supports the iterative "RACE" framework for risk management: recognize, assess, control and evaluate. Other guiding principles discussed include evidence-based decision-making and the precautionary approach; however, there is little discussion of when employing these opposing strategies would be most appropriate. The plan highlights the importance of the effective use of existing surveillance systems, and identifies a gap in the use of mathematical modelling of pandemic flu outbreaks to inform decision-making.

Identified challenges in responding to vulnerable populations include the high provincial disparity in the rural population proportion [406], the high percentage of Indigenous peoples [407] and the high number of recent immigrants in Canada [408]. Vulnerable groups are more likely to face challenges in adhering to certain public health recommendations — such as voluntary isolation and hygienic practices — as a result of language and economic barriers [409]. They may also be less willing and able to access health services. CPIP recognizes that these populations could be marginalized if intervention strategies seek to maximize their reach among the general population, but stops short of proposing targeted strategies for vulnerable and marginalized groups [398].

A government review of Canadian performance during the 2009 H1N1 pandemic found the response to be satisfactory [169]. CPIP was credited with effective stockpiling and distribution of vaccines and antivirals and with contributing to a reduction in the overall pandemic burden. Identified weaknesses included a lack of flexibility, scalability and responsiveness to emerging knowledge and pandemic data as it became available [169]. Recommendations included increased testing of pandemic plans, more effective communication messaging, scaled up data collection and analysis and an increased focus on seasonal influenza preparedness, to be ramped up during a pandemic [169]. The inclusion of mathematical modelling insights was seen as key to informing the Canadian pandemic response; this constitutes an important bridge which must be further developed moving forward, particularly as it relates to determination of optimal resource allocation [410]. Modelling can inform daily progression of the pandemic, resource-requirement estimates and optimal intervention strategies in situations of uncertainty.

7.2.2 Ontario Health Plan for an Influenza Pandemic (OHPIP)

Originally released in 2004, OHPIP was in part a reaction to challenges noted in the Toronto response to the 2002 SARS outbreak [169, 399]. In its next iteration, OHPIP will be merged into the Ontario Influenza Response Plan (OIRP), an inter-sectoral, disease-specific response document that is currently under development. OIRP will shift the emphasis from pandemic preparedness to the development of a more effective seasonal influenza response, which can be scaled up during a pandemic [399]. As such, this is an opportune time to assess the strengths and limitations of OHPIP. We do not evaluate in detail the assumption that pandemic challenges will mirror those of seasonal influenza, but do note that flexibility will be crucial to the success of such an approach.

OHPIP shares the objectives outlined by CPIP: minimize illness, death and societal disruption [398, 399]. With a focus on linking response activities to pandemic severity, OHPIP adheres to the

precautionary principle in the absence of reliable epidemiological data [399]. Though it also identifies evidence-based decision-making as a guiding principle, it does not clarify when or if the latter approach supersedes the former. OHPIP supports health equity, but does not include an ethical framework to support decision-making; the OIRP will include an ethical component, though it is unclear to what extent this will inform the navigation of ethical tensions and resource allocation trade-offs.

OHPIP considers pandemic severity as a product of transmissibility and clinical severity. It embodies the RDM principle of transparent stakeholder engagement. In the new OIRP, the Ontario Ministry of Health and Long-term Care (MOHLTC) will seek to improve communication strategies, especially as they relate to vulnerable populations, social media and health systems [399]. Identified gap areas include a lack of substantive discussion regarding the role of predictive modelling to improve risk-based preparedness efforts through surveillance, cost-effectiveness assessment and identification of vulnerable health systems [399].

The province of Ontario must accommodate vulnerable groups similar to those identified in CPIP; these include rural populations, Indigenous peoples and immigrants. OHPIP also recognises those with substance addiction, the homeless and those without a primary care provider as vulnerable populations [399]. The focus throughout this guidance is on accessing hard-to-reach populations and protecting essential service delivery in emergency situations.

In Ontario, public health functions are performed by municipal or county boards appointed by municipalities and provinces [169]. In the aftermath of the 2009 H1N1 pandemic, representatives were asked to evaluate Ontario's response. Criticisms included inadequate distribution of vaccine supplies to meet demand and barriers to inter-sectoral and inter-jurisdictional collaboration [169]. A key point of focus was the need for a more flexible, proportionate response that could be scaled

up and down as the pandemic evolved; this would support principle-based planning that avoids overreliance on planning assumptions that may prove to be inaccurate.

7.3 Principle-based approaches

7.3.1 Public health ethics

CPIP proposes that, in a pandemic emergency, collective rights should take priority over individual ones, promoting the principles of utility (maximizing benefit), proportionality (measured response), reciprocity (assisting individuals and community in discharge of duties) and equity and distributive justice (fair distribution of resources, benefits and burdens) [398]. OHPIP adopts similar principles, supplementing them with principles of individual liberty, privacy and duty to provide care [411]. Both plans support the building of trust and solidarity [399, 412]. However, these principles do not in themselves constitute a framework, and provide little procedural or strategic insight.

In this section we examine pandemic policy within the classic ethical framework of principlism, based on four keys to ethical public health practice: justice, beneficence, non-malfeasance and autonomy [413]. It has been argued that autonomy and justice should be the central focus, as any infringement on them would compromise the principles of beneficence and non-malfeasance [413]. If we consider beneficence to include the collective good of the community, and non-malfeasance the avoidance of infringement on social and political values, it becomes evident that violating justice or autonomy would compromise both of these ideals. Following this argument, we will suggest that prioritizing justice and autonomy should guide our assessments of ethical pandemic policy. We therefore focus on these two principles, and discuss

beneficence and non-malfeasance within the contexts of justice, autonomy and — in the subsequent section — risk management.

The strength of such a principle-based ethical framework is its simplicity and readiness for application to practice. However, the suitability of principlism for the assessment of ethics in public health has been called into question, as it is more traditionally viewed in the context of individualistic clinical ethics [413]. Upshur, for example, sought to shift the discussion of public health ethics to four more collective principles: the harm principle, least restrictive means principle, reciprocity principle and transparency principle [414]. The harm principle, as set out by John Stuart Mill, asserts that the only ethical infringement upon individual liberty is to prevent harm to others [415]. The least restrictive means principle proposes that more coercive methods should only be initiated once less severe interventions have failed [416]. The reciprocity principle assigns responsibility to social organizations to assist individuals and communities in performing their ethical duties [417]. The transparency principle holds that all stakeholders should be involved in an open decision-making process.

We do not view this discussion as indicative that principlism is inappropriate, but rather as an extension of its principles to the collective ideals of justice and autonomy, allowing their application to community settings. We therefore conclude this section with a review of these two pillars of principlism and how they relate to those presented by Upshur and by CPIP.

7.3.1.1 Justice

Justice requires an assessment of what constitutes an appropriate distribution of limited resources. In conventional medical ethics, "need" is often viewed as the most important factor, where there is a moral imperative to treat as many people as possible [418]. This becomes more

complicated in emergency situations, where resources are limited and may have to be distributed preferentially. For example, the modelling studies presented in **Chapters 5** and **6** suggest that pandemic-associated increases in patient demand could require 7.5–19.5% of acute-care bed capacity in Canada and over 100% of ICU capacity, even under moderate disease assumptions. Given already high bed occupancy rates, this would likely necessitate a diversion of hospital resources, causing service disruption. The "priority" argument would support acting in a utilitarian way so as to maximize the number of lives saved, even if such an approach would mean a disruption of services for other groups or diseases [418]. This is reflected in the primary CPIP and OHPIP objectives, and supports triage of patients to prioritize those most likely to recover within the shortest amount of time. It could also be invoked to support preferential investment in urban settings, which are likely to experience more transmission than rural areas.

Criticisms of the priority argument could be based upon two other ethical arguments. The Kantian "equality argument" states that all lives should be considered of equal value, and prioritizing certain individuals is unjust [418]. The Rawlsian theory of justice proposes that priority should be given to those that are worst off [419]. Both arguments are consistent with an approach that prioritizes saving lives, but they shift the discussion towards the prioritization of life-saving treatments over prevention, despite the fact that prevention may save more lives overall. They also suggest that those at increased risk of adverse health outcomes may have a stronger claim to resources than those more likely to experience uncomplicated infection, but that preference should not be given based upon income level or location alone. This has implications for the prioritization of therapeutic treatment over prophylaxis, and limiting access to critical care to those who require mechanical ventilation. Such trade-offs highlight the tensions that may arise between utility and equity in emergency situations. These principles also refocus the discussion of resource allocation

and triage decisions upon the implications of treatment for chances of survival and future quality of life, and recognizes as unjust the consideration of other intrinsic characteristics such as age, gender, race, religion, socioeconomic status, geographic location or existence of a disability [420].

Another important issue regarding the distribution of limited resources involves whether preferential access to protective measures should be granted to healthcare workers; this relates closely to the reciprocity principle, introduced above. CPIP supports the reciprocity principle, wherein social organizations like public health systems are morally responsible to support those who might incur risks as a result of the discharge of their responsibilities. In the context of pandemic influenza, this is most commonly associated with giving the highest priority to healthcare workers, who may be at increased risk of infection. The "responsibility argument" might advocate against this, suggesting that such an approach fails to hold people accountable for their actions, as proper adherence to personal protective protocols should adequately protect healthcare workers from risks in excess of those in the general population [418]. Utilitarian views, however, are likely to support the reciprocity principle in this case, as protection of healthcare workers has the indirect benefit of limiting transmission among their patients — who may be at increased risk of complications — and minimizing the risk of health service disruption as a result of worker absenteeism. It should also be noted that healthcare providers are at risk of infection in home and community settings, where they are unlikely to be in protective equipment, and therefore their protection becomes an important component of promoting service continuity.

7.3.1.2 Autonomy

Autonomy involves giving individuals maximum liberty to make decisions that will affect their health. In conventional medical ethics the focus tends to be on a patient or study subject, supporting

procedures such as informed consent. The public health transparency principle, advocating for open stakeholder engagement, is a logical extension of autonomy [414]. The harm and least restrictive means principles similarly support autonomy, recognizing a duty to minimize infringement upon individual liberty. In the context of current pandemic plans, the principle of proportionality supports tailoring the intensity of intervention strategies to the severity of the pandemic scenario, avoiding mandatory or costly interventions as much as possible.

These principles are relevant to communication strategies and mandatory public health measures — such as school closure, workplace closure or quarantine — initiated during influenza pandemics. Open communication is crucial to fostering public trust, uptake of public health recommendations and appropriate resource use [421]. Strategies must also avoid exclusively addressing the disease, to the exclusion of population considerations. Such a paternalistic approach can undermine communication efforts, obstructing achievement of optimal health outcomes, especially among populations that are already marginalized [422]. Some areas, such as Toronto, Ontario, are developing all-hazards communication and response strategies specific to particular vulnerable groups; such an effort would support the transparency principle in a way that is also likely to advance justice, beneficence and non-malfeasance [423, 424].

The harm and least restrictive means principles may be of particular relevance to regulations surrounding antiviral prophylaxis. Increasing access to antiviral prophylaxis could deplete stockpiled drug availability for treatment, thereby limiting access to treatment options among infected individuals in the future. The potential benefit of containing an early-stage pandemic must also be weighed against the ethical obligation to ensure that drug resistance does not emerge. Contact tracing and distribution of prophylactics may also occur disproportionately in easy-to-access population groups, such as healthcare workers, which may lead to a further service access

imbalance among vulnerable groups. In this scenario, the harm principle and least restrictive means principle seem to support opposing strategies, wherein the harm principle supports restriction of individual access to prophylaxis; in contrast, the least restrictive means principle might oppose such infringement upon individual liberty unless absolutely necessary. However, the moral imperative to protect and save as many lives as possible, even if this results in some limitation of individual liberties, suggests that individuals should not be allowed to develop personal stockpiles of protective consumables.

7.3.2 Risk decision-making principles

Of the ten principles of RDM, four relate closely to ethical principles discussed in the previous section. Equity, stakeholder engagement, transparency and flexibility reflect the ethical principles of justice, autonomy and proportionality that are important to almost any public health intervention. As such, these are only discussed briefly, given the more thorough analysis in the previous section. We focus our discussion on the tensions between three pairs of related RDM principles as they relate to pandemic policy: risk-based decision-making and the precautionary principle; risk-benefit and cost-effectiveness; and acceptable risk and zero risk tolerance.

7.3.2.1 Risk-based decision-making and the precautionary principle

Risk-based decision-making supports the allocation of resources to maximize risk reduction for a given investment, while the precautionary principle supports action to mitigate a serious threat, even under situations of uncertainty [402]. As influenza pandemics are potentially catastrophic events that are inherently uncertain — where the disease characteristics cannot be known in advance of emergence — plans tend to support a precautionary approach, particularly in the early stages of an outbreak [398, 399]. This raises questions, however, about the point at which

emerging data are sufficient to support a transition to risk-based decision-making, and presents challenges in scaling community and health system responses to pandemic severity. Indeed, a key challenge identified during the 2009 H1N1 pandemic was in adjusting response efforts to pandemic severity as the pandemic developed and dissipated [169].

While high uncertainty and potential consequences justify the precautionary principle in the planning and early stages of a pandemic, it is crucial to invoke risk-based decision-making as early as possible. This could involve the expanded adoption of inter-pandemic mathematical modelling, as well as scaling up surveillance efforts to capitalize on emerging technologies. Planners must acknowledge that pandemic assumptions are likely to be inaccurate, and that an over-reliance on inaccurate assumptions could result in disproportionate response efforts. A principle-based planning and response mandate would facilitate flexibility and the incorporation of empirical data as it became available.

7.3.2.2 Risk-benefit and cost-effectiveness

Both the risk-benefit and cost-effectiveness principles seek to evaluate interventions across a standardized calculation of benefits and costs. The risk-benefit principle advocates for the evaluation of trade-offs in intervention strategies, suggesting that efforts should be made to maximize benefits and minimize hazards. The cost-effectiveness principle advocates for pursuing the least-cost intervention to reduce risk by a given amount [425]. These principles are often prioritized in pandemic influenza preparedness planning, where resources are likely to become scarce and many lives are at stake; this is evident in the utilitarian primary objective to save as many lives as possible [398].

However, an over-reliance on such an economical approach can be problematic in a number of ways. First, if we accept that health outcomes can be aggregated and calculated in economic terms, we face challenges in assigning values to given outcomes, particularly mortality. Some government valuations of life have ranged between six and nine million dollars (USD) [373]. Other analyses assign a value for each life-year lost (LYL); in Canada, CAD$ 50,000 per life-year saved is the commonly accepted threshold for an effective intervention [372]. Second, once we accept that life can be measured in economic terms, there is a space to argue that the dire needs of a few can be outweighed by the smaller needs of many, or by the economic cost of intervening [422]. This can lead to a prioritization of mass prevention, particularly among younger age groups in urban locations, where there is the potential to increase life-years saved. While this is an important component of pandemic response, it would be unethical to scale prevention to an extent that it disrupts treatment-side service delivery, or prevention services in hard-to-reach populations. Lastly, the argument can be made that non-health risks and benefits should be excluded from risk-benefit analysis, and instead only included in cost-effectiveness analyses of intervention strategies with similar risk-benefit ratios and equity impacts [422].

7.3.2.3 Acceptable risk and zero risk

The principle of acceptable risk acknowledges that the complete elimination of risk may not be feasible, and that some will remain even after the appropriate implementation of intervention strategies; the zero risk principle supports efforts to eradicate risk entirely [426, 427]. In the context of pandemic influenza, few would suggest that zero risk is an attainable goal, as some level of residual risk seems unavoidable. This is rarely explicitly stated, however, and levels of acceptable risk in pandemic situations are unclear.

Public and organizational risk acceptability will have important implications for early containment efforts and the thresholds for triggering emergency measures such as school and work closure and quarantine protocols. It is also of relevance to worker absenteeism, which can exacerbate pandemic-related economic burden and essential service disruption [183, 296, 428]. Open communication strategies can foster public trust, facilitate effective emergency protocols, and reduce worker absenteeism. Risk management strategies should not pursue a "zero risk" strategy. Rather, an important component of preparedness should be communication efforts to support knowledge and acceptance of some form of unavoidable risk level.

7.3.2.4 Equity, stakeholder engagement, transparency and flexibility

Equity in risk management refers to the promotion of a fair and proportionate distribution of risks, benefits and costs. Stakeholder engagement and transparency acknowledge the importance of the active involvement of — and open communication with — interested parties. These are essential to policy decisions in democratic societies, and can improve risk reduction outcomes by promoting community trust and adherence with risk management recommendations. Flexibility centres upon the ability to incorporate new risk information to inform decision-making. These four principles can be viewed as the ethical foundation of RDM, and are important considerations for almost all risk reduction efforts. These principles relate closely to the ethical principles of justice, autonomy and proportionality discussed in the previous section. We will therefore refrain from restating their policy implications and trade-offs with other principles, and instead emphasize the congruence between principles of PHE and RDM. Principles from both domains are incorporated into our strategic recommendations below.

7.4 Strategic Recommendations

The previous sections have set out examples of pandemic plans in Canada, presenting principles of PHE and RDM that should inform strategic and procedural development and updating of these plans. Below, we review how these principles could direct ethical and effective strategies across a range of public health interventions.

7.4.1 Regulatory Interventions

Principles of autonomy, proportionality and least restrictive means would support efforts to minimize regulatory interventions, employing them only where absolutely necessary. Whereas government or international health regulations, such as surveillance reporting and adherence to best practices, are important components of pandemic preparedness, regulations on individual citizens should be avoided where possible. Currently, in low-transmissibility or low-severity pandemic scenarios, the only mandatory measure proposed by OHPIP is contact tracing and case management; only in a pandemic that is both highly transmissible and clinically severe is it suggested that other mandatory measures may be required [399].

Taken together, this would suggest that interventions such as mandatory quarantine and school closure should be avoided unless the pandemic is extremely severe and they are accompanied by other control measures. There is little public support for these interventions, and a systematic review of pandemics to date found little evidence of significant impact or cost-effectiveness [355, 429-431]. Similarly, the modelling study presented in **Chapter 5** found that voluntary isolation of infected individuals is more cost-effective, and does not infringe upon individual liberty. Most interventions should be focused across the other four categories. However, there are two key issues where regulation could promote pandemic preparedness.

First, while some might suggest that antivirals be made available without prescriptions during influenza pandemics, in order to reduce patient inflow and transmission in healthcare settings, this should be avoided as it could lead to personal stockpiling, over-reliance on general antiviral prophylaxis and an accumulation of drug-resistant viral strains. Instead, prescriptions should be available via pharmacists and telemedicine, which supports risk reduction and principles of justice and non-malfeasance. Where antiviral prophylaxis is implemented, thresholds should be established *a priori* to determine the groups that will be subject to contact tracing and prophylaxis, and at what point this is to be cut off, with an emphasis on preserving stockpiles for case treatment throughout multiple waves.

Second, regulations based upon the reciprocity principle must be considered based upon quantifiable risk. While ethical principles support the provision of protection to healthcare workers that may be at increased risk, there is a need to base this on empirical data. In the past, those in direct contact with patients — such as healthcare providers and room-cleaning staff — have been prioritized. However, little is known about how the risk levels of these groups differ from those of other healthcare-associated staff (such as administrative staff) or the general public, which may not have equivalent access to protective equipment [422]. Measures to protect healthcare workers are needed, but should be grounded in risk, cost-effectiveness and equity assessments. Meanwhile, increasing knowledge of existing emergency plans has been identified as a gap in current plans, with one study finding a need for more training and information for Canadian healthcare workers [432].

7.4.2 Economic Interventions

Economic interventions are a critical component of any plan, as resources are likely to be limited in pandemic situations and the potential economic burden is high. Cost-effective

interventions such as vaccination, antiviral use, personal protective measures and voluntary isolation should be promoted over school closure, community-contact reduction and quarantine, which can dramatically increase economic burden with relatively little impact on transmission or overall pandemic burden [355, 433].

Economic interventions should seek to reduce the economic barriers to intervention uptake. This is important to support principles of equity, distributive justice and beneficence, for lack of resource access can influence disease exposure, capacity to protect oneself from exposure and capacity to adhere to guidelines during infection. Lower income individuals, for example, may not be able to comply with voluntary isolation guidelines that suggest staying home from work, which could lead to lost income and job insecurity [434, 435].

The same is true for individuals that may be required to stay home to care for a sick family member or a child sent home due to school closure [436, 437]. While business continuity plans are not explicitly addressed in CPIP or OHPIP, further consideration of economic interventions to support flexible work patterns is needed; these may include encouraging employers to support policies such as telecommuting or special pay subsidies for those required to miss work.

Similar findings of low vaccine coverage among low-income groups suggest a possible benefit of economic incentives among high-risk groups. One study found that social assistance and seniors' benefits increased vaccination rates among low-income groups during the Canadian 2009 H1N1 experience [438]. Vaccination and voluntary isolation are among the most effective and cost-effective interventions available, with high benefit–risk ratios; economic interventions have an important role in supporting equitable expansion of their adherence [355].

7.4.3 Advisory Interventions

Advisory interventions provide accurate and timely information about health risks and how to avoid them, as well as justifications for policy decisions [404]. Thus, advisory interventions will centre upon effective, transparent and equitable communication messaging strategies. A crucial component of these efforts will be the engagement of vulnerable groups. Efforts should be made to ensure that all groups — especially those that are high-risk or hard-to-reach — receive information on pandemic risks and available interventions [439]. This could involve working with vulnerable groups to collect specialized data, explicitly addressing population concerns (such as vaccine hesitancy) in public health messaging and the development of multi-media campaign platforms that are accessible to people of different languages, cultures and literacy levels [439]. While general public health messaging is important and may reach more individuals, targeting of vulnerable groups is crucial to supporting trust, autonomy and uptake among populations that may be at increased risk of developing complicated infections, thereby supporting equitable and effective risk reduction.

7.4.4 Community Interventions

Community interventions involve the empowerment of citizens to participate in priority-setting, decision-making, planning and implementation [404]. Successful and ethical advisory interventions require bidirectional communication, and active stakeholder engagement is crucial to supporting uptake and autonomy among vulnerable groups. Engaging community leaders and organizations — as well as members of vulnerable and marginalized populations — builds trust and credibility among communities that are sometimes suspicious of healthcare professionals [440]. Key components of planning in this area could include the involvement of faith- and

community-based organizations in plans to disseminate information, both to public health organizations and to their service population [439]. Such organizations could advise planners on effective communication strategies, act as education and service provision centers, and assist in surveillance efforts. Such efforts would support autonomy, uptake, local ownership and cost-effective health protection campaigns.

7.4.5 Technological Interventions

Technological interventions rely on innovation to improve response capacity and flexibility [404]. With respect to pandemic influenza, this may be most relevant to considerations of what kinds of evidence are incorporated into surveillance and decision-making processes. First, the popularity of social media holds promise for an expansion of real-time surveillance efforts. Second, mathematical modelling, in conjunction with a principle-based approach, can be useful in providing a proxy for risk-based decision-making in the absence of reliable epidemiological data. The continuous development of complex and technologically advanced models can facilitate flexibility and responsiveness of intervention strategies as new data emerge. Lastly, advances in hospital electronic records and regional partnership could help inter-hospital collaboration to maximize resource use efficiency and promote regional hospital-resource adequacy. Another important consideration is the development, acceleration and then maintenance of vaccine manufacturing technology. This has important implications for the speed of deployment and population coverage achieved in the early stages of a pandemic, and should be encouraged alongside efforts to promote more equitable international vaccine distribution. It should be noted that new technologies may not always be supportive of ethical and risk management principles, raising new questions and trade-offs. It will be important to ensure that technological strategies

adhere to public health and risk management principles, and that there is a space for continued discussion of what and how principles should be prioritized in new contexts.

7.5 Conclusion

In the present paper, we consider Canadian pandemic preparedness through the lenses of public health ethics and risk management. While national and provincial plans make reference to a range of principles, there is limited discussion of how these might inform strategic and procedural directions. As plans are currently being revised and updated, this work presents a timely discussion of the tensions between different strategic policy options.

Specifically, we review the *Canadian Pandemic Influenza Plan* and *Ontario Health Plan for an Influenza Pandemic*. We note trade-offs between different principles, but emphasize that there is substantial compatibility between the two domains, and a space for policy interventions positioned at the intersection of ethical and effective risk management practice.

We propose a range of intervention principles and strategies to improve pandemic preparedness. Specific recommendations promote caution in implementing mandatory public health measures, risk-based prioritization of healthcare workers and the uptake of — and capacity to adhere to — pubic health recommendations, particularly among vulnerable groups. Lastly, planners should use caution in rolling out antiviral prophylaxis, and pandemic severity thresholds for discontinuation should be established *a priori*.

Future research should seek to combine empirical data with mathematical modelling to inform risk-based policy decisions, particularly as they relate to thresholds for action, population group

prioritization and resource-planning. There is also a space for deeper consideration of the ethical implications of emerging technology as it applies to pandemic preparedness.

Chapter 8. Synthesis

The goal of this dissertation has been to advance knowledge of, and preparedness for, influenza pandemics. A series of six related articles, prepared for publication in public health journals, has addressed the likely consequences of future influenza pandemics in Canada, assessing the role of mathematical models in preparing for such an event and discussing optimal intervention strategies to mitigate pandemic impacts.

Chapter 2 provides a historical account of the burdens associated with past influenza pandemics, as well as how surveillance, preparedness and response strategies have evolved over time. **Chapters 3** and **4** present the findings of systematic reviews and meta-analyses to quantify the effectiveness of a range of public health measures aimed at interrupting pandemic influenza transmission. **Chapter 5** combines the findings from previous chapters with a review of mathematical modelling methodologies to develop a novel mathematical model, charting the likely health and economic burdens of future influenza pandemics across 192 intervention scenarios. **Chapter 6** extends this analysis by conducting a national-level modelling study, assessing the vulnerability of health systems across all Canadian Census Metropolitan Areas. **Chapter 7** examines the implications of the findings from previous chapters for future practice, through the analytical lenses of public health ethics and risk management. I propose avenues to promote efficient and ethical pandemic preparedness and response across a range of intervention categories.

This concluding chapter seeks to synthesize the findings of this dissertation research, and consider them within their broader context. It begins with a brief summary of research findings (**Section 8.1**). This is followed by a discussion of the implications of research findings within the context of population health research and practice (**Section 8.2**), a critical analysis of the project

as a whole (**Section 8.3**), a brief personal reflection on how my doctoral career has influenced my growth as a researcher (**Section 8.4**), a summary of the knowledge translation strategy (**Section 8.5**) and concluding remarks (**Section 8.6**).

8.1 Summary of findings

This dissertation is made up of six interrelated manuscripts that build upon each other: four chapters reviewed, analyzed and critiqued the existing knowledge base while informing the background, rationale and approach of the two modelling research chapters.

The first review, presented in **Chapter 2**, provides an analysis of the impact of past influenza pandemics, while examining the evolution of our understanding of — and response to — these viruses. This was done as a means of establishing patterns of disease emergence, response and burden. Drawing on international case studies, I argue that pandemic influenza emergence is associated with human development and globalization processes, and highlight the importance of considering outbreaks within the context of shifting global landscapes. While progress in infectious disease prevention, control and treatment has improved our ability to respond to such outbreaks, globalization processes relating to human behaviour, demographics and mobility have increased the threat of pandemic emergence and accelerated global disease transmission.

The second review, presented in **Chapter 3**, provides a systematic review and narrative synthesis of all existing systematic reviews examining the effectiveness of interventions to interrupt pandemic influenza transmission. This was done as an efficient means of digesting a large amount of heterogeneous data in a single review article. Data were collected across five databases (PubMed, Medline, Cochrane, Embase and Cinahl) and the grey literature. While most included reviews were of moderate to high quality, a high degree of statistical heterogeneity precluded meta-analysis. A narrative synthesis suggested that, while pandemic influenza vaccination was effective,

there was insufficient evidence to conclude that antiviral prophylaxis, seasonal influenza cross-protection or a range of non-pharmaceutical strategies would contain pandemic spread when implemented in isolation, pointing to the need for layered intervention strategies.

The third review, presented in **Chapter 4**, provides a systematic review and meta-analysis of the effectiveness of personal protective measures (hand hygiene, facemask use and cough etiquette) in preventing pandemic influenza transmission. This was in response to a knowledge gap noted in the first systematic review and narrative synthesis. A systematic review of primary literature was conducted across five databases (PubMed, Medline, Cochrane, Embase and Cinahl) and the grey literature. Meta-analyses suggested that both hand hygiene and facemask use have provided significant protection during the A(H1N1)pdm pandemic. There was insufficient evidence to draw conclusions on the effectiveness of cough etiquette.

The first original research article, presented in **Chapter 5**, estimates the likely burden of a future influenza pandemic in the Ottawa–Gatineau region across multiple health and economic endpoints. This involved the design and construction of a novel mathematical model, called InFluNet, with data inputs informed by the three review articles presented previously. The potential impact of a future pandemic was modelled under 192 different combinations of pharmaceutical and non-pharmaceutical interventions. While there was substantial variation in pandemic impact across intervention scenarios, findings suggested that the timely implementation of a layered intervention strategy appears likely to protect hospital-resource adequacy in the Ottawa–Gatineau region. However, there is likely to be a substantial economic burden associated with the pandemic, and the uncertain severity of future pandemics necessitates flexibility in preparedness efforts.

The second original research article, presented in **Chapter 6**, extends the analysis presented in **Chapter 5** by assessing the preparedness of health systems across the 33 Canadian Census Metropolitan Areas to accommodate increases in patient demand associated with a second pandemic wave. The aim was to identify vulnerable areas, assess the potential of inter-wave vaccination to mitigate impacts and evaluate the association between demographic and health-system characteristics in order to identify predictors of pandemic consequences and vulnerability. Findings suggest that municipalities in Southwestern Ontario may be least able to accommodate surges in patient demand, and may therefore benefit from preferential access to early vaccine distribution. Inter-wave pandemic vaccination was significantly effective in reducing the burden associated with the second wave of an influenza pandemic, regardless of severity. The strongest predictors of peak acute-care demand and ICU demand were acute-care bed capacity and ICU bed capacity, respectively. Demographic characteristics had weak associations with predicted pandemic consequences.

The sixth paper, presented in **Chapter 7**, provides a policy analysis that synthesizes insights from previous chapters to propose avenues for improvement in Canadian pandemic preparedness and response. Drawing on the tensions and trade-offs in the differential valuation of related principles of public health ethics and risk management, I review pandemic policy within the context of existing national and provincial plans. I leverage insights to recommend policy options across regulatory, economic, advisory, community action and technological interventions, proposing strategies at the intersection of ethical and effective risk management practice. While a comprehensive discussion of the applications of a principle-based approach to pandemic policy is outside the scope of this dissertation, this article contributes to a nuanced discussion of navigating

conflicting principles within contexts of uncertainty and resource scarcity by prioritizing collective principles of justice, autonomy, efficiency and equity.

8.2 Implications within context of population health

This section is intended to situate the results of this dissertation within population health literature, theory and practice. The primary objective of this project was to inform a discussion of the likely consequences of a future pandemic — with a particular focus on health, economic and resource-demand endpoints — alongside an evaluation of optimal intervention strategies. As such, I discuss the implications of findings as they relate to patterns of pandemic emergence and burdens (**Section 8.2.1**), pharmaceutical intervention (**Section 8.2.2**), non-pharmaceutical intervention (**Section 8.2.3**) and hospital planning (**Section 8.2.4**). Within each, I discuss the predictive and evaluative role of mathematical modelling.

In each case, where relevant and appropriate, I contextualize findings within the broader pandemic influenza literature. I also discuss results as they relate to theory; this is done by situating findings within the integrated framework of population health risk assessment, presented in **Figure 14** [404]. At the foundation of this framework is a broad understanding of the determinants of health, broken into three categories: biology and genetics; environment and occupational; and social and behavioral. These categories interact with each other, indicating the complexity of health risk factors. This expanded understanding of health determinants informs risk assessment (Health Risk Science) and management (Health Risk Policy Analysis). In light of these, a broad suite of interventions can be recommended. Such an integrated framework facilitates consideration of population health principles, such as determinants of health and health inequities, within the context of risk assessment and management, helping expand the development of evidence-based health policy. Lastly, I emphasize implications for future research and practice. Consideration is

given to how the results of this dissertation can advance local, provincial and national efforts to support efforts to minimize serious illness, death and societal disruption associated with future pandemics [398, 399].

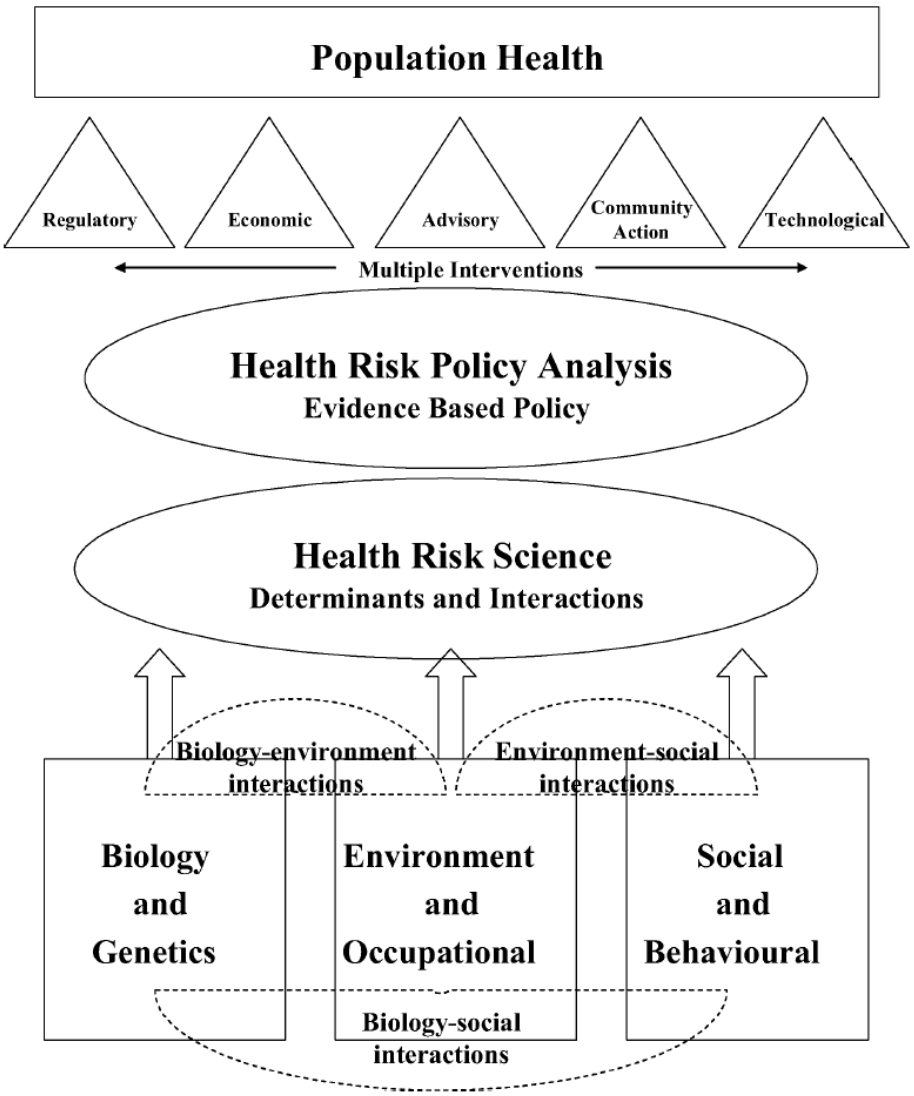


Figure 14. Integrated framework for risk management and population health [404].

8.2.1 Patterns of pandemic emergence and predicted burden

The research presented in this dissertation supports concerns that a more severe pandemic than was experienced in 2009 could have serious health and economic consequences, and that there is a need for improved Canadian pandemic preparedness.

The historical review found that pandemic-associated burden can vary widely, with global pandemic-associated mortality estimates ranging from 151,700–575,400 for the 2009 Swine flu pandemic to 20–50 million for the 1918 Spanish flu pandemic [249]. These figures are supported by data from pandemic literature [54, 64, 73, 77, 78, 148, 149]. Similarly, illness attack rates from modelling studies varied widely depending on disease severity and intervention assumptions. The municipal study (**Chapter 5**) projected illness attack rates for a first-wave pandemic between 8.4% and 53.4%, while the national study of a second-wave pandemic influenza (**Chapter 6**) predicted an average illness attack rate of 23.7–37.2% under assumptions of no intervention, and of 2.5–6.5% under assumptions of 25% inter-wave vaccination. These ranges are large, but tend to fit within commonly accepted expectations for pandemic influenza prevalence in past Canadian modelling studies [157, 330, 441, 442] and North American seroprevalence studies following the A(H1N1)pdm [383, 384]. Andradottir and colleagues, for example, projected an attack rate of 5.4% to 36.8% in a study of Hamilton, Ontario [157].

With respect to hospital-resource adequacy, the Ottawa–Gatineau study found that peak demand ranged from 0.2–13.2% across the spectrum of intervention scenarios, while ICU capacity ranged from 1.1–90.2%; in the national study, peak acute-care and ICU demand ranged from 7.5–19.5% and 39.3–101.8%, respectively, under no intervention scenarios. While comparable data from past studies are scarce, this is lower than one estimate that used FluSurge 2.0 to predict Ontario pandemic influenza-related hospital admissions could peak at 72% of acute-care capacity

and 171% of ICU bed capacity [400]. However, this study, conducted before the 2009 pandemic, does not declare their disease severity assumptions, and included no modelling of interventions or social contact, so it is difficult to compare results.

Lastly, the historical review suggested that economic burden associated with an influenza pandemic could amount to 1–2% of GDP, with a quick recovery after transmission ceases [249]. Media reports in the aftermath of the 2009 pandemic estimated a total cost of CAD $2 billion, though this likely did not include the full range of indirect costs associated with isolation and community intervention [152]. A cost of $2 billion would amount to a per-capita cost of $59.5; our municipal-level study calculated a per-capita cost of $92.8–$1,727.2 across seven intervention scenarios. It should be noted that the higher end of this range was as a result of prolonged school closure, and Canada did not implement school closure during the A(H1N1)pdm. However, this range suggests that previous estimates may undervalue the potential economic burden of future influenza pandemics.

Mathematical models play an important role in predicting and retroactively estimating the burden of influenza pandemics, where much of the transmission process is invisible to more traditional surveillance methods. The results of this dissertation support increased investment in rapid pandemic detection and response to mitigate consequences which may have been underestimated in the past. Influenza modelling should continue to be mainstreamed into policy planning. Future avenues for research include an expansion of predictive and evaluative modelling studies to developing countries, which have to date been understudied in terms of potential pandemic influenza consequences.

The large range of potential consequences suggests that the burden of an influenza pandemic is not determined by disease characteristics alone. Consequences will also depend upon

the ability to address the determinants of health presented at the foundation of **Figure 14**. Biological and genetic determinants relate to the ability to reduce susceptibility and infectivity through pharmaceutical measures; social and behavioural determinants point us towards contact reduction through non-pharmaceutical interventions; and environmental and occupational determinants relate to the ability to maintain essential service continuity. These three issues are discussed in sequence in the following subsections.

8.2.2 Pharmaceutical interventions

In the context of this dissertation, pharmaceutical interventions were considered to include pandemic vaccination, antiviral prophylaxis and antiviral treatment. The systematic review presented in **Chapter 3** found that pandemic influenza vaccination was likely to be significantly beneficial in preventing infection, while there was insufficient evidence to draw conclusions on the effectiveness of antiviral use. Instead, InFluNet estimates of antiviral efficiency were drawn from systematic reviews of regular influenza seasons [204, 231, 357], which were also similar to past pandemic modelling assumptions [232, 324, 335, 336].

While reviews found pandemic vaccination to be significantly effective in mitigating pandemic spread, the concern is that vaccines will not be available in time to impact the first wave of a pandemic [103, 232, 398]. Rather, antivirals and non-pharmaceutical measures may be required to contain transmission until a vaccine becomes available. The value of antivirals is more complicated, as modelling scenarios found that antiviral prophylaxis resulted in larger reductions of all adverse health outcomes and resource demand than did antiviral treatment, and there was little additional impact when modelling prophylaxis and treatment together. However, the ethical principles discussed in **Chapter 7** suggest that there is an ethical imperative to protect antiviral stockpiles for therapeutic use. It should also be noted that the impact of antiviral prophylaxis may

have been overestimated by assuming a large proportion of the population (35%) would receive antiviral prophylaxis early in the outbreak, which may not be feasible. Findings support the conclusions of past research which suggest that distribution of antivirals should prioritize therapeutic use, despite greater disease burden reductions that may be achieved through early mass prophylaxis or a combination of therapeutic and prophylactic distribution [232, 422, 443]. Future research could improve practice in this area by developing a method of determining *a priori* thresholds for the discontinuation of antiviral prophylaxis in order to protect stockpiles for treatment.

Mathematical modelling plays an essential role in improving evidence-based policy analysis. This may be particularly true of pharmaceutical intervention planning, as all measures rely on the effective distribution of consumables to reduce biological vulnerability, as illustrated in **Figure 14**. Prospective mathematical modelling can help inform cost-effective distribution strategies, but this should not be done without a parallel consideration of the ethical implications that are more difficult to model. For example, the InFluNet model could be applied to inform thresholds for discontinuation of antiviral prophylaxis in order to preserve stockpiles for treatment; if we view prophylaxis as most valuable for containment purposes, the InFluNet model could help establish indicators that transmission has broken containment and is transmitting widely in the community. Discontinuation thresholds could be based upon the daily rate of new infections corresponding to the inflection point in the predicted pandemic wave, which from **Chapter 5** would represent a daily increase of over 10%. However, this would have to be balanced against ethical considerations relating to utility, efficiency and reciprocity, and will also depend on the size of the antiviral stockpile in question.

8.2.3 Non-pharmaceutical interventions

As discussed in **Chapter 2**, non-pharmaceutical measures have played an important role in pandemic influenza control efforts, and were the only available means to respond in earlier pandemics [249]. In the context of this dissertation, non-pharmaceutical measures included school closure, voluntary isolation, quarantine, community-contact reduction and personal protective measures.

The systematic review presented in **Chapter 3** found no conclusive evidence of the effectiveness of non-pharmaceutical measures, while the review in **Chapter 4** found a significant protective effect of hand hygiene, a non-significant protective effect of facemask use and no evidence of cough etiquette effectiveness. The non-significant protective effect of facemask use was attributed to the large confidence intervals reported as a result of significant heterogeneity and small sample sizes, and InFluNet assumptions reflected estimates of effect based on pooling across randomized trials and case–control studies, which found a significant effect and reduced heterogeneity. This approach is supported by past methodological reviews which have found that there is little evidence that the results of well-designed observational studies significantly differ from those of comparable randomized control trials [444, 445]. Estimates of effect were comparable to systematic reviews of personal protective measure effectiveness to interrupt transmission of seasonal influenza and other respiratory viruses [225, 277, 446].

Uncertainty regarding non-pharmaceutical measure effectiveness may be due to challenges in conducting prospective, empirical studies of these intervention measures during influenza pandemics. They inherently rely on self-reporting and recall, and results can be difficult to interpret due to subjective definitions of intervention measure adherence. This presents an important space for mathematical modelling to contribute to policy discussions.

This dissertation found that voluntary isolation and personal protective measures had a significant effect on delaying and attenuating pandemic waves, while school closure, quarantine and community-contact reduction offered little additional benefit. The policy analysis in **Chapter 7** also advocates for a focus on voluntary isolation and personal protective measures, invoking principles of least restrictive means and cost-effectiveness to suggest that school closure, quarantine and community-contact reduction should be avoided. Also, if a goal of pandemic intervention is to reduce societal disruption, than the least obstructive measures should be implemented first.

With respect to the integrated framework presented in **Figure 14**, non-pharmaceutical measures reduce pandemic burden by acting on social and behavioural determinants of transmission. By reducing the effective contact rate, these interventions can prevent pandemic transmission without affecting the susceptibility and infectivity of the population. An important implication of this is that, if measures are discontinued prematurely, pandemic transmission can accelerate quickly. Also, delays in intervention implementation dramatically reduce their effectiveness, as a higher proportion of infected individuals in the community will necessitate even stronger adherence to non-pharmaceutical measures.

Mathematical modelling supports the limited empirical evidence that non-pharmaceutical measures are effective. However, the crucial determinant of this effectiveness will be population adherence to recommendations. Therefore, future research in this area should explore economic and advisory strategies to further improve understanding of — and capacity to adhere to — various social distancing measures.

8.2.4 Hospital-resource planning

Important components of this dissertation were the evaluation of likely hospital-resource demand and assessment of the ability to accommodate increases in patient demand. This had previously been identified as a key area of concern, largely due to limited hospital resources and just-in-time resource supply constraining the capacity to scale up service provision [183, 382, 447].

The results of this dissertation suggest that the timely implementation of a layered intervention approach should protect hospital resource capacity under mild and moderate assumptions. However, there appears to be a lack of preparedness to respond to the likely surge in patient-demand that would result from a more severe pandemic. Similarly, hospital systems could quickly become overwhelmed if there are delays in — or a public rejection of — intervention implementation.

A summary of some of the key findings with respect to hospital-resource demand is included in **Section 8.2.1**, while more detailed discussion can be found in **Chapters 5** and **6**. Results suggested that hospital-system vulnerability could be predicted most strongly by supply-side factors relating to acute-care and ICU beds per capita. Specifically, the ability to accommodate surges in patient demand, even in the absence of vaccination, can be approximated by the threshold of 15/10,000 and 3/10,000 for acute-care and ICU beds, respectively; this is higher than the U.S. Department of Homeland Security recommendation of 5 beds per 10,000 population [448]. It is likely that adequate intervention measures would bring the resource-adequacy threshold somewhere in the range of 5–15 acute-care beds per 10,000 population. However, these estimates should be interpreted with caution, as resource adequacy will be influenced by a wide range of factors, including staffing of hospital beds, supplies and equipment, community demographics, intervention measures and pandemic severity [448].

The most vulnerable health systems tended to be concentrated in Southwestern Ontario. A previous modelling study predicted that Ontario would have the highest overall demand for critical care resources, but did not translate these estimates to a finer geographical scale or an estimate of demand as a percentage of capacity [339].

Mathematical modelling is useful in the evaluation of hospital-resource adequacy, as it has the ability to predict daily patient inflow under a wide range of disease and intervention assumptions. The results included in this dissertation have important implications for future research and practice. First, it suggests that there may be a benefit to prioritizing certain regions of Ontario and British Columbia in intervention planning, and that efficient patient referral systems between metropolitan areas will be crucial to proper resource use. Second, it points to the need for continued research towards developing a principle-based approach to hospital triage, positioned at the intersection of ethical and effective resource management.

8.3 Critical analysis

The goal of this section is not to reiterate the strengths and weaknesses identified in the individual manuscripts presented in **Chapters 2–7**. Rather I seek to engage in a broader discussion of some of the over-arching strengths and weaknesses of the dissertation as a whole. In this way, I hope to further contextualize the findings within the literature base, clarifying key points of original knowledge contribution alongside limitations that should be considered in accepting the research results and designing future studies.

8.3.1 Strengths

An effective response to pandemic influenza requires inter-sectoral, whole-of-society collaboration. A major strength of this dissertation is the benefit it received from significant interdisciplinary cooperation. Insight, expertise and contributions were sought from a broad variety

of fields, including mathematics, statistics, computer science, economics, public health and risk management. Not only does this place my dissertation at the intersection of theoretical and applied public health, but it provided solid grounding in multiple disciplinary paradigms and methodologies. The result is a series of articles that are methodologically rigorous and accessible to a range of academic and policy audiences. It also allowed an expansion of the breadth of the dissertation beyond what I would have been able to accomplish alone.

Another strength of this dissertation is its significant and original contribution to the pandemic influenza knowledge base. It has helped inform discussions of the likely consequences of future pandemics, vulnerable populations and optimal intervention strategies. To my knowledge, this dissertation represents the first comprehensive assessment of the preparedness of the Canadian hospital system to accommodate surges in patient demand associated with pandemics of uncertain severity. Two rigorous systematic reviews — whose adherence to international guidelines was ensured by the submission of methodological protocols to the *PROSPERO* database — provided important insights on the past effectiveness of pandemic influenza interventions. These findings then informed the development of the InFluNet model.

The development of a novel mathematical model, parameterized using empirical data and subjected to structural and predictive validation, should help to mainstream mathematical modelling in infectious disease emergency management. The strength of InFluNet is its incorporation of empirical social contact, disease and intervention data to chart pandemic progression against real-world hospital capacity data. The model presented is flexible and scalable to any population size, requires little computer capacity and can be made accessible to public-health practitioners lacking formal modelling training. This should help promote acceptance and use of a sophisticated model that assesses threat of pandemic-associated health and economic

burdens alongside the ability of hospitals to accommodate surges in patient demand. The InFluNet model can be of value for informing pandemic planning and resource distribution strategies for acute care institutions, regional public health authorities and provincial and federal planning bodies. The flexible model allows testing of a wide range of assumptions during the inter-pandemic period, with the ability to revise and update assumptions in real time as data becomes available during a future pandemic.

8.3.2 Limitations

This dissertation is subject to certain limitations. While a more detailed discussion of manuscript-specific limitations is included in relevant chapters, it is important here to consider more general limitations as they relate to data availability and decisions regarding model assumptions and analytical focus.

First, there is reason to question the generalizability of the intervention effectiveness assumptions used in the model simulations. Many of these were taken either from existing systematic reviews are from the meta-analysis presented in **Chapter 4**; where empirical data was unavailable, assumptions relied on approaches from past modelling studies. A possible concern is that this reliance on primary data meant that almost all intervention effectiveness estimates were drawn from studies conducted during the 2009 H1N1 pandemic. This presents challenges in assessing how effectiveness and adherence might vary with disease transmissibility or severity and, despite thorough sensitivity analysis, may limit the generalizability of assumptions to future pandemics with different disease characteristics. Similarly, most primary studies were conducted in developed countries, which could limit generalizability to developing contexts with different social contact patterns, health system capacity, and resource constraints. Further, limited data from systematic reviews precluded accounting for confounding factors and subgroup analysis, and

meant that there were often very large confidence intervals in intervention effectiveness estimates, and their potential impact varied widely. While recognizing this limitation, I chose to rely on empirical data where possible, preferring them to the use of past modelling assumptions that often had not been validated.

Second, while this dissertation presents the most comprehensive assessment of Canadian pandemic preparedness, it does not account for the entire Canadian population. By choosing to model populations across the 33 CMAs, I covered approximately 69.1% of the Canadian population [385]. This approach was chosen as the most efficient way to model pandemic disease risk among a large cross-section of the Canadian population without sacrificing geographic specificity. Further, a reliance on data from the voluntary 2011 Census may have biased age-stratified population estimates. I decided, however, that this potential bias was preferable to relying on the 2006 Census, as population counts were less likely to have been biased than more detailed social and economic data, and the Canadian population grew by 5.9% between 2006 and 2011 [385]. Early estimates suggest that the population grew by 4.8% between 2011 and 2016, so future InFluNet simulations will use updated population estimates when they become available [449].

Third, through much of the dissertation, there is a focus on quantitative research methodologies and analyses. This is not meant to suggest that qualitative methodologies have little to contribute in this area. In fact, it is possible that the dissertation would have benefited from more of a mixed-methods approach. There was a focus upon the quantification of disease transmission dynamics as it relates to social, economic, health and resource parameters. The research objective of developing and implementing a mathematical model led to a focus on quantitative methods. However, qualitative research has valuable insights to provide, particularly as it relates to promoting health equity and fostering public trust, cooperation and adherence to public health

recommendations during influenza pandemics. The discussion presented in **Chapter 7** is intended in part to bridge quantitative and qualitative discussions of pandemic preparedness and response.

Lastly, I would like to emphasize the inherent trade-offs between realism, transparency and usability of mathematical modelling. No models are perfect reflections of reality, and decisions were made regarding what complex assumptions and what simplifications were reasonable. This was in large part based upon research of the dominant drivers of infectious disease transmission and an assessment of data sufficiency to make informed assumptions. There are three areas where this necessary limitation is particularly evident. First, while incorporating age-specific risk estimates, the InFluNet model does not account for many identified high-risk and vulnerable groups, including Indigenous populations, immigrants and those with pre-existing conditions. This is, in part, because a lack of primary data observed during the reviews precluded an informed decision regarding risk assumptions. Also, it is reasonable to assume that high-risk groups may shift across different pandemics, and the greater focus of this study was on charting the dominant trends in disease transmission and resource use. Second, it should be recognized that the choice to model populations at the level of CMAs was based upon choosing a logical geographical unit for policy decisions, but may not reflect how disease transmission and hospital-resource use behave in reality. The finding in **Chapter 6** that regions of Southwestern Ontario are vulnerable to surges in patient demand, for example, ignores referral systems which may direct complicated cases to larger cities such as Toronto. The same is true for Northern populations that may not be counted among CMA populations, but travel south if experiencing complicated infection. A lack of transparency or quantification of these trends make them difficult to incorporate into mathematical models. **Chapter 7** is intended to shift discussion towards these important themes and identify important areas for future research. Third, the model was built as a closed system, excluding

factors outside of Canada that may affect modelling results: this ignores the potential role of international trade and travel in pandemic influenza transmission, as well as the potential benefit of international collaboration protocols such as sharing of surveillance data. While these issues are discussed in detail in **Chapter 2**, they were considered to be outside to scope of the InFluNet model, which simulates influenza pandemics already seeded within a Canadian community.

8.4 Personal reflection

As with the dissertation itself, my own knowledge, understanding and skill as a researcher benefitted from the interdisciplinary collaboration that took place during this project. I had the opportunity to work with subject experts from a variety of fields, gaining valuable understanding of theoretical frameworks and methodologies that position me as an expert in leveraging public health principles to inform policy decision-making to maximize the responsiveness of local health systems in contexts of uncertainty and resource scarcity. Having developed a diverse network of collaborators, made up of academics and public-health practitioners, I look forward to continuing the development of a diverse, high-impact research agenda in the future.

During my career as a doctoral student, I also benefitted from a variety of opportunities to expand my skills and network of public, private and academic contacts for future collaboration. I was a member of Dr. Angel Foster's Women's Health Research Lab and Dr. Robert Smith?'s Mathematical Modelling Research Lab. I acted as an Associate Editor and Blogger for the Interdisciplinary Journal of Health Sciences and a Blogger for the Global Health Africa website, expanding my subject matter expertise and comfort as a peer-reviewer. I developed my reputation as a public health expert through peer-reviewed publications, conference presentations, invited guest lectures and interviews. Lastly, a policy practicum with the public health and risk

management consulting firm Risk Science International afforded me the opportunity to work as a consultant for government projects targeting environmental and public health threats.

Taken together, these experiences contributed to my growth as a public health researcher. I was deeply fortunate to have the opportunity to work across subject areas with students, academics and consultants from numerous backgrounds, increasing my comfort participating in an interdisciplinary research environment. I believe that interdisciplinary research will be critical to approaching many of the complex public health problems we face today, and am grateful to have had the opportunity to develop within such a supportive and collaborative atmosphere.

8.5 Knowledge translation strategy

The primary method for disseminating this research was the submission of manuscripts to scientific, peer-reviewed public health journals. The historical review presented in **Chapter 2** was submitted for consideration to the journal *Pathogens*, and has been accepted and published [249]. The systematic review presented in **Chapter 3** was submitted for consideration to the journal *PLoS ONE*, and has been accepted and published [355]. The article presented in **Chapter 4** has been published at the journal *Epidemics* [409]. The modelling papers presented in **Chapters 5** and **6** have been published in *PLoS ONE* [433] and *Infectious Disease Modelling* [401], respectively. The policy paper presented in **Chapter** 7 has been submitted to *Mirobial Risk Analysis*, and is currently under review. Preference was given to open-access journals to ensure maximal and equitable reach. This was facilitated by financial contributions from the McLaughlin Center and University of Ottawa library. Additional reach was achieved through social media outlets, including Twitter, ResearchGate and LinkedIn.

Research findings were also disseminated through paper and poster presentations at international public health conferences. This was made possible through financial assistance from

the Faculty of Graduate and Postdoctoral Studies, the Institute of Population Health and the McLaughlin Centre at the University of Ottawa. Presentations related to my dissertation were delivered at the *Influenza, 2014* conference at Oxford University in Oxford, United Kingdom, and at the *Canadian Immunization Conference, 2016,* in Ottawa, Canada. These conferences provided invaluable opportunities to disseminate my research, receive feedback and network with leading experts in the field of influenza research.

There are three planned avenues for continued knowledge translation. The first centers upon meetings with relevant members of the Canadian Public Health Agency, including members of the Pandemic Preparedness Division. The second involves the continued development of a publicly accessible decision-support tool to be made available to public-health practitioners and decision-makers. Lastly, I will be considering the value of expanding InFluNet functionality by incorporating demographic and hospital-capacity data for other countries, and by integrating new transmission flow models to allow the modelling of other acute respiratory infections, including seasonal influenza and SARS; this would involve relatively minor alterations to the transmission model and input parameters.

8.6 Conclusion

This dissertation has investigated the threat of future pandemic influenza outbreaks in Canada. It assesses the potential consequences of a future influenza pandemic and proposes optimal intervention strategies to mitigate associated impacts. A historical review examined patterns of disease emergence, spread and response. Two systematic reviews assessed intervention effectiveness for preventing pandemic influenza transmission. Two modelling studies predicted pandemic-associated burdens across health and economic endpoints, with a particular focus towards the adequacy of hospital-resource capacity. A final paper discussed these findings within

the context of existing pandemic policy, through the related lenses of public health ethics and risk management.

Findings suggest that globalization processes are increasing the risk of pandemic emergence, while also improving human capability to respond to such emergencies. Pandemic vaccination, antiviral treatment, voluntary isolation and personal protective measures were identified as the most cost-effective interventions available. Antiviral prophylaxis, community-contact reduction, school closure and quarantine were less effective, and tended to be associated with higher associated economic burdens. The timely implementation of layered intervention strategies appears likely to protect hospital-resource adequacy, though critical care capacity could be at particular risk. Areas of Southwestern Ontario and British Columbia appear to be more vulnerable to surges in patient demand. In situations of resource shortages, decision-making should prioritize principles of justice, autonomy and risk management.

Continued efforts are required across geographical scales to improve surveillance, coordination and resource planning to most effectively mitigate and contain future pandemics. This research presents several interesting avenues for future research. First, in light of the finding that small increases in disease transmissibility or severity significantly increased overall burden and resource constraints, future studies are needed to assess optimal intervention strategies and trigger thresholds under a broad range of disease, intervention, population and resource assumptions. Second, more detailed modelling scenarios, allowing analysis of targeted interventions based on age or risk profile, would allow a more nuanced discussion of the tensions and trade-offs between utilitarian and equity-focused pandemic policies. Third, evaluation studies should focus on developing prospective studies to measure intervention effectiveness in infectious disease emergency situations, as this would reduce risk of bias and provide more reliable

effectiveness estimates. Fourth, research should seek to determine thresholds for "adequate" adherence to public health recommendations such as hand hygiene and facemask use, at both individual and population levels. This would be useful for recommending appropriate behaviour guidelines during pandemic situations. Fifth, risk communication would also benefit from a greater understanding of the role of different routes of transmission, and clarification of the locations and situations where viral contact is most likely. Lastly, future research should continue to advance a principle-based discussion of pandemic preparedness, encouraging a flexible and scalable response.

Chapter 9. Appendices

Appendix 1. PRISMA 2009 checklist for systematic review and narrative synthesis of existing systematic reviews [191].

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	48
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	49–50
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	51
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	51
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	50, 52
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	52
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	51
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	51
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	52
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	53

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	53
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	53
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	53
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	53
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	53
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	53
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	54
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	56
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	61
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Appendix 5–8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression (see Item 16)).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	67–68
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	68–69

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	69–70
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

Appendix 2. Database-specific search strategies for systematic review and narrative synthesis of existing systematic reviews

1. Medline (OVID)

1. Influenza, human/
2. Exp Influenzavirus A/
3. 1 or 2
4. Pandemics/
5. (pandemic* adj3 (influenza* or flu* or grippe)).tw.
6. 4 or 5
7. 3 and 6
8. Systematic review.tw.
9. Meta-analysis.tw.
10. Meta analysis.tw.
11. Or/8–10
12. 7 and 11

2. Embase

1. Exp influenza/
2. Exp influenza A virs/
3. 1 or 2
4. Pandemic/
5. (pandemic* adj3 (influenza* or flu* or grippe)).tw.
6. 4 or 5
7. 3 and 6
8. Systematic review.tw.
9. Meta-analysis.tw.
10. Meta analysis.tw.
11. Or/8–10
12. 7 and 11

3. Pubmed

1. Influenza, human (MeSH Terms)
2. Influenzavirus A (MeSH Terms)
3. 1 or 2
4. Pandemic (MeSH Terms)
5. Pandemic* (Text Word)
6. (Text Word) (influenza* or flu* or grippe)
7. 5 and 6
8. 4 or 7
9. 3 and 8
10. (Text Word) (systematic review or meta-analysis or meta analysis)
11. 9 and 10

4. Cochrane (Wiley)

1. MeSH descriptor: (Influenza, Human) explode all trees
2. MeSH descriptor: (Influenzavirus A) explode all trees
3. 1 or 2
4. MeSH descriptor: (Pandemics) explode all trees
5. pandemic* (Word variations have been searched)
6. influenza* (Word variations have been searched)
7. flu* (Word variations have been searched)
8. grippe (Word variations have been searched)
9. 6 or 7 or 8
10. 5 and 9
11. 4 or 10
12. 3 and 11
13. Systematic review (Word variations have been searched)
14. Meta-analysis (Word variations have been searched)
15. Meta analysis (Word variations have been searched)
16. Or/13–15
17. 12 and 16

5. CINAHL

1. (MH "Influenza+")
2. (MH "Pandemic+")
3. TX (influenza* or flu* or grippe) and TX pandemic*
4. 2 or 3
5. 1 and 4
6. TX (systematic review or meta-analysis or meta analysis)
7. 5 and 6

Appendix 3. AMSTAR screening tool (reproduced with permission from [193])

Item Number	Evaluation Criteria	Scoring
1	Was an 'a priori' design provided? (1)The research question/aim and (2) inclusion criteria should be established before the conduct of the review.	• Yes (1 point)- Must satisfy all five criteria • No (0 points) • Can't Answer (0 points) • Not Applicable (0 points)
2	Was there duplicate study selection and data extraction? (1)There should be at least two independent data extractors and a (2) consensus procedure for disagreements should be in place.	• Yes (1 point)- Must satisfy all five criteria • No (0 points) • Can't Answer (0 points) • Not Applicable (0 points)
3	Was a comprehensive literature search performed? (1) At least two databases must be searched; (2) The report must include years and databases used; (3) keywords and/or MESH terms must be stated; (4) search strategy must be provided where feasible; (5) All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the field, and by reviewing the references in the studies found.	• Yes (1 point)- Must satisfy all five criteria • No (0 points) • Can't Answer (0 points) • Not Applicable (0 points)
4	Was the status of publication (i.e. grey literature) used as an inclusion criteria? (1) Authors should state they searched reports regardless of publication type; (2) Authors should state whether or not they excluded any reports (from the systematic review) based on their publication status, languages, etc.	• Yes (1 point) • No (0 points) • Can't Answer (0 points)
5	Was a list of studies (included and excluded) provided? A list of (1) included and (2) excluded studies should be provided. Note: excluded studies can be provided in an appendix or external link	
6	Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. Ranges of characteristics (age, sex, relevant socioeconomic data, disease status, duration , severity, or other diseases should be reported)	• Yes (1 point) • No (0 points) • Can't Answer (0 points)

		• Not Applicable (0 points)
7	Was the scientific quality of the included studies assessed and documented? A priori methods of assessment should be provided Note: (for example, did they mention an instrument/tool to assess quality?)	• Yes (1 point) • No (0 points) • Can't Answer (0 points) • Not applicable (0 points)
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? Results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	• Yes (1 point) • No (0 points) • Can't Answer (0 points) • Not applicable (0 points)
9	Were the methods used to combine the findings of studies appropriate? For pooled results, a test should be done to ensure studies were comparable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?)	• Yes (1 point) • No (0 points) • Can't Answer (0 points) • Not applicable (0 points)
10	Was the likelihood of publication bias assessed? Assessment of publication bias should include a combination of graphical aids (e.g. full plots, other available tests) and/or statistical tests (e.g. Egger regression test)	• Yes (1 point) • No (0 points) • Can't Answer (0 points) • Not applicable (0 points)
11	Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies	• Yes (1 point) • No (0 points) • Can't Answer (0 points) • Not applicable (0 points)

Appendix 4. Articles excluded during full review for systematic review and narrative synthesis of existing systematic reviews

Reference	Reason for Exclusion
Aledort, J.E.; Lurie, N.; Wasserman, J.; Bozzette, S.A. Non-pharmaceutical public health interventions for pandemic influenza: An evaluation of the evidence base. *BMC public health* **2007**, *7*, (15 August 2007).	Not a systematic review; result of expert panel in light of dearth of relevant literature
Alshabani, K.; Haq, A.; Miyakawa, R.; Soubani, A. Invasive pulmonary aspergillosis following influenza: A systematic review of literature. *American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS* **2014**, *189*.	Conference abstract: authors contacted with no response
Alves Galvão Márcia, G.; Rocha Crispino Santos Marilene, A.; Alves da Cunha Antonio, J.L. Amantadine and rimantadine for influenza a in children and the elderly. In *Cochrane Database of Systematic Reviews*, John Wiley & Sons, Ltd: 2014.	Does not include any studies from a pandemic influenza setting
Aoyagi, Y.; Beck, C.R.; Dingwall, R.; Nguyen-Van-Tam, J.S. Healthcare workers' willingness to work during an influenza pandemic: A systematic review and meta-analysis. *Influenza and other respiratory viruses* **2015**, *9*, 120-130.	Does not deal with interventions to prevent influenza infection; deals with willingness of healthcare workers to attend work
Atashili, J.; Kalilani, L.; Adimora, A.A. Efficacy and clinical effectiveness of influenza vaccines in hiv-infected individuals: A meta-analysis. *BMC infectious diseases* **2006**, *6*, 138.	Does not include any studies from a pandemic influenza setting
Babin, S.M.; Hsieh, Y.H.; Rothman, R.E.; Gaydos, C.A. A meta-analysis of point-of-care laboratory tests in the diagnosis of novel 2009 swine-lineage pandemic influenza a (h1n1). *Diagn. Microbiol. Infect. Dis.* **2011**, *69*, 410-418.	Does not deal with preventing influenza infection; deals with point-of-care laboratory test diagnosis
Baca-Muro, V.I.; Soria-Cedillo, I.F.; Olvera, K.; Garcia-Contreras, F. Prevention of an influenza pandemic in mexico: Establishing a cost-effective alternative for elderly population. *Value in Health* **2009**, *12 (7)*, A425.	Conference poster abstract; authors contacted with no response
Balasingam, S.; Wilder-Smith, A. Randomized controlled trials using human challenge studies for influenza: A systematic review. *Tropical Medicine and International Health* **2015**, *20*, 134.	Does not include any studies from a pandemic influenza setting
Beck, C.R.; Sokal, R.; Arunachalam, N.; Puleston, R.; Cichowska, A.; Kessel, A.; Zambon, M.; Nguyen-Van-Tam, J.S.; Group, U.K.A.E.R. Neuraminidase inhibitors for influenza: A review and public health perspective in	Does not include any studies from a pandemic influenza setting

the aftermath of the 2009 pandemic. *Influenza & Other Respiratory Viruses* **2013**, *7 Suppl 1*, 14-24.	
Bin-Reza, F.; Lopez Chavarrias, V.; Nicoll, A.; Chamberland, M.E. The use of masks and respirators to prevent transmission of influenza: A systematic review of the scientific evidence. *Influenza & Other Respiratory Viruses* **2012**, *6*, 257-267.	Does not include any studies from a pandemic influenza setting
Bozat-Emre, S.; Casaclang, N.; Sinnock, H.C.; Ye, X.; Mahmud, S.M. Effectiveness of seasonal influenza vaccines against influenza a (h1n1) infection in post-pandemic seasons: A systematic review. *Pharmacoepidemiol. Drug Saf.* **2015**, *24*, 178-179.	Conference poster abstract related to post-pandemic seasons
Bozat-Emre, S.; Ye, X.; Morrow, A.; Casaclang, N.; Mahmud, S.M. Effectiveness of the 2009 pandemic h1n1 influenza vaccines in preventing h1n1 infection: A meta-analysis. *Pharmacoepidemiol. Drug Saf.* **2014**, *23*, 161-162.	Conference poster abstract; authors contacted with no response
Brien, S.; Kwong, J.C.; Buckeridge, D.L. The determinants of 2009 pandemic a/h1n1 influenza vaccination: A systematic review. *Vaccine* **2012**, *30*, 1255-1264.	Does not use infection or transmission as outcome measure; reports on predictors of vaccination uptake
Burch, J.; Corbett, M.; Stock, C.; Nicholson, K.; Elliot, A.J.; Duffy, S.; Westwood, M.; Palmer, S.; Stewart, L. Prescription of anti-influenza drugs for healthy adults: A systematic review and meta-analysis. *The Lancet Infectious Diseases* **2009**, *9*, 537-545.	Does not include any studies from a pandemic influenza setting (examines treatment of seasonal influenza)
Cates Christopher, J.; Rowe Brian, H. Vaccines for preventing influenza in people with asthma. In *Cochrane Database of Systematic Reviews*, John Wiley & Sons, Ltd: 2013.	Does not include any studies from a pandemic influenza setting
Cowling, B.J.; Zhou, Y.; Ip, D.K.; Leung, G.M.; Aiello, A.E. Face masks to prevent transmission of influenza virus: A systematic review. *Epidemiology & Infection* **2010**, *138*, 449-456.	Does not include any studies from a pandemic influenza setting
De La Parte, B.; Jimenez, V.; Jesus, M.; Reza, M.; Pardillos Ferrer, L.; Mateos Rodriguez, A.; Montarelo, A. Should asthmatic people recive influenza vaccine and pandemic influenza a (h1n1) vaccine? *Allergy: European Journal of Allergy and Clinical Immunology* **2010**, *65*, 717.	Not a systematic review
Devnani, M. Factors associated with the willingness of health care personnel to work during an influenza public health emergency: An integrative review. *Prehospital and disaster medicine* **2012**, *27*, 551-566.	Does not deal with preventing influenza infection; deals with willingness of healthcare workers to work
Eliakim-Raz, N.; Vinograd, I.; Zalmanovici Trestioreanu, A.; Leibovici, L.; Paul, M. Influenza vaccines in immunosuppressed adults with cancer. In *Cochrane*	Does not include any studies from a pandemic influenza setting

Database of Systematic Reviews, John Wiley & Sons, Ltd: 2013.	
Gadre, S.; Duggal, A. Use of rescue therapies during the h1n1 pandemic: A systematic review exploring global differences in the management of severe acute respiratory distress syndrome. *Chest. Conference: CHEST* **2015**, *148*.	Conference poster abstract and does not deal with preventing influenza infection
Jagannath Vanitha, A.; Asokan, G.V.; Fedorowicz, Z.; Lee Tim, W.R. Neuraminidase inhibitors for the treatment of influenza infection in people with cystic fibrosis. In *Cochrane Database of Systematic Reviews*, John Wiley & Sons, Ltd: 2016.	No studies were found in this review and does not deal with preventing influenza infection
Jefferson, T.; Demicheli, V.; Rivetti, D.; Jones, M.; Di Pietrantonj, C.; Rivetti, A. Antivirals for influenza in healthy adults: Systematic review. *Lancet* **2006**, *367*, 303-313.	Updated in Jefferson et al., 2008
Jefferson, T.; Del Mar, C.; Dooley, L.; Ferroni, E.; Al-Ansary, L.A.; Bawazeer, G.A.; van Driel, M.L.; Nair, S.; Foxlee, R.; Rivetti, A. Physical interventions to interrupt or reduce the spread of respiratory viruses. *The Cochrane database of systematic reviews* **2010a**, Cd006207.	Updated in Jefferson et al., 2011
Jefferson, T.; Di Pietrantonj, C.; Al-Ansary Lubna, A.; Ferroni, E.; Thorning, S.; Thomas Roger, E. Vaccines for preventing influenza in the elderly. In *Cochrane Database of Systematic Reviews*, John Wiley & Sons, Ltd: 2010b.	Does not include studies on pandemic influenza
Jefferson, T.; Jones, M.; Doshi, P.; Del Mar, C.; Dooley, L.; Foxlee, R. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: A cochrane review. *Health Technology Assessment* **2010c**, *14*, 355-458 104p.	Does not include studies on pandemic influenza
Jefferson, T.; Del Mar, C.B.; Dooley, L.; Ferroni, E.; Al-Ansary, L.A.; Bawazeer, G.A.; van Driel, M.L.; Nair, S.; Jones, M.A.; Thorning, S., *et al.* Physical interventions to interrupt or reduce the spread of respiratory viruses. *The Cochrane database of systematic reviews* **2011**, Cd006207	Did not have sufficient data to carry out subgroup analysis for pandemic influenza outbreaks.
Jefferson, T.; Rivetti, A.; Di Pietrantonj, C.; Demicheli, V.; Ferroni, E. Vaccines for preventing influenza in healthy children. *The Cochrane database of systematic reviews* **2012**, *8*, CD004879.	Updated in Jefferson et al., 2014c
Jefferson, T.; Jones, M.A.; Doshi, P.; Del Mar, C.B.; Hama, R.; Thompson, M.J.; Spencer, E.A.; Onakpoya, I.; Mahtani, K.R.; Nunan, D., *et al.* Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database of Systematic Reviews* **2014b**, N.PAG-N.PAG 1p.	Did not have sufficient data to carry out subgroup analysis for pandemic influenza outbreaks.

Jiang, L.; Deng, L.; Wu, T. Chinese medicinal herbs for influenza. In *Cochrane Database of Systematic Reviews*, John Wiley & Sons, Ltd: 2013	Does not include any studies from a pandemic influenza setting
Khazeni, N.; Bravata, D.M.; Holty, J.E.; Uyeki, T.M.; Stave, C.D.; Gould, M.K. Systematic review: Safety and efficacy of extended-duration antiviral chemoprophylaxis against pandemic and seasonal influenza. *Annals of internal medicine* **2009**, *151*, 464-473.	Does not include any studies from a pandemic influenza setting
Lau, L.L.; Nishiura, H.; Kelly, H.; Ip, D.K.; Leung, G.M.; Cowling, B.J. Household transmission of 2009 pandemic influenza a (h1n1): A systematic review and meta-analysis. *Epidemiology (Cambridge, Mass.)* **2012**, *23*, 531-542.	Does not review an intervention; surveys household secondary infection risk
Luke, T.C.; Kilbane, E.M.; Jackson, J.L.; Hoffman, S.L. Meta-analysis: Convalescent blood products for spanish influenza pneumonia: A future h5n1 treatment? *Annals of internal medicine* **2006**, *145*, 599-609 511p.	Does not deal with preventing influenza infection; deals with use of blood products to prevent influenza during Spanish flu
Manzoli, L.; Salanti, G.; De Vito, C.; Boccia, A.; Ioannidis, J.P.; Villari, P. Immunogenicity and adverse events of avian influenza a h5n1 vaccine in healthy adults: Multiple-treatments meta-analysis. *The Lancet Infectious Diseases* **2009**, *9*, 482-492.	Does not include any studies from a pandemic influenza setting
Martin Arias, L.H.; Sanz, R.; Sainz, M.; Treceno, C.; Carvajal, A. Guillain-barre syndrome and influenza vaccines: A meta-analysis. *Vaccine* **2015**, *33*, 3773-3778.	Does not deal with preventing influenza infection; deals with association between vaccination and Guillain-Barré syndrome
Mateus, A.L.; Otete, H.E.; Beck, C.R.; Dolan, G.P.; Nguyen-Van-Tam, J.S. Effectiveness of travel restrictions in the rapid containment of human influenza: A systematic review. *Bulletin of the World Health Organization* **2014**, *92*, 868-880D.	Only review mathematical modelling studies
Mathie Robert, T.; Frye, J.; Fisher, P. Homeopathic oscillococcinum® for preventing and treating influenza and influenza-like illness. In *Cochrane Database of Systematic Reviews*, John Wiley & Sons, Ltd: 2015.	Does not include any studies from a pandemic influenza setting
McMillan, M.; Kralik, D.; Porritt, K.; Marshall, H. Influenza vaccination during pregnancy: A systematic review of effectiveness and safety. *JBI Database of Systematic Reviews & Implementation Reports* **2014**, *12*, 281-381 101p.	Does not include any studies from a pandemic influenza setting

Mitchell, M.D.; Mikkelsen, M.E.; Umscheid, C.A.; Lee, I.; Fuchs, B.D.; Halpern, S.D. A systematic review to inform institutional decisions about the use of extracorporeal membrane oxygenation during the h1n1 influenza pandemic. *Critical Care Medicine* **2010**, *38*, 1398-1404.	Does not deal with preventing influenza infection; deals with extracorporeal membrane oxygenation as a rescue therapy
Morton, M.J.; Jeng, K.; Beard, R.; Dugas, A.; Pines, J.M.; Rothman, R.E. Systematic review of interventions to mitigate the effect of emergency department crowding in the event of a respiratory disease outbreak. *Academic Emergency Medicine* **2012**, *19*, S64-S65.	Conference poster abstract that does not deal with preventing influenza infection
Muthuri, S.G.; Myles, P.R.; Venkatesan, S.; Leonardi-Bee, J.; Nguyen-Van-Tam, J.S. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009-2010 influenza a(h1n1) pandemic: A systematic review and meta-analysis in hospitalized patients. *Journal of Infectious Diseases* **2013**, *207*, 553-563.	Does not deal with preventing influenza infection
Muthuri, S.G.; Venkatesan, S.; Myles, P.R.; Leonardi-Bee, J.; Al Khuwaitir, T.S.; Al Mamun, A.; Anovadiya, A.P.; Azziz-Baumgartner, E.; Baez, C.; Bassetti, M., *et al.* Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza a h1n1pdm09 virus infection: A meta-analysis of individual participant data. *The Lancet Respiratory Medicine* **2014**, *2*, 395-404	Does not deal with preventing influenza infection
Muthuri, S.G.; Venkatesan, S.; Myles, P.R.; Leonardi-Bee, J.; Lim, W.S.; Al Mamun, A.; Anovadiya, A.P.; Araujo, W.N.; Azziz-Baumgartner, E.; Baez, C., *et al.* Impact of neuraminidase inhibitors on influenza a(h1n1)pdm09-related pneumonia: An individual participant data meta-analysis. *Influenza and other respiratory viruses* **2016**, *10*, 192-204.	Does not deal with preventing influenza infection
Ortiz, J.R.; Rudd, K.E.; Clark, D.V.; Jacob, S.T.; West, T.E. Clinical research during a public health emergency: A systematic review of severe pandemic influenza management. *Critical Care Medicine* **2013**, *41*, 1345-1352.	Does not deal with preventing influenza infection
Ott, J.J.; Klein Breteler, J.; Tam, J.S.; Hutubessy, R.C.; Jit, M.; de Boer, M.R. Influenza vaccines in low and middle income countries: A systematic review of economic evaluations. *Human Vaccines Immunotherapy.* **2013**, *9*, 1500-1511.	Does not include any studies from a pandemic influenza setting
Pfister, R.; Kochanek, M.; Leygeber, T.; Brun-Buisson, C.; Cuquemelle, E.; Machado, M.B.P.; Piacentini, E.; Hammond, N.E.; Ingram, P.R.; Michels, G. Procalcitonin	Does not deal with preventing influenza infection

for diagnosis of bacterial pneumonia in critically ill patients during 2009 h1n1 influenza pandemic: A prospective cohort study, systematic review and individual patient data meta-analysis. *Crit. Care* **2014**, *18 (2) (no pagination)*.	
Prieto-Lara, E.; Llanos-Mendez, A. Safety and immunogenicity of prepandemic h5n1 influenza vaccines: A systematic review of the literature. *Vaccine* **2010**, *28*, 4328-4334.	Does not deal with preventing influenza infection
Rodrigo, C.; Leonardi-Bee, J.; Nguyen-Van-Tam, J.S.; Lim, W.S. Effect of corticosteroid therapy on influenza-related mortality: A systematic review and meta-analysis. *Journal of Infectious Diseases* **2015**, *212*, 183-194.	Does not deal with preventing influenza infection
Rudd, K.E.; Ortiz, J.R.; Clark, D.V.; Jacob, S.T.; West, T.E. A systematic review of clinical interventions for patients with severe pandemic influenza a (h1n1) virus infection. *American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS* **2012**, *185*.	Does not deal with preventing influenza infection
Shun-Shin, M.; Thompson, M.; Heneghan, C.; Perera, R.; Harnden, A.; Mant, D. Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: Systematic review and meta-analysis of randomised controlled trials. *BMJ* **2009**, *339*, b3172.	Does not include any studies from a pandemic influenza setting
Smith, S.M.; Sonego, S.; Wallen, G.R.; Waterer, G.; Cheng, A.C.; Thompson, P. Use of non-pharmaceutical interventions to reduce the transmission of influenza in adults: A systematic review. *Respirology* **2015**, *20*, 896-903.	Does not include any studies from a pandemic influenza setting
Thomas Roger, E.; Jefferson, T.; Lasserson Toby, J. Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions. In *Cochrane Database of Systematic Reviews*, John Wiley & Sons, Ltd: 2016; Vol. 6.	Does not include any studies from a pandemic influenza setting
Thomas Roger, E.; Lorenzetti Diane, L. Interventions to increase influenza vaccination rates of those 60 years and older in the community. In *Cochrane Database of Systematic Reviews*, John Wiley & Sons, Ltd: 2014.	Does not deal with preventing influenza infection; deals with increasing seasonal vaccine uptake
Thorlund, K.; Awad, T.; Boivin, G.; Thabane, L. Systematic review of influenza resistance to the neuraminidase inhibitors. *BMC infectious diseases* **2011**, *11*, 134.	Does not deal with preventing influenza infection
Venkatesan, S.; Myles, P.R.; Leonardi-Bee, J.; Nguyen-Van-Tam, J.S. Impact of outpatient neuraminidase inhibitor treatment on hospitalisation in patients infected with influenza a (h1n1)pdm09: An ipd analysis. *International Journal of Infectious Diseases* **2016**, *45*, 248.	Does not deal with preventing influenza infection

Wang, K.; Shun-Shin, M.; Gill, P.; Perera, R.; Harnden, A. Neuraminidase inhibitors for preventing and treating influenza in children (published trials only). In *Cochrane Database of Systematic Reviews*, John Wiley & Sons, Ltd: 2012.	Does not include any studies from a pandemic influenza setting
Yang, J.W.; Fan, L.C.; Miao, X.Y.; Mao, B.; Li, M.H.; Lu, H.W.; Liang, S.; Xu, J.F. Corticosteroids for the treatment of human infection with influenza virus: A systematic review and meta-analysis. *Clinical Microbiology and Infection* **2015**, *21*, 956-963.	Does not deal with preventing influenza infection

Appendix 5. Results of pandemic vaccination analyses reporting relative effects

Pandemic	Study	N Studies	Population Size (N)	Vaccine Type	Outcome	Risk Control Group	Risk With Intervention	Relative Effect (95% CI)
2009 H1N1	Breteler et al., 2013	1	269,128	Two doses of PANFLU1	Laboratory-confirmed influenza	687/244,091 (2.8/1,000)	9/25,037 (0.35/1,000)	RR*: 0.127 (0.066–0.246)
2009 H1N1	Demicheli et al., 2014	1	7,328	2009 pandemic inactivated vaccine	ILI**	50/2,407 (20.8/1,000)	11/4,921 (2.2/1,000)	RR: 0.11 (0.06–0.21)
2009 H1N1	Manzoli et al., 2011	18	18,444	One dose non-adjuvanted pandemic vaccine	Influenza seroconversion	Not reported	Not reported	RR: 1.05 (1.03–1.07)
2009 H1N1	Manzoli et al., 2011	18	18,444	Two doses non-adjuvanted pandemic vaccine	Influenza seroconversion	Not reported	Not reported	RR: 1.01 (1.00–1.03)
2009 H1N1	Manzoli et al., 2011	18	18,444	One dose adjuvanted pandemic vaccine	Influenza seroconversion	Not reported	Not reported	RR: 1.10 (1.04–1.17)
2009 H1N1	Manzoli et al., 2011	18	18,444	Two dose adjuvanted pandemic vaccine	Influenza seroconversion	Not reported	Not reported	RR: 1.05 (1.02–1.07)
2009 H1N1	Yin et al., 2012	11	283,826	A(H1N1)pdm09 vaccine	Laboratory-confirmed influenza	6,229/258,154 (24.1/1,000)	71/25,708 (2.8/1,000)	OR= 0.14 (0.07–0.27)
1968 H2N2	Dimecheli et al., 2014	3	3,065	1968 inactivated polyvalent parenteral vaccine	ILI	127/1,377 (92.2/1,000)	149/1,688 (88.2/1,000)	RR: 0.71 (0.57–0.88)

1968 H2N2	Dimecheli et al., 2014	1	2072	1968 inactivated polyvalent parenteral vaccine	Influenza	32/1,042 (30.7/1,000)	15/1,030 (14.7/1,000)	RR: 0.47 (0.26–0.87)
1968 H2N2	Dimecheli et al., 2014	4	4580	Inactivated monovalent parenteral vaccine	ILI	169/1,790 (94.4/1,000)	107/2,790 (38.4/1,000)	RR: 0.35 (0.25–0.48)
1968 H2N2	Dimecheli et al., 2014	1	1923	Inactivated monovalent parenteral vaccine	Influenza	32/1,042 (30.7/1,000)	2/881 (2.3/1,000)	RR: 0.07 (0.02–0.31)
1968 H2N2	Dimecheli et al., 2014	2	1000	Inactivated polyvalent aerosol vaccine	ILI	86/335 (256.7/1,000)	117/665 (175.9/1,000)	RR: 0.66 (0.46–0.95)
1968 H2N2	Dimecheli et al., 2014	2	1009	Inactivated monovalent aerosol vaccine	ILI	86/335 (256.7/1,000)	103/674 (152.8/1,000)	RR: 0.54 (0.32–0.91)
1968 H2N2	Dimecheli et al., 2014	1	19887	Live aerosol vaccine	Influenza	1429/9942 (143.7/1,000)	1,407/9,945 (141.5/1,000)	RR: 0.98 (0.92–1.05)
1918 H1N1	Chien et al., 2010	12	Not reported	Mixed killed bacterial vaccines	Influenza incidence	166,870/1,723,172 (96.84/1,000)	20,087/233,320 (86.09/1,000)	RR: 0.89 (Not reported)

*RR = relative risk

**ILI = influenza-like illness (based on reporting of symptoms rather than clinical diagnosis)

Appendix 6. Results of analyses of antiviral prophylaxis and treatment

Pandemic	Study	N Studies	Population Size (N)	Antiviral Type	Outcome	Risk Control Group	Risk With Intervention	Relative Effect (95% CI)
2009 H1N1	Fielding et al., 2014	19	1527	Oseltamivir treatment within 48 hours of symptom onset	Duration of viral shedding	No treatment: 4–9 days	3–5 days	Not reported
2009 H1N1	Fielding et al., 2014	11	1527	Oseltamivir treatment within 48 hours of symptom onset	Duration of viral shedding	Treatment >48 hours after symptom onset: 5–7 days	3–5 days	Not reported
2009 H1N1	Mizumoto et al., 2013	8	Not reported	Oseltamivir mass prophylaxis	Secondary infection risk	Median SIR 16.6% (quartile 8.4–32.4%)	Median SIR 2.1% (quartile 0–12.2%)	Not reported
1968 H2N2	Jefferson et al., 2008	3	613	Amantadine prophylaxis	Influenza cases	62/307 (202.0/1,000)	17/306 (55.6/1,000)	0.27 (0.17–0.46)
1968 H2N2	Jefferson et al., 2008	6	11,962	Amantadine prophylaxis	ILI	1,682/5,298 (317.5/1,000)	1,647/6,664 (247.2/1,000)	0.78 (0.74–0.83)

Appendix 7. Results of seasonal vaccination analyses reporting comparative effects

Pandemic	Study	N Studies	Population Size (N)	Vaccine Type	Outcome	Risk Control Group	Risk With Intervention	Relative Effect (95% CI)
2009 H1N1	Li et al., 2015	4 RCTs	1,515	Seasonal influenza vaccine	Laboratory-confirmed infection	11/633 (17.4/1,000)	19/882 (21.5/1,000)	RR: 1.13 (0.56–2.29)
2009 H1N1	Li et al., 2015	16 case–control	40,868	Seasonal influenza vaccine	Laboratory-confirmed infection	8191/28,814 (284.3/1,000)	2,592/12,054 (215.0/1,000)	OR: 0.80 (0.61–1.05)
2009 H1N1	Yin et al., 2012	11 Case–control	31,699	Seasonal trivalent influenza vaccine	Laboratory confirmed influenza	6,599/21,907 (301.2/1,000)	2,282/9,792 (233.0/1,000)	OR: 0.81 (0.58–1.13)
2009 H1N1	Yin et al., 2012	6 (Excluded 5 studies with high risk of bias	28,292	Seasonal trivalent influenza vaccine	Laboratory confirmed influenza	5,851/19,613 (298.3/1,000)	1,827/8,679 (210.5/1,000)	OR: 0.66 (0.48–0.91)

Appendix 8. Results of analyses of personal protective measures

Pandemic	Study	N Studies	Population Size (N)	Intervention	Outcome	Risk Control Group	Risk With Intervention	Relative Effect (95% CI)
2009 H1N1	Wong et al., 2014	1	149	Hand hygiene + mask use	Laboratory-confirmed influenza	19/82 (231.7/1,000)	10/67 (149.3/1,000)	0.64 (0.32–1.29)
2009 H1N1	Wong et al., 2014	1	149	Hand hygiene + mask use	ILI	14/82 (170.7/1,000)	6/67 (89.6/1,000)	0.52 (0.21–1.29)

Appendix 9. AMSTAR scoring of included articles

Source	Criterion											Total	Category
	1	2	3	4	5	6	7	8	9	10	11		
Breteler et al., 2013	1	1	1	1	1	1	1	1	1	0	1	10	High
Chien et al., 2010	1	0	0	1	0	1	1	1	1	1	1	8	Moderate
Demicheli et al., 2014	1	1	1	1	1	1	1	1	1	1	1	11	High
Fielding et al., 2014	0	1	0	1	1	1	0	0	1	0	0	5	Moderate
Jackson et al., 2013	1	1	1	1	0	1	0	0	1	1	1	8	Moderate
Jefferson et al., 2008	1	1	1	1	0	1	1	1	1	0	1	9	High
Jefferson et al., 2014	1	1	1	1	1	1	1	1	1	1	1	11	High
Li et al., 2015	1	1	1	1	1	1	1	1	1	1	1	11	High
Li et al., 2016	1	1	1	1	0	1	1	1	1	0	1	9	High
Manzoli et al., 2011	0	1	1	1	0	0	1	1	1	1	1	8	Moderate
Mizumoto et al., 2013	1	0	0	0	1	1	0	0	1	0	1	5	Moderate
Mukerji et al., 2015	1	0	0	0	0	1	0	0	0	0	1	3	Low
Osterholm et al., 2012	1	0	0	1	0	1	0	0	1	0	1	5	Moderate
Perez Velasco et al., 2012	1	1	1	1	1	1	1	1	1	0	1	10	High
Wong et al., 2014	1	1	0	1	1	1	1	1	1	1	1	10	High
Yin et al., 2012	1	1	1	1	1	1	1	1	1	1	1	11	High
Yin et al., 2011	1	1	1	1	1	1	1	1	0	0	1	9	High

Appendix 10. PRISMA 2009 checklist for systematic review and meta-analysis of personal protective measure effectiveness [191].

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	78
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	78
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	79–80
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	80
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	78, 80
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	82–83
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	80–81
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	81
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	82–83
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	83
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	83

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	84
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	84
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	84
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	84
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	85
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	85
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	86–89
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	92, 95–98
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Appendix 13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	95–97
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	93, 95–98
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression (see Item 16)).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	99
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	100–101

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	103
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

Appendix 11. Search strategy for relevant databases for systematic review and meta-analysis of personal protective measure effectiveness

Search conducted June 30, 2016 by Patrick Saunders-Hastings

1. Medline (OVID)

Population
1. Influenza, Human/
2. Exp Influenza A virus A/
3. 1 or 2
4. Pandemics/
5. (pandemic* adj3 (influenza* of flu* or grippe)).tw.
6. 4 or 5
7. 3 and 6

Hand Hygiene:
8. Exp Hand Hygiene/
9. (handwashing or hand washing or hand-washing).tw.
10. ((hand*) adj3 (hygien* or disinfect* or sanitiz* or sanitis* or wash* or scrub* or cleans*)).tw.
11. Or/8–10

Cough/Respiratory Etiquette:
12. Cough/
13. (cough* and (influenza* or flu* or grippe)).tw.
14. ((respirat* or breath* or sneez* or cough*) adj3 (etiquette* or custom* or maneuver* or practic*)).tw.
15. Or/12–14

Masks:
16. Masks/
17. (mask* and (influenza* or flu* or grippe)).tw.
18. (facemask* and (influenza* or flu* or grippe)).tw.
19. (N95* and (influenza* or flu* or grippe)).tw.
20. (N-95* and (influenza* or flu* or grippe)).tw.
21. Or/16–20

Total:
22. 11 or 15 or 21
23. 7 and 22

2. Embase

Population

1. Exp influenza/
2. Exp influenza A virus/
3. 1 or 2
4. Pandemic/
5. (pandemic* adj3 (influenza* or flu* or grippe)).tw.
6. 4 or 5
7. 3 and 6

Hand Hygiene:

8. Exp Hand washing/
9. (handwashing or hand washing or hand-washing).tw.
10. ((hand*) adj3 (hygien* or disinfect* or sanitiz* or sanitis* or wash* or scrub* or cleans*)).tw.
11. Or/8–10

Cough/Respiratory Etiquette:

12. Coughing/
13. (cough* and (influenza* or flu* or grippe)).tw.
14. ((respirat* or breath* or sneez* or cough*) adj3 (etiquette* or custom* or maneuver* or practic*)).tw.
15. Or/12–14

Masks:

16. Exp Mask/
17. (mask* and (influenza* or flu* or grippe).tw.
18. (facemask* and (influenza* or flu* or grippe).tw.
19. (N95* and (influenza* or flu* or grippe).tw.
20. (N-95* and (influenza* or flu* or grippe).tw.
21. Or/16–20

Total:

22. 11 or 15 or 21
23. 7 and 22

3. PubMed

Population

1. Influenza, human (MeSH Terms)
2. Influenzavirus A (MeSH Terms)
3. 1 or 2
4. Pandemic* (MeSH Terms)
5. Pandemic* (Text Word)
6. ((influenza*(Text Word)) or flu* (Text Word)) or grippe (Text Word)
7. 5 and 6
8. 4 or 7
9. 3 and 8

Hand Hygiene:

10. Hand hygiene (MeSH Terms)
11. Hand washing (MeSH Terms)
12. ((handwashing (Text Word)) OR (hand washing (Text Word)) or (hand-washing (Text Word)))
13. (hand* (Text Word))
14. (hygien* (Text Word) or disinfect* (Text Word) or sanitz* (Text Word) or santis* (Text Word) or wash* (Text Word) or scrub* (Text Word) or cleans*(Text Word))
15. 13 and 14
16. 10 or 11 or 12 or 15

Cough Etiquette:

17. Cough*(MeSH Terms)
18. (cough*(Text Word))
19. 6 and 18
20. (respirat* (Text Word) or breath* (Text Word) or sneez* (Text Word) or cough* (Text Word))
21. (etiquette* (Text Word) or custom* (Text Word) or maneuver* (Text Word) or practic* (Text Word))
22. 20 and 21
23. 17 or 19 or 22

Masks:

24. Mask* (MeSH Terms)
25. (mask* (Text Word) or facemask* (Text Word) or N95* (Text Word) or N-95* (Text Word))
26. 6 and 25
27. 24 or 26

Total:

28. 16 or 23 or 27

29. 9 and 28

4. Cochrane Library (Wiley)

Population
1. MeSH descriptor: (Influenza, Human) explode all trees
2. MeSH descriptor: (Influenzavirus A) explode all trees
3. 1 or 2
4. MeSH descriptor: (Pandemics) explode all trees
5. pandemic* (Word variations have been searched)
6. influenza* (Word variations have been searched)
7. flu* (Word variations have been searched)
8. grippe (Word variations have been searched)
9. 6 or 7 or 8
10. 5 and 9
11. 4 or 10
12. 3 and 11

Hand Hygiene:
13. MeSH descriptor: (Hand Hygiene) explode all trees
14. MeSH descriptor: (Hand Disinfection) explode all trees
15. (handwashing or hand washing or hand-washing) (Word variations have been searched)
16. ((hand*) adj3 (hygien* or disinfect* or sanitiz* or sanitis* or wash* or scrub* or cleans*)) (Word variations have been searched)
17. 13 or 14 or 15 or 16

Cough Etiquette:
18. MeSH descriptor: (Cough) explode all trees
19. ((cough*) and (influenza* or flu* or grippe)) (Word variations have been searched)
20. ((respirat* or breath* or sneez* or cough*) adj3 (etiquette* or custom* or maneuver* or practic*)) (Word variations have been searched)
21. Or/18–20

Masks:
22. MeSH descriptor: (Masks) explode all trees
23. (mask* or facemask* or N95* or N-95*) (Word variations have been searched)
24. (influenza* or flu* or grippe) (Word variations have been searched)
25. 23 and 24
26. 22 or 25

Total:
27. 17 or 21 or 26

28. 12 and 27

5. CINAHL

Population
1. (MH "Influenza+")
2. (MH "Pandemic+")
3. TX pandemic*
4. TX (influenza* or flu* or grippe)
5. 3 and 4
6. 2 or 5
7. 1 and 6

Hand Hygiene:
8. (MH hand hygiene)
9. (MH hand washing)
10. (MH hand disinfection)
11. TX (handwashing or hand washing or hand-washing)
12. (TX hand*)
13. TX (hygien* or disinfect* or sanitiz* or sanitis* or wash* or scrub* or cleans*)
14. 12 and 13
15. 8 or 9 or 10 or 11 or 14

Cough Etiquette:
16. (MH cough*)
17. TX cough*
18. 4 and 17
19. TX (respirat* or breath* or sneez* or cough*)
20. TX (etiquette* or custom* or maneuver* or practic*)
21. 19 and 20
22. 16 or 18 or 21

Masks:
23. (MH Mask*)
24. TX (mask* or facemask* or N95* or N-95*)
25. 4 and 24
26. 23 or 25

Total:
27. 15 or 22 or 26
28. 7 and 27

Appendix 12. Articles excluded during full review for systematic review and meta-analysis of personal protective measure effectiveness

Reference	Reason for exclusion (exclusion category: description)
Agolory, S.G.; Barbot, O.; Averhoff, F.; Weiss, D.; Wilson, E.; Egger, J.; Miller, J.; Ogbuanu, I.; Walton, S.; Kahn, E. Implementation of non-pharmaceutical interventions by new york city public schools to prevent 2009 influenza a. *PloS one* **2013**, *8*, e50916.	Outcome: Study does not evaluate influenza transmission.
Alexander, D.C.; Winter, A.L.; Eshaghi, A.; Dooling, K.; Frenette, C.; De Villa, E.; Varia, M.; Marchand-Austin, A.; Jamieson, F.; Gubbay, J.B. Transmission of influenza a pandemic (h1n1) 2009 virus in a long-term care facility in ontario, canada. *Infection control and hospital epidemiology* **2010**, *31*, 1300-1302.	Outcome: Risk of pandemic influenza infection not examined.
Ang, B.; Poh, B.F.; Win, M.K.; Chow, A. Surgical masks for protection of health care personnel against pandemic novel swine-origin influenza a (h1n1)-2009: Results from an observational study. *Clinical Infectious Diseases* **2010**, *50*, 1011-1014.	Outcome: Risk of pandemic influenza infection not examined.
Becker, C. Influenza pandemic - not all face masks are equally protective. *Pharmazeutische Zeitung* **2006**, *151*, 38-40.	Study type: Commentary
Brantsaeter, A.B. Did vaccines and hygiene recommendations affect the pandemics?. *Pavirket vaksine og hygienerad pandemien?* **2011**, *131*, 662.	Study type: Commentary
Canini, L.; Andreoletti, L.; Ferrari, P.; Angelo, R.D.; Blanchon, T.; Lemaitre, M.; Filleul, L.; Ferry, J.P.; Desmaizieres, M.; Smadja, S., *et al.* Surgical mask to prevent influenza transmission in households: A cluster randomized trial. *PloS one* **2010**, *5*, e13998.	Population: Population not exposed to pandemic influenza.
Cauteren, D.V.; Vaux, S.; Valk, H.d.; Strat, Y.L.; Vaillant, V.; Levy-Bruhl, D. Burden of influenza, healthcare seeking behaviour and hygiene measures during the a(h1n1)2009 pandemic in france: A population based study. *BMC public health* **2012**, *12*, 947.	Outcome: Study does not examine risk of pandemic influenza transmission.
Cohen, N.J.; Callahan, D.B.; Gonzalez, V.; Balaban, V.; Wang, R.T.; Pordell, P.; Beato, R.; Oyervides, O.; Huang, W.T.; Massoudi, M.S. Respiratory illness in households of school-	Study type: Letter to the editor

dismissed students during pandemic (h1n1) 2009. *Emerg Infect Dis* **2011**, *17*, 1756-1757.	
Cowling, B.J.; Chan, K.H.; Fang, V.J.; Cheng, C.K.; Fung, R.O.; Wai, W.; Sin, J.; Seto, W.H.; Yung, R.; Chu, D.W., *et al.* Facemasks and hand hygiene to prevent influenza transmission in households: A cluster randomized trial. *Annals of internal medicine* **2009**, *151*, 437-446.	Population: Not pandemic influenza
Cowling, B.J.; Leung, G.M. Simple physical interventions such as hand washing and wearing masks can reduce spread of respiratory viruses. *Evidence-Based Medicine* **2010**, *15*, 3.	Study type: Commentary
Dawes, M. Using physical barriers to reduce the spread of respiratory viruses. *BMJ* **2008**, *336*, 55-56.	Study type: Commentary
Delabre, R.M.; Lapidus, N.; Salez, N.; Mansiaux, Y.; de Lamballerie, X.; Carrat, F. Risk factors of pandemic influenza a/h1n1 in a prospective household cohort in the general population: Results from the copanflu-france cohort. *Influenza and other respiratory viruses* **2015**, *9*, 43-50.	Population: Not pandemic influenza
Deris, Z.Z.; Hasan, H.; Sulaiman, S.A.; Wahab, M.S.; Naing, N.N.; Othman, N.H. The prevalence of acute respiratory symptoms and role of protective measures among malaysian hajj pilgrims. *J Travel Med* **2010**, *17*, 82-88.	Population: Not pandemic influenza
Dominguez, A.; Alonso, J.; Astray, J.; Baricot, M.; Canton, R.; Castilla, J.; Castro, A.; Delgado, M.; Godoy, P.; Gonzalez-Candelas, F., *et al.* Risk factors of influenza (h1n1) 2009 hospitalization and effectiveness of pharmaceutical and nonpharmaceutical interventions in its prevention. A case-control study. *Revista espanola de salud publica* **2011**, *85*, 3-17.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection
Dos Santos, R.P.; Konkewicz, L.R.; Nagel, F.; Lisboa, T.; Jacoby, T.; Gastal, S.L.; Kuplich, N.M.; Sander, G.; Pires, M.; Lovatto, C.G. The 2009 h1n1 influenza a pandemic and hand hygiene practices in a hospital in the south of brazil. *Infection control and hospital epidemiology* **2010**, *31*, 1313-1315.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection
Dzyakanava, V.; Burningham, K.; Stahl, J. Virucidal efficacy of topical antiseptics versus a novel strain of influenza h1n1. *International Journal of Infectious Diseases* **2010**, *14*, e248.	Outcome: Study does not examine risk of pandemic influenza infection

Elachola, H.; Assiri, A.M.; Memish, Z.A. Mass gathering-related mask use during 2009 pandemic influenza a (h1n1) and middle east respiratory syndrome coronavirus. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases* **2014**, *20*, 77-78.	Study type: Letter to the editor
Flisser, A.; Cruz-Licea, V.; Gonzalez-Dominguez, F. Preventive measures associated with probable cases of a (h1n1) influenza in inhabitants of the federal district of mexico city. *American Journal of Tropical Medicine and Hygiene* **2010**, *83*, 356-357.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection
Gerald, L.B.; Gerald, J.K.; Zhang, B.; McClure, L.A.; Bailey, W.C.; Harrington, K.F. Can a school-based hand hygiene program reduce asthma exacerbations among elementary school children? *The Journal of allergy and clinical immunology* **2012**, *130*, 1317-1324.	Outcome: Examining asthma exacerbations, not pandemic influenza transmission.
Grayson, M.L.; Melvani, S.; Druce, J.; Barr, I.G.; Ballard, S.A.; Johnson, P.D.; Mastorakos, T.; Birch, C. Efficacy of soap and water and alcohol-based hand-rub preparations against live h1n1 influenza virus on the hands of human volunteers. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **2009**, *48*, 285-291.	Population: Study sheds light on risk of transmission; however, does not explicitly examine transmission of a pandemic influenza.
Harwood, J.L.; LaVan, J.T.; Brand, G.J.; nd. Two aircraft carriers' perspectives: A comparative of control measures in shipboard h1n1 outbreaks. *Disaster Med Public Health Prep* **2012**, *7*, 29-35.	Comparison: there is no comparison group
Hobday, R.A.; Cason, J.W. The open-air treatment of pandemic influenza. *American journal of public health* **2009**, *99 Suppl 2*, S236-242.	Study type: Review article
Lapidus, N.; de Lamballerie, X.; Salez, N.; Setbon, M.; Delabre, R.M.; Ferrari, P.; Moyen, N.; Gougeon, M.-L.; Vely, F.; Leruez-Ville, M., et al. Factors associated with post-seasonal serological titer and risk factors for infection with the pandemic a/h1n1 virus in the French general population. PloS one 2013, 8, e60127.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection
Larson, E.L.; Cohen, B.; Baxter, K.A. Analysis of alcohol-based hand sanitizer delivery systems: Efficacy of foam, gel, and wipes against influenza a (h1n1) virus on hands. *American Journal of Infection Control* **2012**, *40*, 806-809 804p.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection

Liu, Y.X.; Suo, J.J.; Du, M.M.; Gao, Z.Y.; Yi, J.M.; Xing, Y.B.; Liu, G.; Zhang, S.B.; Liu, L.; Yao, W., *et al.* Assessment of the risk of nosocomial 2009 h1n1 influenza infection among obstetric care workers. *International Journal of Gynecology and Obstetrics* **2011**, *112*, 140-141.	Study type: case series
Loeb, M.; Dafoe, N.; Mahony, J.; John, M.; Sarabia, A.; Glavin, V.; Webby, R.; Smieja, M.; Earn, D.J.; Chong, S., *et al.* Surgical mask vs n95 respirator for preventing influenza among health care workers: A randomized trial. *Jama* **2009**, *302*, 1865-1871.	Population: Not exposed to pandemic influenza
Loustalot, F.; Silk, B.J.; Gaither, A.; Shim, T.; Lamias, M.; Dawood, F.; Morgan, O.W.; Fishbein, D.; Guerra, S.; Verani, J.R., *et al.* Household transmission of 2009 pandemic influenza a (h1n1) and nonpharmaceutical interventions among households of high school students in san antonio, texas. *Clinical Infectious Diseases* **2011**, *52*, S146-S153.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection
Mielke, M.; Nassauer, A. Pandemic influenza: Nonpharmaceutical protective measures in ambulatory care. *Grippeverdacht in der Hausarztpraxis. So schutzen Sie Ihr Team und andere Patienten.* **2009**, *151*, 32-34.	Study type: Guidance document / commentary
Miller, J.R.; Short, V.L.; Wu, H.M.; Waller, K.; Mead, P.; Kahn, E.; Bahn, B.A.; Dale, J.W.; Nasrullah, M.; Walton, S.E., *et al.* Use of nonpharmaceutical interventions to reduce transmission of 2009 pandemic influenza a (ph1n1) in pennsylvania public schools. *The Journal of school health* **2013**, *83*, 281-289.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection
Mitka, M. Face masks, respirators might help during pandemic flu outbreak. *Jama* **2007**, *297*, 2338.	Study type: Editorial/commentary
Savolainen-Kopra, C.; Haapakoski, J.; Peltola, P.A.; Ziegler, T.; Korpela, T.; Anttila, P.; Amiryousefi, A.; Huovinen, P.; Huvinen, M.; Noronen, H., *et al.* Hand washing with soap and water together with behavioural recommendations prevents infections in common work environment: An open cluster-randomized trial. *Trials* **2012**, *13*, no pagination.	Population: does not specifically address pandemic influenza infection rates

Simmerman, J.M.; Suntarattiwong, P.; Levy, J.; Gibbons, R.V.; Cruz, C.; Shaman, J.; Jarman, R.G.; Chotpitayasunondh, T. Influenza virus contamination of common household surfaces during the 2009 influenza a (h1n1) pandemic in bangkok, thailand: Implications for contact transmission. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **2010**, *51*, 1053-1061.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection
Suess, T.; Remschmidt, C.; Schink, S.; Luchtenberg, M.; Haas, W.; Krause, G.; Buchholz, U. Facemasks and intensified hand hygiene in a german household trial during the 2009/2010 influenza a(h1n1) pandemic: Adherence and tolerability in children and adults. *Epidemiol Infect* **2011**, *139*, 1895-1901.	Outcome: Study does not examine risk of pandemic influenza transmission.
Tang, J.W.; Li, Y. Transmission of influenza a in human beings. *Lancet Infectious Diseases* **2007**, *7*, 758.	Study type: Commentary
Weedon, K.M.; Rupp, A.H.; Heffron, A.C.; Kelly, S.F.; Zheng, X.; Shulman, S.T.; Gutman, P.; Wang, D.; Zhou, Y.; Noskin, G.A., *et al.* The impact of infection control upon hospital-acquired influenza and respiratory syncytial virus. *Scandinavian journal of infectious diseases* **2013**, *45*, 297-303.	Population: Compares hand hygiene impact across seasons, not within pandemic period. Given that practices also changed during pandemic season (N95 masks and isolation), these cannot be compared.
Yeom, J.S.; Lee, J.H.; Bae, I.G.; Oh, W.S.; Moon, C.S.; Park, K.H.; Lee, J.H.; Kim, E.S.; Kwak, Y.G.; Lee, C.S. 2009 h1n1 influenza infection in korean healthcare personnel. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* **2011**, *30*, 1201-1206.	Outcome: Study did not quantify risk of pandemic influenza transmission.
Zakhashvili, K.; Imnadze, P.; Tarkhan-Mouravi, O. Analysis of first cluster outbreak of the pandemic influenza (h1n1) in georgia. *International Journal of Infectious Diseases* **2010**, *14*, e90-e91.	Outcome: Study did not quantify risk of pandemic influenza transmission.

Appendix 13. Summary of individual study results

RCT Studies	Population Size	Intervention(s)	Outcome(s)	Risk (Control Group)	Risk (intervention group)	Estimate of Effect (95% CI)
Azor-Martinez et al., 2014	1,616	Hand sanitizer	% total absent days (95% CI)	1 (0.9–1.1)	0.38 (0.32–0.45)	RR: 2.64 (2.16–3.21)
Azor-Martinez et al., 2014	1,616	Hand sanitizer	Incidence of episodes/100 children/day (95% CI)	0.28 (0.22–0.33)	0.11 (0.08–0.15)	RR: 2.50 (1.73–3.62)
Suess et al., 2012	302	Facemasks	Laboratory-confirmed secondary influenza infection	13/56 (232.1/1,000)	6/58 (103.4/1,000)	OR: 0.28 (0.08–0.97)
Suess et al., 2012	302	Facemasks and hand hygiene	Laboratory-confirmed secondary influenza infection	13/56 (232.1/1,000)	4/50 (80/1,000)	OR: 0.26 (0.07–0.93)

Cohort Studies	Population Size	Intervention(s)	Outcome(s)	Risk (Control Group)	Risk (Intervention Group)	Estimate of Effect (95% CI)
Jaeger et al., 2011	63	Mask or N95 respirator use	Healthcare-associated, laboratory-confirmed influenza infection	9/43 (209.3/1,000)	0/20 (0/1,000)	P=0.047
Kuster et al., 2013	563	Hand hygiene	Laboratory-confirmed influenza infection	Not reported	Not reported	Adherence to hand hygiene recommendations per 10% increase: OR: 0.84 (0.73–0.98)/AOR: 0.86 (0.74–0.99)
Kuster et al., 2013	563	Facial protection	Laboratory-confirmed influenza infection	Not reported	Not reported	Adherence to facial protection recommendations per 10% increase: OR: 0.92 (0.79–1.07)/AOR: N/A
Merck et al., 2014	2,865	Handwashing frequency (≥20 vs 2–4 times daily)	Self-reported influenza-like illness	Not reported	Not reported	CRR: 1.23 (0.82–1.85); ARR: 1.06 (0.68–1.67)

Remschmidt et al., 2013	230	Always/often cleaned hands in general	Self-reported ILI secondary household infection	10/116 (86.2/1,000)	16/144 (111.1/1,000)	OR: 1.30 (0.6–3.0)
Remschmidt et al., 2013	48	Always/mostly cleaned hands after physical contact with index patient	Self-reported ILI secondary household infection	2/19 (105.3/1,000)	1/29 (34.5/1,000)	OR: 0.30 (0.02–3.60)
Remschmidt et al., 2013	256	Always/mostly cleaned hands after contact with physical items used by the index patient	Self-reported ILI secondary household infection	21/202 (104.0/1,000)	5/54 (92.6/1,000)	OR: 0.90 (0.30–2.40)

Case–Control Studies	Population Size	Cases	Controls	Interventions	Risk (Control Group)	Risk (Intervention Group)	Estimate of Effect (95% CI)
Cheng et al., 2010	836	Exposed healthcare workers who became infected with influenza	Exposed healthcare workers who did not become infected with influenza	Exposed person wore surgical mask use during contact with index case	4/268 (14.9/1,000)	0/568 (0/1,000)	p=0.01
Cheng et al., 2010	836	Exposed healthcare workers who became infected with influenza	Exposed healthcare workers who did not become infected with influenza	Index case wore mask during contact with the exposed	4/304 (13.2/1,000)	0/532 (0/1,000)	p=0.017
Cheng et al., 2010	836	Exposed healthcare workers who became infected with influenza	Exposed healthcare workers who did not become infected with influenza	Exposed person practiced hand hygiene after contact with index case	3/262 (11.5/1,000)	1/574 (1.74/1,000)	p=0.094

Deng et al., 2011	280	Exposed healthcare workers who became infected with influenza	Exposed healthcare workers who did not become infected with influenza	Exposed person used disposable tissues to wash hands	41/172 (238.4/1,000)	13/98 (132/1,000)	OR: 0.49 (0.25–0.97)
Deng et al., 2011	280	Exposed healthcare workers who became infected with influenza	Exposed healthcare workers who did not become infected with influenza	Exposed person used a surgical mask	21/76 (276.3/1,000)	33/194 (170.1/1,000)	OR: 0.54 (0.29–1.01)
Godoy et al., 2012	3,087	Individuals hospitalizaed with laboratory-confirmed influenza	Two patients with unplanned hospitalization not due to influenza and one outpatient control not related to influenza	Frequency of handwashing (5–10 times daily vs 1–4 times daily baseline)	320/1056 (303.0/1,000)	285/1156 (247.4/1,000)	COR: 0.73 (0.60–0.89); AOR 0.65 (0.52–0.84)

Godoy et al., 2012	3,087	Individuals hospitalizaed with laboratory-confirmed influenza	Two patients with unplanned hospitalization not due to influenza and one outpatient control not related to influenza	Frequency of handwashing (>10 times daily vs 1–4 times daily baseline)	320/1056 (303.0/1,000)	181/825 (219.4/1,000)	COR: 0.58 (0.46–0.73) AOR: 0.59 (0.44–0.79)
Godoy et al., 2012	3,087	Individuals hospitalizaed with laboratory-confirmed influenza	Two patients with unplanned hospitalization not due to influenza and one outpatient control not related to influenza	Use of alcohol-based sanitizers (sometimes vs never)	533/2069 (267.3/1,000)	231/973 (237.4/1,000)	COR: 0.83 (0.68–1.01); AOR: 0.82 (0.65–1.02)
Godoy et al., 2012	3,087	Individuals hospitalizaed with laboratory-confirmed influenza	Two patients with unplanned hospitalization not due to influenza and one outpatient control not related to influenza	Handwashing after touching contaminated surfaces (occasionally/always vs never)	196/599 (327.2/1,000)	600/2452 (244.7/1,000)	COR: 0.58 (0.46–0.73); AOR: 0.65 (0.50–0.84)

Li et al., 2011	1,644	Handwashing ("frequent"/"infrequent")	Laboratory-confirmed influenza infection	88/293 (300.3/1,000)	417/1,277 (326.6/1,000)	OR: 1.13 (0.86–1.49)	
Liu et al., 2011	216	Individuals who developed secondary infection from infected household member	Individuals who did not develop secondary infection from infected household member	Have the habit of washing hands (yes/no)	Not reported	Not reported	OR: 0.71 (0.48–0.94)
Torner et al., 2015	478	Child outpatients with confirmed influenza infection	Child outpatients with illness unrelated to influenza or acute respiratory tract infection	Handwashing frequency (≥5 vs 1–4 times daily)	123/230 (534.8/1,000)	112/239 (468.6/1,000)	COR: 0.69 (0.45–1.04); AOR: 0.62 (0.39–0.99)

Torner et al., 2015	478	Child outpatients with confirmed influenza infection	Child outpatients with illness unrelated to influenza or acute respiratory tract infection	Use of alcohol-based sanitizers (sometimes vs never)	158/328 (481.7/1,000)	77/142 (542.3/1,000)	COR: 1.36 (0.85–2.17); AOR: 1.54 (0.80–2.66)
Torner et al., 2015	478	Child outpatients with confirmed influenza infection	Child outpatients with illness unrelated to influenza or acute respiratory tract infection	Handwashing after touching contaminated surfaces (sometimes vs never)	50/93 (537.6/1,000)	184/376 (489.4/1,000)	COR: 0.73 (0.41–1.32); AOR: 0.62 (0.29–1.31)
Zhang et al., 2013	262 households	Household with quarantined individual with influenza infection that experienced a secondary infection	Household with quarantined individual with influenza infection that did not experience a secondary infection	Handwashing frequency (≥3 times daily)	Not reported	Not reported	OR: 0.71 (0.48–0.94)

Zhang et al., 2012	164	Full-time, exposed healthcare worker infected with confirmed pandemic influenza	Full-time, exposed healthcare worker that did not experience ILI or influenza	Mask-wearing (always vs seldom/never)	2/12 (166.7/1,000)	33/152 (217.1/1,000)	P=0.344
Zhang et al., 2012	255	Full-time, exposed healthcare worker infected with confirmed pandemic influenza	Full-time, exposed healthcare worker that did not experience ILI or influenza	Number of masks used daily (≥2)	18/84 (214.3/1,000)	33/171 (193.0/1,000)	P=0.798
Zhang et al., 2012	28	Full-time, exposed healthcare worker infected with confirmed pandemic influenza	Full-time, exposed healthcare worker that did not experience ILI or influenza	Use of N95 respiratory (vs never wore mask)	2/12 (166.7/1,000)	3/16 (187.5/1,000)	P=0.796

Zhang et al., 2012	255	Full-time, exposed healthcare worker infected with confirmed pandemic influenza	Full-time, exposed healthcare worker that did not experience ILI or influenza	Hand-washing after caring for patient	2/2 (1,000/1,000)	49/253 (193.7/1,000)	N/A
Zhang et al., 2012	255	Full-time, exposed healthcare worker infected with confirmed pandemic influenza	Full-time, exposed healthcare worker that did not experience ILI or influenza	Hand drying (disposable paper towel vs work clothes/reusable towel	24/95 (252.6/1,000)	11/86 (127.9/1,000)	P=0.065

Cross-Sectional Studies	Population Size	Comparison	Interventions	Risk (Control Group)	Risk (Intervention Group)	Estimate of Effect (95% CI)
Kim et al., 2012	15,945	Children with/without H1N1 infection	Handwashing (frequent/ infrequent)	Not reported	Not reported	OR: 0.99 (0.96–1.02)
Kim et al., 2012	15,945	Children with/without H1N1 infection	Facemasks (continuous vs non-users)	239/4,403 (54.3/1,000)	14/480 (29.2/1,000)	OR: 0.51 (0.30–0.88)
Kim et al., 2012	15,945	Children with/without H1N1 infection	Facemasks (irregular vs non-users)	239/4,403 (54.3/1,000)	164/2,983 (55.0/1,000)	OR: 1.02 (0.83–1.25)

Toyokawa et al., 2011	97	Healthcare workers with/without H1N1 infection	Hand hygiene (frequent/infrequent)	6/76 (79.0/1,000)	1/21 (47.6/1,000)	OR: 0.58 (0.07–5.13)
Toyokawa et al., 2011	87	Healthcare workers with/without H1N1 infection	Surgical masks use in ED (frequent/infrequent)	4/83 (41.2/1,000)	1/4 (250/1,000)	OR: 6.59 (0.55–78.3)
Toyokawa et al., 2011	87	Healthcare workers with/without H1N1 infection	N95 respiratory use in ED (frequent/infrequent)	4/77 (52.0/1,000)	1/10 (100/1,000)	OR: 2.28 (0.20–20.2)

RR = relative rate; CRR = crude relative rate; ARR = adjusted relative rate; OR = odds ratio; COR = crude odds ratio; AOR = adjusted odds ratio.

Appendix 14. Ottawa–Gatineau CMA profile [385]

Table A13.1 outlines the parameter values of interest for the study population.

Table A13.1. Ottawa–Gatineau CMA profile.

Population By Age	
0–4	71,245
5–18	204,920
19–29	190,640
30–64	622,640
65+	156,875
Total	1,246,320
Average Earnings/Employment	
Earnings Per Week (CAD)	$962.73
Earnings Per Day (CAD)	$192.55
Unemployment Rate (%)	6.5
Hospital Resources	
Acute Beds	1,822
ICU beds	269
Other Beds	2,245
Total Beds	4,336

Appendix 15. Results of basic analysis: symptomatic infection

Table A15.1 provides the best-guess results for the number of symptomatic infections predicted for each of the 192 intervention bundles.

Table A15.1. Predicted number of symptomatic infections (95% confidence intervals).

Non-pharmaceutical intervention component	Pharmaceutical intervention component							
	None	**V**	**AVT**	**AVP**	**V+AVT**	**V+AVP**	**AVT+AVP**	**V+AVT+AVP**
None	677,545.6 (675,672.7–679,418.5)	624,361.0 (622,704.8–626,017.1)	676,264.3 (674,397.7–678,130.9)	658,482.4 (656,726.4–660,238.4)	622,681.4 (621,032.4–624,330.4)	602,439.4 (600,895.8–603,983.0)	656,784.5 (655,036.0–658,533.1)	600,393.7 (598,857.7–601,929.6)
SC	669,926.3 (668,396.9–671,455.8)	615,810.6 (614,462.5–617,158.8)	668,568.7 (557,044.7–670,092.7)	650,145.8 (648,706.4–651,585.2)	614,039.0 (612,696.9–615,391.0)	593,213.0 (591,951.1–594,474.9)	648,352.9 (646,919.8–649,785.9)	591,062.2 (589,806.9–592,317.6)
CCR	673,285.1 (671,438.9–675,131.4)	618,840.9 (617,212.0–620,132.4)	671,954.8 (670,114.9–673,794.7)	653,202.5 (651,473.8–654,931.1)	617,095.2 (615,473.5–618,717.0)	595,677.8 (594,161.9–597,193.7)	651,434.2 (649,713.0–653,155.4)	593,541.2 (592,032.9–595,049.6)
PPM	566,469.3 (564,972.2–567,966.3)	481,604.2 (480,337.0–482,871.3)	563,665.9 (562,174.7–565,157.1)	517,570.0 (516,202.4–518,937.6)	477,916.2 (476,656.2–479,176.2)	427,382.3 (426,248.4–428,516.2)	513,693.6 (512,333.3–515,053.8)	422,936.1 (421,810.9–424,061.3)
VI	429,995.3 (428,933.3–431,057.3)	361,321.5 (360,432.4–362,210.6)	427,631.6 (426,579.9–428,689.2)	398,100.5 (397,117.1–399,083.9)	359,612.4 (358,728.8–360,496.1)	327,559.5 (326,750.9–328,368.1)	395,034.3 (394,056.5–396,012.2)	324,237.1 (323,434.8–325,039.4)
Q	422,404.3 (421,358.8–423,449.9)	352,957.7 (352,086.3–353,829.1)	419,983.8 (418,941.7–421,024.9)	389,727.7 (388,761.6–396,693.7)	351,256.3 (350,390.3–352,122.3)	318,687.9 (317,898.1–319,477.7)	386,599.7 (385,639.3–387,560.1)	315,327.6 (314,544.2–316,111.0)
SC+CCR	664,585.0 (663,081.3–666,088.7)	608,993.0 (607,670.7–610,315.2)	663,171.3 (661,673.1–664,669.5)	643,580.7 (642,167.4–644,994.0)	607,140.6 (605,824.4–608,456.8)	585,006.4 (583,770.7–586,242.1)	641,703.0 (640,296.1–643,109.9)	582,748.2 (581,519.0–583,977.4)
SC+PPM	551,833.9 (550,620.1–553,047.6)	466,171.1 (465,151.2–467,191.1)	548,868.3 (547,659.6–550,076.9)	502,294.3 (501,183.0–503,405.5)	462,338.3 (461,324.7–463,351.9)	412,295.5 (411,382.3–413,208.8)	498,262.3 (497,157.6–499,367.0)	408,108.7 (407,2020.8–409,014.7)

SC+VI	404,037.0 (403,239.7–404,834.4)	340,858.5 (340,192.0–341,524.9)	401,751.4 (400,957.6–402,545.2)	377,595.9 (376,848.2–378,343.7)	339,254.4 (338,592.1–339,916.6)	313,099.3 (312,483.3–313,715.3)	374,688.0 (373,944.7–375,431.3)	309,995.2 (309,384.1–310,606.3)
SC+Q	397,015.4 (396,229.6–397,801.3)	333,341.0 (332,686.7–333,995.3)	394,691.0 (393,908.7–395,473.3)	370,017.0 (369,281.5–370,752.6)	331,784.6 (331,098.5–332,398.8)	305,329.2 (304,725.9–305,932.4)	367,067.3 (366,336.2–367,798.3)	302,193.4 (301,595.0–302,791.7)
CCR+PPM	554,925.6 (553,450.3–556,400.9)	467,353.0 (466,111.1–468,594.8)	551,950.3 (550,480.8–553,419.7)	503,121.8 (501,779.4–504,464.3)	463,477.3 (462,242.9–464,711.7)	410,710.8 (409,607.5–411,814.1)	499,033.5 (497,698.7–500,368.3)	406,098.0 (405,003.8–407,192.1)
CCR+VI	418,722.9 (417,684.0–419,761.7)	348,947.7 (348,083.6–349,811.7)	416,265.3 (415,230.9–417,299.6)	384,181.9 (383,223.5–385,140.3)	345,958.0 (345,099.5–346,816.4)	313,135.0 (312,354.4–313,915.6)	381,359.4 (380,406.8–382,311.9)	309,735.0 (308,961.0–310,509.1)
CCR+Q	414,791.9 (413,761.5–415,822.4)	344,659.4 (343,804.4–345,514.4)	412,305.8 (411,279.8–413,331.7)	379,839.2 (378,889.7–380,788.6)	341,645.6 (340,796.2–342,494.9)	308,614.1 (307,843.2–309,385.0)	377,003.0 (376,059.4–377,946.6)	305,198.5 (304,434.3–305,962.8)
PPM+VI	219,412.5 (218,760.7–220,064.2)	155,234.1 (154,784.2–155,684.0)	216,115.5 (215,472.0–216,758.9)	176,698.9 (176,177.4–177,220.5)	152,190.3 (151,748.7–152,631.9)	122,052.8 (121,707.6–122,398.1)	173,209.5 (172,697.4–173,721.6)	119,291.8 (118,954.4–119,629.3)
PPM+Q	209,894.0 (209,268.9–210,519.1)	147,486.9 (147,060.2–147,913.7)	206,643.7 (206,027.0–207,136.1)	168,239.4 (167,763.0–168,735.8)	144,530.3 (144,111.8–144,948.9)	115,608.6 (115,283.2–115,934.1)	164,838.6 (164,351.6–165,325.7)	112,951.4 (112,633.5–113,269.3)
SC+CCR+PPM	538,366.3 (537,174.5–539,558.1)	450,131.1 (449,136.5–451,125.7)	535,216.1 (534,029.5–536,402.7)	485,995.2 (484,909.2–487,081.1)	446,110.6 (445,122.6–447,098.6)	394,095.3 (393,211.9–394,978.6)	481,748.6 (480,669.5–482,827.7)	89,405.9 (388,530.6–390,281.1)
SC+CCR+VI	392,272.7 (391,494.9–393,050.6)	328,574.7 (327,928.5–329,220.9)	390,043.7 (389,369.7–390,817.6)	363,723.5 (362,996.5–364,450.4)	325,769.8 (325,128.0–326,411.7)	299,054.2 (298,460.2–299,648.1)	361,060.5 (360,338.2–361,782.8)	295,888.4 (295,299.4–296,477.3)
SC+CCR+Q	388,785.1 (388,013.4–389,556.8)	324,732.6 (324,092.7–325,372.6)	386,403.6 (385,635.5–387,171.7)	359,808.0 (359,087.4–360,528.7)	321,912.9 (321,277.3–322,548.6)	295,038.2 (294,450.9–295,625.5)	357,138.6 (356,422.6–357,854.6)	291,863.0 (291,280.7–292,445.3)
SC+PPM+VI	207,908.3 (207,424.6–208,392.0)	149,873.1 (149,530.9–150,215.4)	204,853.9 (204,376.1–205,331.7)	171,437.2 (171,036.7–171,837.8)	147,034.9 (146,698.8–147,371.1)	120,501.3 (120,229.3–120,773.3)	168,134.1 (167,740.5–168,527.7)	117,821.1 (117,555.0–118,087.1)

SC+PPM+Q	199,537.5 (199,070.8–200,004.2)	142,904.2 (142,577.2–143,231.1)	196,550.5 (196,089.9–197,011.1)	163,795.8 (163,412.0–164,179.6)	140,100.7 (139,779.7–140,421.7)	114,484.0 (114,225.7–114,742.2)	160,563.8 (160,186.9–160,940.7)	111,893.9 (111,641.5–112,146.4)
CCR+PPM+VI	203,770.7 (203,160.2–204,381.2)	141,972.4 (141,559.7–142,385.1)	200,536.9 (199,934.9–201,138.9)	161,963.3 (161,482.9–162,443.6)	139,066.3 (138,661.7–139,470.9)	110,768.1 (110,455.5–111,080.6)	157,867.3 (157,397.9–158,336.7)	108,178.0 (107,872.8–108,483.1)
CCR+PPM+Q	199,101.2 (198,504.2–199,698.3)	138,272.4 (137,871.0–138,673.9)	195,896.8 (195,308.3–196,485.4)	157,905.4 (157,437.4–158,373.3)	135,413.1 (135,019.7–135,806.5)	107,729.2 (107,426.1–108,032.3)	153,868.1 (153,411.0–154,325.2)	105,191.9 (104,896.1–105,487.7)
SC+CCR+PPM+VI	193,101.9 (192,647.5–193,556.4)	137,165.9 (136,850.3–137,481.4)	190,106.0 (189,657.6–190,554.4)	157,202.8 (156,832.2–157,573.3)	134,411.7 (134,102.1–134,721.2)	109,358.7 (109,111.2–109,606.1)	153,353.4 (152,990.8–153,715.9)	106,856.3 (106,614.6–107,098.1)
SC+CCR+PPM+Q	189,014.7 (188,568.8–189,460.7)	133,807.2 (133,499.1–134,115.2)	186,025.1 (185,585.3–186,465.0)	153,539.8 (153,177.6–153,902.1)	131,093.3 (130,791.1–131,395.5)	106,520.4 (106,279.6–106,761.2)	149,706.7 (149,352.4–150,060.9)	104,050.6 (103,815.4–104,285.8)

Appendix 16. Results of basic analysis: acute–care hospital admissions

Table A16.1 provides the best-guess results for the number of hospitalizations predicted for each of the 192 intervention bundles.

Table A16.1. Predicted number of hospitalizations (95% confidence intervals).

Non-pharmaceutical intervention component	Pharmaceutical intervention component							
	None	**V**	**AVT**	**AVP**	**V+AVT**	**V+AVP**	**AVT+AVP**	**V+AVT+AVP**
None	2,472.0 (2,467.7–2,476.3)	909.7 (908.2–911.3)	2,218.6 (2,214.7–2,222.4)	2,110.8 (2,107.2–2,114.3)	815.4 (814.0–816.7)	769.5 (768.2–770.7)	2,101.7 (2,098.2–2,105.3)	765.4 (764.2–766.7)
SC	2,430.1 (2,426.5–2,433.6)	890.9 (889.6–892.1)	2,180.5 (2,177.3–2,183.7)	2,069.7 (2,066.7–2,072.7)	798.2 (797.1–799.4)	751.4 (750.3–752.4)	2,060.3 (2,057.3–2,063.2)	747.2 (746.2–748.2)
CCR	2,452.3 (2,448.1–2,456.6)	899.7 (898.2–901.2)	2,200.7 (2,196.9–2,204.5)	2,089.0 (2,085.5–2,092.6)	806.3 (804.9–807.6)	758.6 (757.4–759.8)	2,079.8 (2,076.3–2,083.3)	745.5 (753.2–755.7)
PPM	1,956.7 (1,953.2–1,960.2)	655.8 (653.6–657.9)	1,749.4 (1,746.2–1,752.5)	1,550.0 (1,547.2–1,552.8)	584.3 (583.2–585.3)	504.0 (503.1–504.9)	1,534.3 (1,531.5–1,537.1)	497.4 (496.5–498.4)
VI	1,479.9 (1,477.6–1,482.1)	492.0 (491.3–492.8)	1,322.5 (1,320.5–1,324.6)	1,194.0 (1,192.3–1,195.8)	440.3 (439.6–440.9)	388.6 (388.0–389.2)	1,182.0 (1,180.3–1,183.8)	383.7 (383.2–384.3)
Q	1,448.9 (1,447.3–1,450.5)	478.9 (478.4–479.5)	1,294.5 (1,293.1–1,296.0)	1,164.8 (1,163.6–1,166.0)	428.5 (428.0–429.0)	376.7 (376.3–377.1)	1,152.7 (1,151.5–1,153.9)	371.9 (371.5–372.3)
SC+CCR	2,405.9 (2,402.4–2,409.4)	878.7 (877.4–879.9)	2,158.6 (2,155.4–2,161.7)	2,043.2 (2,040.3–2,046.1)	787.1 (786.0–788.3)	739.4 (737.4–739.5)	2,033.5 (2,030.6–2,036.4)	734.1 (733.1–735.1)
SC+PPM	1,881.2 (1878.3–1,884.1)	625.3 (624.3–626.3)	1,680.9 (1,678.3–1,683.5)	1,482.8 (1,480.5–1,485.0)	556.7 (555.9–557.6)	478.6 (477.9–479.4)	1,466.8 (1,464.5–1,469.0)	472.6 (471.8–473.3)

SC+VI	1,338.2 (1,336.5–1,339.9)	444.1 (443.5–444.6)	1,195.4 (1,193.8–1,196.9)	1,087.9 (1,086.6–1,089.2)	397.3 (396.8–367.8)	354.6 (354.2–355.0)	1,076.6 (1,075.3–1,077.9)	350.1 (349.7–350.5)
SC+Q	1,309.9 (1,308.7–1,311.1)	432.5 (432.1–432.8)	1,169.8 (1,168.8–1,170.9)	1,061.8 (1,060.8–1,062.7)	386.9 (386.5–387.2)	344.6 (344.3–344.9)	1,050.4 (1,049.4–1,051.3)	340.1 (339.8–340.4)
CCR+PPM	1,905.0 (1,901.6–1,908.4)	631.9 (630.8–633.1)	1,702.3 (1,699.2–1,705.4)	1,496.2 (1,493.5–1,498.9)	562.6 (561.6–563.7)	480.9 (480.0–481.8)	1,480.0 (1,477.3–1,482.8)	474.2 (473.3–475.1)
CCR+VI	1,433.6 (1,431.4–1,435.9)	378.1 (377.5–378.6)	472.6 (471.8–473.3)	1,144.7 (1,143.0–1,146.4)	420.8 (420.1–421.4)	369.1 (368.6–369.7)	1,133.9 (1,132.2–1,135.6)	364.2 (363.7–364.8)
CCR+Q	1,417.7 (1,416.2–1,419.3)	465.9 (465.4–466.4)	1,266.3 (1,264.9–1,267.7)	1,129.7 (1,128.5–1,130.9)	414.8 (414.3–415.2)	363.1 (362.8–363.5)	1,118.9 (1,117.7–1,120.1)	358.3 (357.9–358.7)
PPM+VI	686.5 (685.2–687.7)	194.3 (193.9–194.6)	607.6 (606.5–608.7)	484.9 (484.1–485.8)	171.2 (170.9–171.5)	134.7 (134.5–135.0)	474.5 (473.7–475.3)	131.5 (131.3–131.7)
PPM+Q	654.6 (653.8–655.5)	184.2 (184.0–184.5)	579.2 (578.4–579.9)	460.8 (460.2–461.3)	162.3 (162.1–162.5)	127.5 (127.4–127.7)	450.6 (450.1–451.2)	124.4 (124.3–124.6)
SC+CCR+PPM	1,822.7 (1,819.9–1,825.6)	599.3 (598.3–600.2)	1,627.8 (1,625.2–1,630.3)	1,423.9 (1,421.7–1,426.1)	533.1 (532.3–534.0)	454.1 (453.4–454.8)	1,407.5 (1,405.3–1,409.7)	447.4 (446.7–448.1)
SC+CCR+VI	1,290.8 (1,289.1–1,292.4)	425.3 (424.7–425.8)	1,153.5 (1,152.0–1,154.9)	1,039.9 (1,038.6–1,041.2)	378.5 (378.0–379.0)	336.1 (335.7–336.5)	1,029.7 (1,028.5–1,031.0)	331.6 (331.2–332.0)
SC+CCR+Q	1,277.4 (1,276.2–1,278.5)	419.4 (419.0–419.8)	1,140.4 (1,139.4–1,141.5)	1,026.5 (1,025.6–1,027.4)	373.2 (372.9–373.6)	330.9 (330.6–331.2)	1,016.4 (1,015.5–1,017.3)	326.4 (326.1–326.7)
SC+PPM+VI	610.0 (609.1–610.8)	175.2 (175.0–175.5)	539.8 (539.0–540.5)	441.3 (440.7–441.9)	154.7 (154.5–154.9)	124.8 (124.7–125.0)	431.7 (431.2–432.2)	121.9 (121.7–122.0)

SC+PPM+Q	583.0 (582.4–583.6)	166.9 (166.8–167.1)	516.5 (516.0–517.1)	421.1 (420.6–421.5)	147.0 (146.9–147.2)	118.7 (118.6–118.8)	411.8 (411.4–412.2)	115.8 (115.7–115.9)
CCR+PPM+VI	633.6 (632.5–634.8)	176.9 (176.6–177.2)	560.4 (599.4–561.4)	442.4 (441.7–443.2)	155.7 (155.5–156.0)	122.0 (121.8–122.2)	430.3 (429.6–431.0)	119.0 (118.8–119.2)
CCR+PPM+Q	618.2 (617.4–619.0)	172.2 (172.0–172.4)	546.7 (546.0–547.4)	430.9 (430.4–431.5)	151.5 (151.3–151.7)	118.6 (118.5–118.7)	419.0 (418.5–419.5)	115.7 (115.5–115.8)
SC+CCR+PPM+VI	562.5 (561.7–563.3)	159.9 (159.7–160.1)	497.4 (496.7–498.1)	402.5 (402.0–403.1)	140.8 (140.6–141.0)	113.1 (112.9–113.2)	392.2 (391.7–392.7)	110.5 (110.4–110.7)
SC+CCR+PPM+Q	549.5 (548.9–550.1)	155.8 (155.7–156.0)	485.8 (485.3–486.3)	393.3 (392.9–393.7)	137.2 (137.0–137.3)	110.3 (110.2–110.4)	382.4 (382.1–382.8)	107.6 (107.5–107.7)

Appendix 17. Results of basic analysis: peak acute-care hospitalization demand

Table A17.1 provides the best-guess results for the peak acute care hospital demand (as a percentage of all acute hospital beds in the Ottawa–Gatineau CMA) for each of the 192 intervention bundles.

Table A17.1. Predicted peak acute care hospital bed demand (95% confidence intervals).

Non-pharmaceutical intervention component	Pharmaceutical intervention component							
	None	**V**	**AVT**	**AVP**	**V+AVT**	**V+AVP**	**AVT+AVP**	**V+AVT+AVP**
None	13.8 (13.1–14.5)	4.9 (4.6–5.1)	12.4 (11.7–13.0)	11.4 (10.8–11.9)	4.4 (4.1–4.6)	4.0 (3.8–4.2)	11.3 (10.7–11.9)	4.0 (3.8–4.2)
SC	13.3 (12.6–14.0)	4.7 (4.5–4.9)	11.9 (11.3–12.5)	10.9 (10.4–11.5)	4.2 (4.0–4.4)	3.8 (3.6–4.0)	10.9 (10.3–11.4)	3.8 (3.6–4.0)
CCR	13.6 (12.9–14.3)	4.8 (4.5–5.0)	12.2 (11.6–12.8)	11.2 (10.6–11.7)	4.3 (4.1–4.5)	3.9 (3.7–4.1)	11.1 (10.6–11.7)	3.9 (3.7–4.1)
PPM	10.5 (10.0–11.0)	3.5 (3.3–3.7)	9.4 (8.9–9.9)	8.3 (7.9–8.7)	3.1 (3.0–3.3)	2.7 (2.6–2.8)	8.2 (7.8–8.6)	2.7 (2.6–2.8)
VI	0.7 (0.7–0.8)	0.2 (0.2–0.2)	0.6 (0.6–0.7)	0.8 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.8 (0.8–0.9)	0.3 (0.3–0.3)
Q	0.7 (0.6–0.7)	0.2 (0.2–0.2)	0.6 (0.6–0.6)	0.8 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.8 (0.8–0.9)	0.3 (0.3–0.3)
SC+CCR	13.1 (12.4–13.7)	4.6 (4.4–4.8)	11.7 (11.1–12.3)	10.7 (10.2–11.3)	4.1 (3.9–4.3)	3.7 (3.5–3.9)	10.7 (10.1–11.2)	3.7 (3.5–3.9)

SC+PPM	10.0 (9.5–10.5)	3.3 (3.2–3.5)	9.0 (8.5–9.4)	7.9 (7.5–8.3)	3.0 (2.8–3.1)	2.6 (2.4–2.7)	7.8 (7.5–8.2)	2.6 (2.4–2.7)
SC+VI	1.2 (1.1–1.3)	0.4 (0.4–0.4)	1.1 (1.0–1.1)	1.2 (1.1–1.3)	0.4 (0.3–0.4)	0.4 (0.4–0.4)	1.2 (1.1–1.3)	0.4 (0.4–0.4)
SC+Q	1.2 (1.1–1.2)	0.4 (0.4–0.4)	1.0 (1.0–1.1)	1.2 (1.1–1.2)	0.3 (0.3–0.4)	0.4 (0.4–0.4)	1.2 (1.1–1.2)	0.4 (0.4–0.4)
CCR+PPM	10.3 (9.8–10.8)	3.4 (3.2–3.6)	9.2 (8.8–9.7)	8.1 (7.7–8.5)	3.1 (2.9–3.2)	2.6 (2.5–2.8)	8.0 (7.6–8.4)	2.6 (2.5–2.7)
CCR+VI	0.7 (0.6–0.7)	0.2 (0.2–0.2)	0.2 (0.2–0.2)	0.8 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.8 (0.8–0.9)	0.3 (0.3–0.3)
CCR+Q	0.7 (0.6–0.7)	0.2 (0.2–0.2)	0.6 (0.6–0.6)	0.8 (0.8–0.9)	0.2 (0.2–0.2)	0.3 (0.3–0.3)	0.8 (0.8–0.9)	0.3 (0.3–0.3)
PPM+VI	0.5 (0.4–0.5)	0.1 (0.1–0.1)	0.4 (0.4–0.4)	0.5 (0.5–0.6)	0.1 (0.1–0.1)	0.1 (0.1–0.2)	0.5 (0.5–0.5)	0.1 (0.1–0.2)
PPM+Q	0.4 (0.4–0.5)	0.1 (0.1–0.1)	0.4 (0.4–0.4)	0.5 (0.5–0.5)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.5 (0.5–0.5)	0.1 (0.1–0.1)
SC+CCR+PPM	9.8 (9.3–10.3)	3.2 (3.1–3.4)	8.8 (8.3–9.2)	7.7 (7.3–8.1)	2.9 (2.8–3.0)	2.5 (2.4–2.6)	7.6 (7.3–8.0)	2.5 (2.3–2.6)
SC+CCR+VI	1.2 (1.1–1.2)	0.4 (0.4–0.4)	1.0 (1.0–1.1)	1.2 (1.1–1.2)	0.3 (0.3–0.4)	0.4 (0.4–0.4)	1.2 (1.1–1.2)	0.4 (0.4–0.4)
SC+CCR+Q	1.1 (1.1–1.2)	0.4 (0.4–0.4)	1.0 (1.0–1.1)	1.2 (1.1–1.2)	0.3 (0.3–0.4)	0.4 (0.4–0.4)	1.2 (1.1–1.2)	0.4 (0.4–0.4)

SC+PPM+VI	0.8 (0.7–0.8)	0.2 (0.2–0.2)	0.7 (0.6–0.7)	0.7 (0.7–0.8)	0.2 (0.2–0.2)	0.2 (0.2–0.2)	0.7 (0.7–0.7)	0.2 (0.2–0.2)
SC+PPM+Q	0.7 (0.7–0.8)	0.2 (0.2–0.2)	0.7 (0.6–0.7)	0.7 (0.7–0.7)	0.2 (0.2–0.2)	0.2 (0.2–0.2)	0.7 (0.6–0.7)	0.2 (0.2–0.2)
CCR+PPM+VI	0.4 (0.4–0.5)	0.1 (0.1–0.1)	0.4 (0.4–0.4)	0.5 (0.5–0.5)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.5 (0.5–0.5)	0.1 (0.1–0.1)
CCR+PPM+Q	0.4 (0.4–0.5)	0.1 (0.1–0.1)	0.4 (0.4–0.4)	0.5 (0.5–0.5)	0.1 (0.1–0.1)	0.1 (0.1–0.1)	0.5 (0.5–0.5)	0.1 (0.1–0.1)
SC+CCR+PPM+VI	0.7 (0.7–0.8)	0.2 (0.2–0.2)	0.6 (0.6–0.7)	0.7 (0.6–0.7)	0.2 (0.2–0.2)	0.2 (0.2–0.2)	0.7 (0.6–0.7)	0.2 (0.2–0.2)
SC+CCR+PPM+Q	0.7 (0.7–0.7)	0.2 (0.2–0.2)	0.6 (0.6–0.7)	0.7 (0.6–0.7)	0.2 (0.2–0.2)	0.2 (0.2–0.2)	0.6 (0.6–0.7)	0.2 (0.2–0.2)

Appendix 18. Results of basic analysis: intensive–care unit admissions

Table A18.1 provides the best-guess results for the number of ICU admissions predicted for each of the 192 intervention bundles.

Table A18.1. Predicted number of ICU admissions (95% confidence intervals).

Non-pharmaceutical intervention component	Pharmaceutical intervention component							
	None	**V**	**AVT**	**AVP**	**V+AVT**	**V+AVP**	**AVT+AVP**	**V+AVT+AVP**
None	579.8 (578.7–580.8)	213.9 (213.5–214.2)	520.4 (519.5–521.3)	495.4 (494.5–496.2)	191.7 (191.4–192.1)	181.0 (180.7–181.3)	493.4 (492.5–494.2)	180.1 (179.8–180.4)
SC	570.1 (569.2–570.9)	209.5 (209.2–209.8)	511.6 (510.8–512.4)	485.9 (485.2–486.6)	187.8 (187.5–188.0)	176.8 (176.5–177.0)	483.8 (483.1–484.5)	175.8 (175.6–176.1)
CCR	575.8 (574.8–576.8)	211.7 (211.4–212.1)	516.8 (515.8–517.7)	490.8 (490.0–491.6)	189.8 (189.5–190.1)	178.6 (178.3–178.9)	488.7 (487.9–489.6)	177.7 (177.4–178.0)
PPM	464.3 (463.5–465.1)	155.3 (155.0–155.5)	415.1 (414.3–415.8)	366.5 (365.8–367.1)	138.3 (138.1–138.6)	118.8 (118.6–119.0)	362.7 (362.0–363.4)	117.2 (117.0–117.4)
VI	355.4 (354.9–356.0)	118.3 (118.1–118.5)	317.6 (317.2–318.1)	286.1 (285.7–286.6)	105.8 (105.7–106.0)	93.1 (93.0–93.3)	283.3 (282.9–283.7)	92.0 (91.8–92.1)
Q	348.1 (347.7–348.5)	115.1 (115.0–115.3)	311.0 (310.7–311.4)	279.2 (278.9–279.5)	103.0 (102.9–103.1)	90.3 (90.2–90.4)	276.3 (276.0–276.6)	89.1 (89.0–89.2)
SC+CCR	565.0 (564.2–565.8)	206.9 (206.6–207.1)	507.0 (506.3–507.7)	480.2 (479.5–480.9)	185.3 (185.1–185.6)	173.9 (173.7–174.2)	478.0 (477.3–478.7)	172.9 (172.7–173.2)
SC+PPM	446.1 (445.4–446.8)	148.0 (147.7–148.2)	398.6 (398.0–399.2)	350.4 (349.9–350.9)	131.7 (131.5–131.9)	112.8 (112.6–112.9)	346.5 (346.0–347.1)	111.3 (111.1–111.5)

SC+VI	322.2 (321.8–322.6)	107.2 (107.0–107.3)	287.8 (287.5–288.2)	261.6 (261.3–261.9)	95.9 (95.8–96.0)	85.4 (85.3–85.5)	258.9 (258.6–259.2)	84.3 (84.2–84.4)
SC+Q	315.5 (315.3–315.8)	104.4 (104.3–104.5)	281.8 (281.6–282.1)	255.4 (255.2–255.6)	93.4 (93.3–93.5)	83.0 (83.0–83.1)	252.7 (252.5–252.9)	81.9 (81.9–82.0)
CCR+PPM	452.0 (451.1–452.8)	149.5 (149.2–149.8)	403.8 (403.1–404.5)	353.5 (352.9–354.2)	133.1 (132.8–133.3)	113.2 (113.0–113.4)	349.6 (349.0–350.3)	111.6 (111.4–111.8)
CCR+VI	344.5 (344.0–345.1)	90.9 (90.8–91.1)	113.6 (113.5–113.8)	274.4 (274.0–274.8)	101.2 (101.0–101.3)	88.5 (88.4–88.6)	271.8 (271.4–272.2)	87.3 (87.2–87.4)
CCR+Q	340.8 (340.4–341.1)	112.0 (111.9–112.2)	304.4 (304.0–304.7)	270.8 (270.6–271.1)	99.7 (99.6–99.8)	87.1 (87.0–87.2)	268.2 (268.0–268.5)	85.9 (85.8–86.0)
PPM+VI	163.3 (163.0–163.6)	46.2 (46.2–46.3)	144.5 (144.3–144.8)	114.9 (114.8–115.1)	40.7 (40.7–40.8)	32.0 (31.9–32.0)	112.4 (112.3–112.6)	31.2 (31.2–31.3)
PPM+Q	155.7 (155.5–155.9)	43.9 (43.8–43.9)	137.7 (137.6–137.9)	109.2 (109.1–109.4)	38.6 (38.6–38.7)	30.3 (30.3–30.3)	106.8 (106.7–106.9)	29.5 (29.5–29.6)
SC+CCR+PPM	432.1 (431.4–432.7)	141.7 (141.5–141.9)	385.8 (385.2–386.4)	336.2 (335.7–336.7)	126.0 (125.8–126.2)	106.8 (106.7–107.0)	332.2 (331.7–332.7)	105.2 (105.1–105.4)
SC+CCR+VI	311.0 (310.7–311.4)	102.7 (102.6–102.8)	277.9 (277.6–278.3)	250.2 (249.9–250.5)	91.4 (91.3–91.5)	81.0 (80.9–81.1)	247.8 (247.5–248.1)	79.9 (79.8–80.0)
SC+CCR+Q	307.9 (307.6–308.1)	101.3 (101.2–101.4)	274.9 (274.6–275.1)	247.1 (246.8–247.3)	90.2 (90.1–90.2)	79.8 (79.7–79.8)	244.6 (244.4–244.8)	78.7 (78.6–78.8)
SC+PPM+VI	146.3 (146.1–146.5)	42.1 (42.0–42.1)	129.4 (129.3–129.6)	105.5 (105.3–105.6)	37.1 (37.1–37.2)	29.9 (29.8–29.9)	103.2 (103.0–103.3)	29.2 (29.1–29.2)

SC+PPM+Q	139.9 (139.7–140.0)	40.1 (40.0–40.1)	123.9 (123.7–124.0)	100.6 (100.5–100.7)	35.3 (35.3–35.3)	28.4 (28.4–28.4)	98.4 (98.3–98.5)	27.7 (27.7–27.7)
CCR+PPM+VI	150.7 (150.4–151.0)	42.1 (42.0–42.2)	133.2 (133.0–133.5)	104.9 (104.7–105.0)	37.1 (37.0–37.1)	29.0 (28.9–29.0)	101.9 (101.8–102.1)	28.3 (28.2–28.3)
CCR+PPM+Q	147.0 (146.8–147.2)	41.0 (40.9–41.0)	130.0 (129.8–130.1)	102.1 (102.0–102.3)	36.1 (36.0–36.1)	28.2 (28.1–28.2)	99.3 (99.2–99.4)	27.5 (27.4–27.5)
SC+CCR+PPM+VI	134.9 (134.7–135.1)	38.4 (38.4–38.5)	119.3 (119.1–119.4)	96.2 (96.1–96.3)	33.8 (33.8–33.8)	27.1 (27.0–27.1)	93.7 (93.6–93.8)	26.4 (26.4–26.5)
SC+CCR+PPM+Q	131.8 (131.7–131.9)	37.4 (37.4–37.5)	116.5 (116.4–116.6)	94.0 (93.9–94.1)	32.9 (32.9–33.0)	26.4 (26.4–26.4)	91.3 (91.3–91.4)	25.7 (25.7–25.8)

Appendix 19. Results of basic analysis: peak intensive-care unit demand

Table A19.1 provides the best-guess results for the peak ICU bed demand (as a percentage of all ICU hospital beds in the Ottawa–Gatineau CMA) for each of the 192 intervention bundles.

Table A19.1. Predicted peak ICU bed demand (95% confidence intervals).

Non-pharmaceutical intervention component	Pharmaceutical intervention component							
	None	**V**	**AVT**	**AVP**	**V+AVT**	**V+AVP**	**AVT+AVP**	**V+AVT+AVP**
None	90.2 (85.7–94.7)	32.1 (30.5–33.7)	80.9 (76.8–84.9)	74.7 (71.0–78.4)	28.7 (27.3–30.1)	26.3 (25.0–27.6)	74.3 (70.6–78.0)	26.2 (24.9–27.5)
SC	87.2 (82.9–91.6)	30.9 (29.4–32.5)	78.2 (74.3–82.1)	72.2 (68.6–75.8)	27.7 (26.3–29.1)	25.4 (24.1–26.7)	71.8 (68.2–75.4)	25.2 (24.0–26.5)
CCR	89.0 (84.5–93.4)	31.5 (30.0–33.1)	79.8 (75.8–83.8)	73.6 (69.9–77.2)	28.2 (26.8–29.6)	25.8 (24.6–27.1)	73.1 (69.5–76.8)	25.7 (24.4–27.0)
PPM	70.2 (66.7–73.7)	23.6 (22.4–24.8)	62.9 (59.7–66.0)	55.7 (53.0–58.5)	21.1 (20.0–22.1)	18.4 (17.5–19.3)	55.3 (52.6–58.1)	18.2 (17.3–19.1)
VI	4.7 (4.5–4.9)	1.6 (1.5–1.6)	4.2 (4.0–4.4)	5.7 (5.4–6.0)	1.4 (1.3–1.5)	1.9 (1.8–2.0)	5.7 (5.4–6.0)	1.9 (1.8–2.0)
Q	4.6 (4.4–4.8)	1.5 (1.4–1.6)	4.1 (3.9–4.3)	5.6 (5.4–5.9)	1.4 (1.3–1.4)	1.9 (1.8–2.0)	5.6 (5.3–5.9)	1.9 (1.8–2.0)
SC+CCR	85.8 (81.5–90.1)	30.3 (28.8–31.8)	76.9 (73.0–80.7)	70.9 (67.3–74.4)	27.1 (25.8–28.5)	24.8 (23.6–26.1)	70.5 (66.9–74.0)	24.7 (23.4–25.9)

SC+PPM	67.3 (63.9–70.7)	22.5 (21.4–23.6)	60.3 (57.2–63.3)	53.4 (50.7–56.0)	20.1 (19.1–21.1)	17.5 (16.6–18.4)	52.9 (50.3–55.6)	17.4 (16.5–18.2)
SC+VI	8.2 (7.8–8.6)	2.7 (2.6–2.9)	7.3 (7.0–7.7)	8.3 (7.9–8.8)	2.4 (2.3–2.6)	2.8 (2.6–2.9)	8.3 (7.9–8.7)	2.7 (2.6–2.9)
SC+Q	8.0 (7.6–8.4)	2.7 (2.5–2.8)	7.2 (6.8–7.6)	8.2 (7.8–8.6)	2.4 (2.3–2.5)	2.7 (2.6–2.8)	8.1 (7.7–8.5)	2.7 (2.5–2.8)
CCR+PPM	69.0 (65.5–72.4)	23.1 (21.9–24.2)	61.8 (58.7–64.9)	54.6 (51.8–57.3)	20.6 (19.6–21.6)	17.9 (17.0–18.8)	54.2 (51.5–56.9)	17.7 (16.8–18.6)
CCR+VI	4.6 (4.3–4.8)	1.5 (1.4–1.6)	1.5 (1.4–1.6)	5.6 (5.3–5.9)	1.4 (1.3–1.4)	1.9 (1.8–1.9)	5.6 (5.3–5.9)	1.8 (1.8–1.9)
CCR+Q	4.5 (4.3–4.8)	1.5 (1.4–1.6)	4.1 (3.9–4.3)	5.6 (5.3–5.8)	1.3 (1.3–1.4)	1.8 (1.7–1.9)	5.5 (5.3–5.8)	1.8 (1.7–1.9)
PPM+VI	3.0 (2.9–3.2)	0.9 (0.8–0.9)	2.7 (2.6–2.8)	3.3 (3.2–3.5)	0.8 (0.7–0.8)	0.9 (0.9–0.9)	3.3 (3.1–3.4)	0.9 (0.8–0.9)
PPM+Q	2.9 (2.8–3.1)	0.8 (0.8–0.9)	2.6 (2.5–2.7)	3.2 (3.0–3.3)	0.7 (0.7–0.8)	0.8 (0.8–0.9)	3.1 (3.0–3.3)	0.8 (0.8–0.9)
SC+CCR+PPM	65.9 (62.6–69.2)	21.9 (20.8–23.0)	59.0 (56.0–61.9)	52.0 (49.4–54.6)	19.6 (18.6–20.6)	17.0 (16.1–17.8)	51.6 (49.0–54.2)	16.8 (16.0–17.7)
SC+CCR+VI	7.9 (7.5–8.3)	2.6 (2.5–2.8)	7.1 (6.8–7.5)	8.1 (7.7–8.5)	2.3 (2.2–2.5)	2.7 (2.5–2.8)	2.0 (7.6–8.4)	2.6 (2.5–2.8)
SC+CCR+Q	7.9 (7.5–8.3)	2.6 (2.5–2.7)	7.0 (6.7–7.4)	8.0 (7.6–8.4)	43.9 (40.8–47.1)	2.6 (2.5–2.8)	8.0 (7.6–8.4)	2.6 (2.5–2.7)

SC+PPM+VI	5.0 (4.7–5.2)	1.4 (1.3–1.5)	4.4 (4.2–4.6)	4.6 (4.3–4.8)	1.2 (1.2–1.3)	1.2 (1.2–1.3)	4.5 (4.2–4.7)	1.2 (1.2–1.3)
SC+PPM+Q	4.8 (4.5–5.0)	1.3 (1.3–1.4)	4.3 (4.0–4.5)	4.4 (4.1–4.6)	1.2 (1.1–1.2)	1.2 (1.1–1.2)	4.3 (4.1–4.5)	1.2 (1.1–1.2)
CCR+PPM+VI	2.9 (2.7–3.0)	0.8 (0.7–0.8)	2.6 (2.4–2.7)	3.1 (2.9–3.2)	0.7 (0.7–0.7)	0.8 (0.8–0.9)	3.0 (2.9–3.2)	0.8 (0.8–0.8)
CCR+PPM+Q	2.8 (2.7–3.0)	0.8 (0.7–0.8)	2.5 (2.4–2.6)	3.0 (2.8–3.1)	0.7 (0.6–0.7)	0.8 (0.8–0.8)	2.9 (2.8–3.1)	0.8 (0.7–0.8)
SC+CCR+PPM+VI	4.6 (4.4–4.9)	1.3 (1.2–1.4)	4.1 (3.9–4.3)	4.2 (4.0–4.4)	1.1 (1.1–1.2)	1.1 (1.1–1.2)	4.1 (3.9–4.3)	1.1 (1.1–1.2)
SC+CCR+PPM+Q	4.5 (4.3–4.8)	1.3 (1.2–1.3)	4.0 (3.8–4.2)	4.1 (3.9–4.3)	1.1 (1.1–1.2)	1.1 (1.0–1.2)	4.0 (3.8–4.2)	1.1 (1.0–1.1)

Appendix 20. Results of basic analysis: mortality

Table 20.1 provides the best-guess results for the number of deaths predicted for each of the 192 intervention bundles.

Table 20.1. Predicted number of deaths (95% confidence intervals).

Non-pharmaceutical intervention component	Pharmaceutical intervention component							
	None	**V**	**AVT**	**AVP**	**V+AVT**	**V+AVP**	**AVT+AVP**	**V+AVT+AVP**
None	363.0 (339.6–386.5)	131.7 (123.3–140.1)	325.6 (304.6–346.6)	305.6 (286.0–325.1)	117.9 (110.4–125.5)	109.6 (102.6–116.5)	303.9 (284.5–323.4)	108.8 (101.9–115.8)
SC	355.3 (333.1–377.6)	128.3 (120.4–136.3)	318.6 (298.6–338.5)	298.2 (279.6–316.7)	114.8 (107.7–122.0)	106.4 (99.8–113.0)	296.4 (278.0–314.9)	105.6 (99.1–112.2)
CCR	358.3 (335.2–381.5)	129.5 (121.2–137.8)	321.3 (300.5–342.1)	300.6 (281.3–319.9)	115.9 (108.4–123.3)	107.2 (100.4–114.1)	298.9 (279.7–318.1)	106.5 (99.6–113.3)
PPM	249.9 (230.7–269.1)	81.0 (74.6–87.5)	222.9 (205.7–240.1)	191.6 (176.4–206.9)	72.0 (66.2–77.7)	60.5 (55.5–65.4)	189.1 (174.0–204.3)	59.5 (54.6–64.4)
VI	184.5 (170.8–198.2)	59.6 (55.0–64.1)	164.5 (152.2–176.8)	145.3 (134.3–156.3)	53.3 (49.2–57.4)	46.1 (42.5–49.6)	143.5 (140.0–146.9)	45.4 (41.8–48.9)
Q	179.2 (165.8–192.7)	57.5 (53.1–62.0)	159.8 (147.7–171.8)	140.7 (129.9–151.5)	51.5 (47.5–55.4)	44.3 (40.9–47.8)	138.8 (128.1–149.5)	43.7 (40.2–47.1)
SC+CCR	349.8 (327.9–371.7)	125.7 (117.9–133.5)	313.5 (293.9–333.2)	292.3 (274.0–310.5)	112.4 (105.4–119.4)	103.7 (97.2–110.1)	290.5 (272.3–308.7)	102.9 (96.5–109.3)
SC+PPM	238.0 (220.0–255.9)	76.6 (70.6–82.6)	212.1 (196.0–228.2)	181.8 (167.6–195.9)	68.0 (62.7–73.3)	57.0 (52.5–61.6)	179.3 (165.3–193.3)	56.2 (51.7–60.7)

SC+VI	165.0 (153.6–176.4)	53.2 (49.5–57.0)	147.1 (136.9–157.3)	131.2 (121.9–140.4)	47.6 (44.3–51.0)	41.7 (38.7–44.6)	129.4 (120.3–138.6)	41.0 (38.1–44.0)
SC+Q	160.3 (149.1–171.5)	51.5 (47.8–55.1)	142.9 (132.9–152.9)	127.1 (118.0–136.1)	46.0 (42.8–49.3)	40.2 (37.3–43.1)	125.4 (116.4–134.3)	39.6 (36.8–42.4)
CCR+PPM	240.1 (221.2–258.9)	77.0 (70.7–83.3)	214.0 (197.1–230.9)	182.4 (167.6–197.3)	68.4 (62.8–74.0)	56.9 (52.1–61.7)	179.9 (165.2–194.6)	56.0 (51.2–60.7)
CCR+VI	176.6 (163.2–189.9)	56.5 (52.2–60.8)	56.5 (52.2–60.9)	137.3 (126.6–148.0)	50.2 (46.3–54.1)	43.2 (39.8–46.6)	135.8 (125.2–146.3)	42.5 (39.1–45.9)
CCR+Q	173.9 (160.7–187.1)	55.5 (51.2–59.9)	155.0 (143.2–166.8)	135.0 (124.4–145.5)	49.3 (45.5–53.2)	42.3 (39.0–45.7)	133.4 (123.0–143.9)	41.7 (38.3–45.0)
PPM+VI	71.2 (64.1–78.3)	20.2 (18.3–22.2)	62.9 (56.6–69.2)	50.2 (45.3–55.1)	17.8 (16.1–19.5)	14.1 (12.8–15.4)	49.0 (4.2–53.8)	13.8 (12.5–15.0)
PPM+Q	67.6 (60.8–74.4)	19.1 (17.3–21.0)	59.7 (53.7–65.7)	47.5 (42.9–52.2)	16.8 (15.2–18.4)	13.4 (12.1–14.6)	46.4 (41.9–51.0)	13.0 (11.8–14.2)
SC+CCR+PPM	227.4 (209.9–244.9)	72.4 (66.7–78.2)	202.5 (186.9–218.2)	172.2 (158.5–185.8)	64.2 (59.1–69.4)	53.4 (49.1–57.8)	169.6 (156.1–183.2)	52.5 (48.2–56.8)
SC+CCR+VI	157.2 (146.2–168.3)	50.4 (46.8–54.0)	140.2 (130.4–150.1)	123.6 (114.7–132.5)	44.7 (41.5–47.9)	39.0 (36.2–41.8)	122.1 (113.3–130.9)	38.4 (35.6–41.1)
SC+CCR+Q	155.1 (144.1–166.0)	49.5 (46.0–53.0)	138.1 (128.4–147.9)	121.5 (112.8–130.3)	43.9 (40.8–47.1)	38.2 (35.5–41.0)	120.1 (111.4–128.8)	37.6 (34.9–40.4)
SC+PPM+VI	62.8 (57.2–68.3)	18.1 (16.6–19.6)	55.4 (50.6–60.3)	45.3 (41.4–49.2)	16.0 (14.6–17.3)	13.0 (12.0–14.1)	44.3 (40.5–48.1)	12.7 (11.7–13.7)

SC+PPM+Q	59.7 (54.4–64.9)	17.2 (15.8–18.7)	52.8 (48.2–57.5)	43.1 (39.4–46.9)	15.1 (13.9–16.4)	12.4 (11.4–13.4)	42.1 (38.5–45.8)	12.1 (11.1–13.0)
CCR+PPM+VI	65.1 (58.5–71.6)	18.3 (16.5–20.0)	57.5 (51.6–63.3)	45.4 (40.9–49.9)	16.1 (14.5–17.6)	12.7 (1.6–13.9)	44.1 (39.8–48.5)	12.4 (11.3–13.6)
CCR+PPM+Q	63.3 (56.9–69.7)	17.8 (16.0–19.5)	55.9 (50.3–61.6)	44.2 (39.8–48.5)	15.6 (14.1–17.1)	12.4 (11.2–13.5)	42.9 (38.7–47.1)	12.1 (11.0–13.2)
SC+CCR+PPM+VI	57.3 (52.2–62.4)	16.4 (15.1–17.8)	50.6 (46.1–55.1)	41.0 (37.5–44.6)	14.5 (12.2–15.7)	11.8 (10.8–12.7)	40.0 (36.5–43.4)	11.5 (10.6–12.4)
SC+CCR+PPM+Q	55.9 (50.9–60.8)	16.0 (14.6–17.3)	49.3 (44.9–53.7)	40.1 (36.6–43.6)	14.1 (12.9–15.3)	11.5 (10.5–12.4)	38.9 (35.5–42.3)	11.2 (10.3–12.1)

Appendix 21. Economic analyses for seven intervention bundles of interest

Tables A21.1–A21.7 present the cost-breakdown for the seven key intervention bundles of interest. Intervention bundles involving either no interventions or pharmaceutical measures only produced estimates of economic burden dominated by mortality and healthcare utilization. Meanwhile, lost school and work days were responsible for much of the economic burden associated with non-pharmaceutical measures such as voluntary isolation and school closure.

Table A21.1. Economic analysis for "No Intervention" scenario.

Category	Total	Unit Cost	Cost
Total hospital bed days	2,472	1,042	10,303,296
Total ICU bed days	580	2,084	12,087,200
Total deaths (Infant)	4	2,355,172	9,420,688
Total deaths (child)	4	2,207,744	8,830,976
Total deaths (young adult)	27	1,956,694	52,830,738
Total deaths (adult)	179	1,374,086	245,961,394
Total deaths (seniors)	150	424,296	63,644,400
Total lost school days	786	92	72,194
Total lost work days (YA + Adults)	9,448	193	1,819,212
Total lost work days (Senior)	435	193	83,759
Total vaccinations	0	20	0
Total antivirals	0	25	0
Total masks	0	4	0
Total			405,053,858

Table A21.2. Economic analysis for "Vaccination and Antiviral Therapy" scenario.

Category	Total	Unit Cost	Cost
Total hospital bed days	815	1,042	3,396,920
Total ICU bed days	192	2,084	4,001,280
Total deaths (Infant)	1	2,355,172	2,355,172
Total deaths (child)	1	2,207,744	2,207,744
Total deaths (young adult)	9	1,956,694	17,610,246
Total deaths (adult)	58	1,374,086	79,696,988
Total deaths (seniors)	49	424,296	20,790,504
Total lost school days	256	92	23,514
Total lost work days (YA + Adults)	3,118	193	600,371
Total lost work days (Senior)	133	193	25,609
Total vaccinations	436,212	20	8,724,240
Total antivirals	311,341	25	7,783,530
Total masks	0	4	0
Total			147,216,118

Table A21.3. Economic analysis for "Vaccination, Antiviral Therapy, and Antiviral Prophylaxis" scenario.

Category	Total	Unit Cost	Cost
Total hospital bed days	765	1,042	3,188,520
Total ICU bed days	180	2,084	3,751,200
Total deaths (Infant)	1	2,355,172	2,355,172
Total deaths (child)	1	2,207,744	2,207,744
Total deaths (young adult)	8	1,956,694	15,653,552
Total deaths (adult)	54	1,374,086	74,200,644
Total deaths (seniors)	45	424,296	19,093,320
Total lost school days	238	92	21,860
Total lost work days (YA + Adults)	2,942	193	566,482
Total lost work days (Senior)	124	193	23,876
Total vaccinations	436,212	20	8,724,240
Total antivirals	361,935	25	9,048,375
Total masks	0	4	0
Total			138,834,986

Table A21.4. Economic analysis for "Community-Contact Reduction, Personal Protective Measures, and Voluntary Isolation" scenario.

Category	Total	Unit Cost	Cost
Total hospital bed days	634	1,042	2,642,512
Total ICU bed days	151	2,084	3,146,840
Total deaths (Infant)	1	2,355,172	2,355,172
Total deaths (child)	1	2,207,744	2,207,744
Total deaths (young adult)	4	1,956,694	7,826,776
Total deaths (adult)	35	1,374,086	48,093,010
Total deaths (seniors)	25	424,296	10,607,400
Total lost school days	54,921	92	5,044,494
Total lost work days (YA + Adults)	197,799	193	38,086,197
Total lost work days (Senior)	3,032	193	583,812
Total vaccinations	0	20	0
Total antivirals	0	25	0
Total masks	186,948	4	747,792
Total			121,341,749

Table A21.5. Economic analysis for "Community-Contact Reduction, Personal Protective Measures, Voluntary Isolation and Antiviral Therapy" scenario.

Category	Total	Unit Cost	Cost
Total hospital bed days	560	1,042	2,334,080
Total ICU bed days	133	2,084	2,771,720
Total deaths (Infant)	1	2,355,172	2,355,172
Total deaths (child)	1	2,207,744	2,207,744
Total deaths (young adult)	4	1,956,694	7,826,776
Total deaths (adult)	31	1,374,086	42,596,666
Total deaths (seniors)	22	424,296	9,334,512
Total lost school days	54,024	92	4,962,104
Total lost work days (YA + Adults)	194,391	193	37,429,987
Total lost work days (Senior)	2,972	193	572,259
Total vaccinations	0	20	0
Total antivirals	100,264	25	2,506,608
Total masks	186,948	4	747,792
Total			115,645,420

Table A21.6. Economic analysis for "School Closure, Community Contact Reduction, Personal Protective Measures, Voluntary Isolation and Quarantine" scenario.

Category	Total	Unit Cost	Cost
Total hospital bed days	550	1,042	2,292,400
Total ICU bed days	132	2,084	2,750,880
Total deaths (Infant)	1	2,355,172	2,355,172
Total deaths (child)	1	2,207,744	2,207,744
Total deaths (young adult)	4	1,956,694	7,826,776
Total deaths (adult)	24	1,374,086	32,978,064
Total deaths (seniors)	25	424,296	10,607,400
Total lost school days	9,916,572	92	910,837,138
Total lost work days (YA + Adults)	6,125,219	193	1,179,410,918
Total lost work days (Senior)	3,114	193	599,601
Total vaccinations	0	20	0
Total antivirals	0	25	0
Total masks	186,948	4	747,792
Total			2,152,613,885

Table A21.7. Economic analysis for "School Closure, Community Contact Reduction, Personal Protective Measures, Voluntary Isolation, Quarantine, Vaccination, Antiviral Therapy and Antiviral Prophylaxis" scenario.

Category	Total	Unit Cost	Cost
Total hospital bed days	108	1,042	450,144
Total ICU bed days	26	2,084	541,840
Total deaths (Infant)	0	2,355,172	0
Total deaths (child)	0	2,207,744	0
Total deaths (young adult)	1	1,956,694	1,956,694
Total deaths (adult)	5	1,374,086	6,870,430
Total deaths (seniors)	5	424,296	2,121,480
Total lost school days	8,649,572	92	794,463,188
Total lost work days (YA + Adults)	5,313,083	193	1,023,034,132
Total lost work days (Senior)	1,632	193	314,242
Total vaccinations	436,212	20	8,724,240
Total antivirals	103,725	25	2,593,125
Total masks	186,948	4	747,792
Total			1,841,817,306

Appendix 22. Results of sensitivity analysis

Tables A22.1–A22.4 present outcome measure counts for best-guess (BG), worst-case (WC), and best-case (BC) scenarios for each individual intervention. Below each WC and BC scenario is a measure of the percent change in each outcome measure, relative to the BG scenario. Sensitivity analysis were conducted across four pandemic scenarios where transmissibility was calculated to approximate an R_o of either 1.65 (1957 pandemic) or 1.80 (1918 pandemic) and the hospitalization rate was calibrated to approximate a rate of either 0.4% or 1.0%.

Table A22.1. Sensitivity of health outcome predictions to change in intervention parameter assumptions for a pandemic strain with the transmissibility of the 1957 pandemic and a hospitalization rate of 0.4%.

Intervention	Measure	Outcome					
		Symptomatic Cases	Hospitalizations	ICU	Peak Hospital Demand	Peak ICU Demand	Deaths
No Intervention	Count	677,545.6	2,472.0	579.8	13.8	90.2	363.0
SC — BG	Count	669,919.6	2,430.1	570.1	13.3	87.2	355.3
SC — WC	Count	682,470.7	2,480.2	581.8	14.0	91.3	364.9
	Percent change	1.9%	2.1%	2.0%	5.0%	4.6%	2.7%
SC — BC	Count	643,517.9	2,321.0	544.9	12.1	79.9	334.9
	Percent change	-3.9%	-4.5%	-4.4%	-9.0%	-8.4%	-5.7%
CCR — BG	Count	673,282.2	2,452.3	575.8	13.6	89.0	358.3
CCR — WC	Count	675,443.6	2,462.3	577.8	13.7	89.6	360.7
	Percent change	0.3%	0.4%	0.4%	0.8%	0.7%	0.7%
CCR — BC	Count	671,058.4	2,442.0	573.7	13.5	88.4	355.8
	Percent change	-0.6%	-0.8%	-0.7%	-1.6%	-1.3%	-1.4%
PPM — BG	Count	566,467.1	1,956.7	464.3	10.5	70.2	249.9
PPM — WC	Count	673,750.5	2,454.6	576.2	13.6	89.1	358.9
	Percent change	18.9%	25.4%	24.1%	29.7%	26.9%	43.6%
PPM — BC	Count	106,153.1	3,12.3	71.3	2.8	15.4	30.9
	Percent change	-81.3%	-84.0%	-84.6%	-73.5%	-78.0%	-87.6%
VI — BG	Count	429,992.9	1,479.9	355.4	0.7	4.7	184.5
VI — WC	Count	508,807.0	1,789.6	426.6	2.3	15.6	236.4

	Percent change	18.3%	20.9%	20.0%	237.6%	233.5%	28.1%
VI — BC	Count	407,053.3	1,391.4	335.1	0.4	2.5	170.1
	Percent change	-20.0%	-22.2%	-21.4%	-84.5%	-84.3%	-28.0%
Q — BG	Count	422,402.4	1,448.9	348.1	0.7	4.6	179.2
Q — WC	Count	503,849.9	1,768.5	421.8	2.3	15.4	232.4
	Percent change	19.3%	22.1%	21.2%	239.4%	235.3%	29.7%
Q — BC	Count	398,705.2	1,357.8	327.2	0.4	2.4	164.6
	Percent change	-5.6%	-6.3%	-6.0%	-47.8%	-47.7%	-8.1%
V — BG	Count	624,359.9	909.7	213.9	4.9	32.1	131.7
V — WC	Count	667,013.6	1,827.8	428.7	10.1	66.4	268.4
	Percent change	6.8%	100.9%	100.4%	108.4%	107.2%	103.8%
V — BC	Count	4,375.1	1.4	0.3	0.0	0.0	0.2
	Percent change	-99.3%	-99.8%	-99.8%	-99.9%	-99.9%	-99.9%
AVT — BG	Count	676,261.7	2,218.6	520.4	12.4	80.9	325.6
AVT — WC	Count	676,838.9	2,468.1	578.9	13.8	90.0	362.3
	Percent change	0.1%	11.2%	11.2%	11.3%	11.3%	11.3%
AVT — BC	Count	676,720.4	1,481.7	347.5	8.3	54.0	217.6
	Percent change	0.0%	0.0%	0.1%	5.4%	0.8%	0.2%
AVP — BG	Count	658,479.8	2,110.8	495.4	11.4	74.7	305.6
AVP — WC	Count	658,842.0	2,422.4	568.0	13.3	87.3	353.6
	Percent change	0.1%	14.8%	14.7%	17.3%	16.8%	15.7%
AVP — BC	Count	673,938.2	1,385.8	325.0	7.4	48.8	200.3
	Percent change	2.3%	-34.3%	-34.4%	-34.7%	-34.6%	-34.5%

Table A22.2. Sensitivity of health outcome predictions to change in intervention parameter assumptions for a pandemic strain with the transmissibility of the 1918 pandemic and a hospitalization rate of 0.4%.

Intervention	Measure	Outcome					
		Symptomatic Cases	Hospitalizations	ICU	Peak Hospital Demand	Peak ICU Demand	Deaths
No Intervention	Count	713,919.5	2,632.9	612.4	16.0	103.1	400.2
SC — BG	Count	708,301.8	2,603.5	605.4	15.5	100.1	395.2
SC — WC	Count	717,502.1	2,637.2	613.4	16.2	104.0	401.1
	Percent change	1.3%	1.3%	1.3%	4.4%	3.9%	1.5%
SC — BC	Count	688,700.8	2,526.6	587.7	14.3	92.8	381.3
	Percent change	-2.8%	-3.0%	-2.9%	-8.0%	-7.2%	-3.5%
CCR — BG	Count	711,061.4	2,620.7	609.9	15.8	101.8	397.4
CCR — WC	Count	712,504.5	2,626.9	611.1	15.9	102.5	398.8
	Percent change	0.2%	0.2%	0.2%	0.6%	0.7%	0.3%
CCR — BC	Count	709,592.0	2,596.2	391.7	15.6	73.0	605.0
	Percent change	-0.4%	-1.2%	-35.9%	-1.9%	-28.8%	51.7%
PPM — BG	Count	651,004.0	2,348.7	553.9	12.7	83.4	333.9
PPM — WC	Count	711,370.9	2,622.0	610.1	15.8	102.0	397.7
	Percent change	9.3%	11.6%	10.2%	25.1%	22.3%	19.1%
PPM — BC	Count	281,302.8	858.7	198.5	6.9	41.5	88.2
	Percent change	-56.8%	-63.4%	-64.2%	-45.7%	-50.3%	-73.6%
VI — BG	Count	517,475.0	1,855.1	442.1	0.9	5.8	255.9
VI — WC	Count	581,944.8	2,112.3	498.9	2.9	19.0	303.2
	Percent change	12.5%	13.9%	12.8%	232.9%	228.8%	18.5%
VI — BC	Count	498,423.1	1,779.5	425.4	0.5	3.0	242.1
	Percent change	-14.4%	-15.8%	-14.7%	-84.3%	-84.0%	-20.1%
Q — BG	Count	512,432.0	1,833.7	437.4	0.9	5.7	251.6
Q — WC	Count	578,733.5	2,098.7	496.0	2.9	18.8	300.4
	Percent change	12.9%	14.5%	13.4%	234.7%	230.4%	19.4%
Q — BC	Count	492,790.4	1,755.7	420.1	0.4	3.0	237.5

	Percent change	-3.8%	-4.3%	-3.9%	-47.7%	-47.6%	-5.6%
V — BG	Count	670,681.0	991.2	230.9	5.8	37.5	149.8
V — WC	Count	706,942.8	1,958.6	455.5	11.9	76.5	297.7
	Percent change	5.4%	97.6%	97.3%	105.4%	103.9%	98.8%
V — BC	Count	13,155.2	4.1	0.9	0.0	0.2	0.4
	Percent change	-98.0%	-99.6%	-99.6%	-99.5%	-99.6%	-99.7%
AVT — BG	Count	712,964.6	2,364.7	550.0	14.4	92.5	359.3
AVT — WC	Count	713,372.2	2,629.7	611.7	16.0	102.9	399.6
	Percent change	0.1%	11.2%	11.2%	11.3%	11.3%	11.2%
AVT — BC	Count	713,307.3	1,579.0	367.2	9.6	61.8	240.0
	Percent change	0.0%	0.0%	0.1%	4.7%	0.7%	0.2%
AVP — BG	Count	702,167.6	2,285.8	531.6	13.4	87.0	345.1
AVP — WC	Count	698,623.8	2,596.4	603.6	15.6	100.5	393.4
	Percent change	-0.5%	13.6%	13.5%	16.1%	15.5%	14.0%
AVP — BC	Count	717,796.4	1,505.3	349.9	8.8	57.0	227.0
	Percent change	2.2%	-34.1%	-34.2%	-34.5%	-34.5%	-34.2%

Table A22.3. Sensitivity of health outcome predictions to change in intervention parameter assumptions for a pandemic strain with the transmissibility of the 1957 pandemic and hospitalization rate of 1.0%.

Intervention	Measure	Outcome					
		Symptomatic Cases	Hospitalizations	ICU	Peak Hospital Demand	Peak ICU Demand	Deaths
No Intervention	Count	675,698.9	4,893.4	1,148.8	27.3	178.5	717.1
SC — BG	Count	667,946.9	4,808.6	1,129.2	26.3	172.5	701.5
SC — WC	Count	680,669.8	4,909.8	1,152.8	27.6	180.6	720.8
	Percent change	1.9%	2.1%	2.1%	5.1%	4.7%	2.8%
SC — BC	Count	641,209.9	4,589.0	1,078.4	23.9	157.9	660.4
	Percent change	-4.0%	-4.6%	-4.5%	-9.0%	-8.5%	-5.9%
CCR — BG	Count	671,368.1	4,853.8	1,140.7	26.9	176.0	707.6
CCR — WC	Count	673,563.9	4,873.9	1,144.8	27.1	177.1	712.5
	Percent change	0.3%	0.4%	0.4%	0.8%	0.6%	0.7%
CCR — BC	Count	669,108.4	4,833.1	1,136.4	26.6	174.8	702.7
	Percent change	-0.7%	-0.8%	-0.7%	-1.6%	-1.3%	-1.4%
PPM — BG	Count	562,395.5	3,853.2	914.8	20.7	138.7	490.0
PPM — WC	Count	671,844.6	4,858.4	1,141.5	26.9	176.3	708.8
	Percent change	19.5%	26.1%	24.8%	29.9%	27.1%	44.7%
PPM — BC	Count	102,187.0	597.9	136.5	5.3	29.5	59.2
	Percent change	-81.8%	-84.5%	-85.1%	-74.3%	-78.7%	-87.9%
VI — BG	Count	426,327.9	2,910.6	699.5	1.4	9.3	361.2
VI — WC	Count	505,743.8	3,529.0	842.0	4.6	31.0	464.4
	Percent change	18.6%	21.2%	20.4%	237.5%	233.5%	28.6%
VI — BC	Count	403,230.5	2,734.3	659.0	0.7	4.9	332.8
	Percent change	-20.3%	-22.5%	-21.7%	-84.5%	-84.3%	-28.3%
Q — BG	Count	418,648.4	2,848.6	684.8	1.3	9.1	350.8
Q — WC	Count	500,721.9	3,486.8	832.2	4.6	30.6	456.5
	Percent change	19.6%	22.4%	21.5%	239.3%	235.4%	30.1%
Q — BC	Count	394,791.5	2,667.0	643.0	0.7	4.8	321.9

	Percent change	-5.7%	-6.4%	-6.1%	-47.8%	-47.7%	-8.2%
V — BG	Count	623,468.2	1,811.3	426.0	9.7	63.8	262.0
V — WC	Count	665,541.0	3,626.8	851.2	20.1	131.7	531.8
	Percent change	6.7%	100.2%	99.8%	107.5%	106.4%	103.0%
V — BC	Count	4,357.5	2.8	0.7	0.0	0.1	0.3
	Percent change	-99.3%	-99.8%	-99.8%	-99.8%	-99.9%	-99.9%
AVT — BG	Count	674,591.3	4,396.2	1,032.1	24.5	160.2	643.9
AVT — WC	Count	674,988.5	4,885.7	1,147.1	27.2	178.1	715.7
	Percent change	0.1%	11.1%	11.1%	11.2%	11.2%	11.2%
AVT — BC	Count	675,608.4	2,945.2	691.0	16.4	107.3	431.9
	Percent change	0.0%	0.0%	0.1%	2.7%	0.4%	0.1%
AVP — BG	Count	656,540.0	4,180.5	981.9	22.5	147.9	603.9
AVP — WC	Count	656,880.9	4,794.2	1,125.2	26.3	172.6	698.3
	Percent change	0.1%	14.7%	14.6%	17.1%	16.7%	15.6%
AVP — BC	Count	672,615.9	2,753.5	646.1	14.7	97.0	397.3
	Percent change	2.4%	-34.1%	-34.2%	-34.5%	-34.4%	-34.2%

Table A22.4. Sensitivity of health outcome predictions to change in intervention parameter assumptions for a pandemic strain with the transmissibility of the 1918 pandemic and hospitalization rate of 1.0%

Intervention	Measure	Outcome					
		Symptomatic Cases	Hospitalizations	ICU	Peak Hospital Demand	Peak ICU Demand	Deaths
No Intervention	Count	712,553.4	5,216.9	1,214.4	31.7	204.2	791.7
SC — BG	Count	706,873.6	5,157.4	1,200.3	30.7	198.1	781.7
SC — WC	Count	716,149.3	5,225.3	1,216.5	32.0	206.1	793.6
	Percent change	1.3%	1.3%	1.3%	4.4%	4.0%	1.5%
SC — BC	Count	687,160.4	5,003.9	1,165.0	28.2	183.8	754.1
	Percent change	-2.8%	-3.0%	-2.9%	-8.0%	-7.2%	-3.5%
CCR — BG	Count	709,661.9	5,192.2	1,209.4	31.3	201.6	786.2
CCR — WC	Count	711,121.9	5,204.7	1,211.9	31.5	202.9	789.0
	Percent change	0.2%	0.2%	0.2%	0.7%	0.6%	0.4%
CCR — BC	Count	708,172.2	5,179.5	1,206.9	31.0	200.6	783.3
	Percent change	-0.4%	-0.5%	-0.4%	-1.4%	-1.2%	-0.7%
PPM — BG	Count	648,707.8	4,644.8	1,096.4	25.0	164.9	658.5
PPM — WC	Count	709,975.7	5,195.0	1,209.9	31.3	201.9	786.9
	Percent change	9.4%	11.8%	10.4%	25.2%	22.4%	19.5%
PPM — BC	Count	274,245.3	1,661.5	384.1	13.4	80.5	170.2
	Percent change	-57.7%	-64.2%	-65.0%	-46.5%	-51.2%	-74.2%
VI — BG	Count	515,054.4	3,664.3	874.1	1.7	11.5	503.9
VI — WC	Count	579,966.5	4,178.2	987.8	5.7	37.8	598.3
	Percent change	12.6%	14.0%	13.0%	232.7%	228.9%	18.7%
VI — BC	Count	495,861.7	3,513.3	840.7	0.9	6.0	476.6
	Percent change	-14.5%	-15.9%	-14.9%	-84.2%	-84.0%	-20.4%
Q — BG	Count	509,956.5	3,621.5	864.6	1.7	11.3	495.5
Q — WC	Count	576,724.8	4,151.0	981.9	5.7	37.4	592.8
	Percent change	13.1%	14.6%	13.6%	235.0%	230.1%	19.6%
Q — BC	Count	490,166.7	3,465.6	830.0	0.9	5.9	467.3

	Percent change	-3.9%	-4.3%	-4.0%	-47.6%	-47.6%	-5.7%
V — BG	Count	670,041.2	1,974.5	460.0	11.5	74.7	298.2
V — WC	Count	705,855.8	3,889.3	905.1	23.6	152.0	590.5
	Percent change	5.3%	97.0%	96.7%	104.5%	103.3%	98.1%
V — BC	Count	13,099.8	8.1	1.9	0.1	0.3	0.9
	Percent change	-98.0%	-99.6%	-99.6%	-99.5%	-99.6%	-99.7%
AVT — BG	Count	711,731.3	4,689.8	1,091.6	28.4	183.3	711.7
AVT — WC	Count	712,004.8	5,210.5	1,213.0	31.6	203.8	790.6
	Percent change	0.0%	11.1%	11.1%	11.2%	11.2%	11.1%
AVT — BC	Count	712,485.2	3,140.2	730.6	19.0	122.8	476.9
	Percent change	0.0%	0.0%	0.1%	2.4%	0.4%	0.1%
AVP — BG	Count	700,792.0	4,532.4	1,055.0	26.6	172.3	683.2
AVP — WC	Count	697,189.4	5,144.1	1,196.9	30.8	198.9	778.2
	Percent change	-0.5%	13.5%	13.5%	16.0%	15.4%	13.9%
AVP — BC	Count	716,872.9	2,993.1	696.0	17.5	113.3	450.9
	Percent change	2.3%	-34.0%	-34.0%	-34.3%	-34.3%	-34.0%

Appendix 23. Census Metropolitan Area profiles [385]

CMA	Province	Population by Age						Hospital resources		
		0 to 4	5 to 18	19 to 29	30 to 64	65+	Total	Acute beds	ICU beds	Total beds
St. John's	NL	10,725	29,275	32,385	99,530	25,055	196,970	576	83	1,022
Halifax	NS	19,965	58,125	65,070	196,060	51,105	390,325	861	97	1,565
Moncton	NB	7,410	22,195	19,090	69,675	20,265	138,635	453	39	705
Saint John	NB	6,740	21,045	16,880	63,780	19,315	127,760	366	41	640
Saguenay	QC	7,735	22,285	21,050	79,175	27,540	157,785	454	75	1,206
Sherbrooke	QC	10,860	30,825	30,845	95,715	33,640	201,885	655	112	1,800
Trois-Rivieres	QC	7,175	20,680	21,085	73,450	29,385	151,775	436	92	1,477
Montreal	QC	222,225	601,070	558,885	1,882,195	559,845	3,824,220	7,023	1,570	25,324
Quebec City	QC	40,775	115,790	103,515	379,410	126,235	765,725	1,807	401	6,474
Ottawa–Gatineau	ON–QC	71,245	204,920	190,640	622,640	156,875	1,246,320	1,822	162	4,336
Kingston	ON	7,865	24,080	26,010	75,625	25,975	159,555	266	68	880
Peterborough	ON	5,665	17,710	17,645	54,785	23,165	118,970	239	24	392
Oshawa	ON	20,965	66,845	48,830	174,910	44,625	356,175	306	33	914
Toronto	ON	318,900	953,325	844,425	2,759,750	706,665	5,583,065	5,094	638	11,074
Hamilton	ON	38,350	120,505	101,820	344,810	115,565	721,050	1,067	160	2,241
St. Catharine's–Niagara	ON	18,365	61,335	51,600	185,750	75,125	392,175	377	30	874
Windsor	ON	17,330	61,055	39,105	154,170	47,585	319,245	382	48	860

Kitchener–Cambridge–Waterloo	ON	28,790	82,960	76,615	229,335	59,455	477,155	390	49	819
Brantford	ON	7,950	24,060	18,255	64,625	20,615	135,505	115	15	262
Guelph	ON	8,195	23,885	22,200	67,835	18,980	141,095	130	22	569
London	ON	26,150	78,245	73,950	225,340	71,100	474,785	808	117	1,694
Barrie	ON	10,795	35,990	25,920	90,790	23,525	187,020	205	21	325
Greater Sudbury	ON	8,080	25,290	22,535	79,025	25,835	160,765	305	23	502
Thunder Bay	ON	5,660	18,500	17,025	59,525	20,880	121,590	363	28	526
Winnipeg	MB	40,550	123,550	113,135	349,930	102,850	730,015	1,582	228	2,757
Regina	SK	13,225	34,855	35,630	99,225	27,625	210,560	480	40	720
Saskatoon	SK	16,625	43,545	49,545	119,300	31,585	260,600	585	45	853
Calgary	AL	80,855	201,450	200,125	613,670	118,750	1,214,850	1,747	261	2,782
Edmonton	AL	73,645	189,575	203,075	561,330	132,250	1,159,875	1,900	266	3,429
Kelowna	BC	8,305	26,805	25,015	85,270	34,450	179,845	268	31	458
Abbotsford–Mission	BC	10,705	31,400	25,205	78,835	24,040	170,185	220	16	793
Vancouver	BC	115,185	354,565	359,040	1,171,635	312,905	2,313,330	2,770	229	6,639
Victoria	BC	14,775	45,330	74,720	151,445	63,435	349,705	611	35	1,670
Total	CA	1,301,785	3,771,070	3,530,870	11,358,545	3,176,245	23,138,515	34,663	5,098	86,582
Average	CA	39,448	114,275	106,996	344,198	96,250	701,167	1,050	154	2,624
Total Canada	CA	1,877,095	5,460,255	4,805,170	16,389,110	4,945,065	33,476,695	54,746	7,604	139,299
% Population Covered by CMA	CA	69.3510451	69.063990 6	73.4806468 9	69.3054412 4	64.2306016 2	69.1182776 6	63.3160413 5	67.0477119 8	62.1555072 2

Appendix 24. Symptomatic cases by CMA and disease scenario

Results presented reflect the average value across five simulations. Confidence intervals were not included due to a very small degree of variance across simulations, which suggests that the timing of an outbreak — as it relates to school terms — has only a small impact on overall pandemic burden.

Census Metropolitan Area	Scenario											
	Ro=1.65; HR=0.4%*			Ro=1.80; HR=0.4%%			Ro=1.65; HR=1.0%			Ro=1.80; HR=1.0%		
	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)
St. John's	77,880	15,849	79.6%	91,778	34,755	62.1%	77,213	15,633	79.8%	91,351	34,454	62.3%
Halifax	141,322	18,755	86.7%	177,135	49,308	72.2%	139,667	18,464	86.8%	176,136	48,716	72.3%
Moncton	56,287	14,059	75.0%	64,989	27,897	57.1%	55,831	13,872	75.2%	64,684	27,659	57.2%
Saint John	52,080	13,572	73.9%	59,903	26,333	56.0%	51,658	13,391	74.1%	59,618	26,110	56.2%
Saguenay	63,985	14,828	76.8%	74,294	30,539	58.9%	63,509	14,648	76.9%	71,982	30,295	57.9%
Sherbrooke	79,304	15,869	80.0%	93,686	35,089	62.5%	78,595	15,646	80.1%	93,233	34,751	62.7%
Trois-Rivieres	61,758	14,728	76.2%	71,544	29,936	58.2%	61,321	14,556	76.3%	71,266	29,710	58.3%
Montreal	581,001	22,432	96.1%	1,261,059	80,047	93.7%	560,902	22,003	96.1%	1,238,751	78,531	93.7%
Quebec City	239,994	20,667	91.4%	332,432	62,507	81.2%	235,979	20,314	91.4%	329,964	61,585	81.3%
Ottawa–Gatineau	331,460	21,323	93.6%	510,590	69,360	86.4%	323,765	20,913	93.5%	505,680	68,139	86.5%
Kingston	64,080	14,690	77.1%	74,568	30,406	59.2%	63,565	14,500	77.2%	74,229	30,145	59.4%
Peterborough	48,864	13,203	73.0%	56,002	25,118	55.1%	48,514	13,047	73.1%	55,764	34,932	37.4%
Oshawa	128,408	17,978	86.0%	159,902	46,311	71.0%	126,572	17,632	86.1%	158,781	45,630	71.3%
Toronto	649,859	22,340	96.6%	1,615,869	81,211	95.0%	622,822	21,933	96.5%	1,557,957	79,508	94.9%
Hamilton	227,092	20,251	91.1%	311,977	60,659	80.6%	222,996	19,871	91.1%	309,460	59,674	80.7%
St. Catharine's–Niagara	141,360	18,679	86.8%	177,412	49,185	72.3%	139,610	18,374	86.8%	176,353	48,562	72.5%
Windsor	116,900	17,552	85.0%	143,927	43,986	69.4%	115,281	17,213	85.1%	142,931	43,351	69.7%

Kitchener–Cambridge–Waterloo	164,047	19,018	88.4%	211,564	52,462	75.2%	161,544	18,664	88.4%	210,051	51,676	75.4%
Brantford	54,532	13,724	74.8%	62,996	27,111	57.0%	54,043	13,523	75.0%	62,667	26,857	57.1%
Guelph	56,759	13,885	75.5%	65,684	27,795	57.7%	56,268	13,688	75.7%	65,355	27,541	57.9%
London	164,212	19,124	88.4%	211,408	52,672	75.1%	161,849	18,786	88.4%	209,982	51,925	75.3%
Barrie	72,825	15,167	79.2%	85,811	32,899	61.7%	72,022	14,904	79.3%	85,291	32,512	61.9%
Greater Sudbury	64,541	14,750	77.1%	75,125	30,582	59.3%	63,999	14,549	77.3%	74,769	30,308	59.5%
Thunder Bay	49,969	13,377	73.2%	57,301	25,585	55.3%	49,603	13,215	73.4%	57,053	25,390	55.5%
Winnipeg	228,614	20,214	91.2%	314,954	60,684	80.7%	224,410	19,830	91.2%	312,365	59,693	80.9%
Regina	81,673	15,883	80.6%	96,922	35,579	63.3%	80,864	15,638	80.7%	96,405	35,202	63.5%
Saskatoon	98,314	16,748	83.0%	118,758	39,801	66.5%	97,232	16,476	83.1%	118,071	39,336	66.7%
Calgary	325,256	21,214	93.5%	498,553	68,793	86.2%	317,730	20,804	93.5%	493,486	67,577	86.3%
Edmonton	315,223	21,085	93.3%	478,096	67,978	85.8%	308,184	20,684	93.3%	473,405	66,802	85.9%
Kelowna	71,679	15,375	78.6%	83,975	32,891	60.8%	71,084	15,170	78.7%	83,589	32,597	61.0%
Abbotsford–Mission	66,845	14,684	78.0%	78,300	31,027	60.4%	66,163	14,445	78.2%	77,853	30,691	60.6%
Vancouver	472,259	22,231	95.3%	864,668	76,882	91.1%	458,898	21,822	95.2%	853,350	75,516	91.2%
Victoria	128,820	18,295	85.8%	159,565	46,850	70.6%	127,572	18,051	85.9%	158,506	46,376	70.7%

*R_0 = basic reproductive rate; HR = hospitalization rate (as a percentage of symptomatic cases)

Appendix 25. Cases of acute-care hospital admission, by CMA and disease scenario

Results presented reflect the average value across five simulations. Confidence intervals were not included due to a very small degree of variance across simulations, which suggests that the timing of an outbreak — as it relates to school terms — has only a small impact on overall pandemic burden. Table 25.1 presents percent reductions as a result of inter-wave vaccination, by CMA and disease scenario. Table 25.2 presents hospitalization proportions, by CMA and disease scenario.

Table 25.1 Predicted number of hospitalizations by CMA, disease scenario and vaccination status.

Census Metropolitan Area	Scenario											
	Ro=1.65; HR=0.4%*			Ro=1.80; HR=0.4%%			Ro=1.65; HR=1.0%			Ro=1.80; HR=1.0%		
	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)
St. John's	261	20	92.3%	315	44	86.0%	523	40	92.4%	633	89	85.9%
Halifax	464	23	95.0%	604	61	89.9%	925	46	95.0%	1,213	122	89.9%
Moncton	212	20	90.6%	249	40	83.9%	425	40	90.6%	501	81	83.8%
Saint John	204	20	90.2%	238	40	83.2%	408	40	90.2%	479	79	83.5%
Saguenay	223	19	91.5%	264	40	84.8%	446	38	91.5%	530	81	84.7%
Sherbrooke	289	22	92.4%	350	49	86.0%	579	43	92.6%	703	97	86.2%
Trois-Rivieres	213	19	91.1%	251	39	84.5%	426	38	91.1%	506	79	84.4%
Montreal	1,801	29	98.4%	4,199	100	97.6%	3512	58	98.3%	8,314	800	90.4%
Quebec City	818	27	96.7%	1,200	81	93.3%	1,623	54	96.7%	2,402	161	93.3%
Ottawa–Gatineau	1,115	28	97.5%	1,837	90	95.1%	2,195	56	97.4%	3,665	179	95.1%
Kingston	231	20	91.3%	274	42	84.7%	462	39	91.6%	550	84	84.7%
Peterborough	184	19	89.7%	214	36	83.2%	368	37	89.9%	430	73	83.0%
Oshawa	527	28	94.7%	680	72	89.4%	1,047	55	94.7%	1,360	143	89.5%
Toronto	2,074	31	98.5%	5,482	107	98.0%	4,015	61	98.5%	10,788	212	98.0%
Hamilton	846	29	96.6%	1,227	86	93.0%	1,674	58	96.5%	2,453	171	93.0%
St. Catharine's–Niagara	535	27	95.0%	698	70	90.0%	1,065	53	95.0%	1,400	140	90.0%

Windsor	511	29	94.3%	649	73	88.8%	1,014	57	94.4%	1,298	145	88.8%
Kitchener–Cambridge–Waterloo	612	27	95.6%	824	74	91.0%	1,215	53	95.6%	1,649	147	91.1%
Brantford	229	22	90.4%	269	44	83.6%	457	43	90.6%	539	87	83.9%
Guelph	220	20	90.9%	259	41	84.2%	440	40	90.9%	519	83	84.0%
London	606	27	95.5%	814	73	91.0%	1,203	53	95.6%	1,630	146	91.0%
Barrie	313	24	92.3%	377	54	85.7%	624	49	92.1%	755	108	85.7%
Greater Sudbury	243	21	91.4%	289	44	84.8%	486	41	91.6%	580	88	84.8%
Thunder Bay	187	19	89.8%	217	37	82.9%	374	37	90.1%	436	74	83.0%
Winnipeg	834	28	96.6%	1,212	84	93.1%	1,649	56	96.6%	2,423	167	93.1%
Regina	303	22	92.7%	369	50	86.4%	606	44	92.7%	740	100	86.5%
Saskatoon	357	23	93.6%	443	55	87.6%	712	45	93.7%	889	109	87.7%
Calgary	1,055	27	97.4%	1,727	86	95.0%	2,079	54	97.4%	3,448	171	95.0%
Edmonton	1,031	27	97.4%	1,669	86	94.8%	2,034	54	97.3%	3,333	170	94.9%
Kelowna	267	21	92.1%	319	46	85.6%	533	43	91.9%	641	93	85.5%
Abbotsford–Mission	283	23	91.9%	338	50	85.2%	564	46	91.8%	677	100	85.2%
Vancouver	1,444	28	98.1%	2,850	93	96.7%	283	55	80.6%	5,672	185	96.7%
Victoria	392	21	94.6%	503	54	89.3%	784	42	94.6%	1,012	107	89.4%

*R_0 = basic reproductive rate; HR = hospitalization rate (as a percentage of symptomatic cases)

Table 25.2 Predicted proportion of hospitalizations (per 10,000 population) by CMA, disease scenario and vaccination status.

Census Metropolitan Area	Scenario							
	Ro=1.65; HR = 0.4%		Ro=1.80; HR=0.4%		Ro=1.65; HR=1.0%		Ro=1.80; HR=1.0%	
	No vaccination	25% Pre-vaccination	No vaccination	25% Pre-vaccination	No vaccination	25% Pre-vaccination	No vaccination	25% Pre-vaccination
St. John's	13.3	1.0	16.0	2.2	26.6	2.0	32.1	4.5
Halifax	11.9	0.6	15.5	1.6	23.7	1.2	31.1	3.1
Moncton	15.3	1.4	18.0	2.9	30.7	2.9	36.1	5.8
Saint John	16.0	1.6	18.6	3.1	31.9	3.1	37.5	6.2
Saguenay	14.1	1.2	16.7	2.5	28.3	2.4	33.6	5.1
Sherbrooke	14.3	1.1	17.3	2.4	28.7	2.1	34.8	4.8
Trois-Rivieres	14.0	1.3	16.5	2.6	28.1	2.5	33.3	5.2
Montreal	4.7	0.1	11.0	0.3	9.2	0.2	21.7	2.1
Quebec City	10.7	0.4	15.7	1.1	21.2	0.7	31.4	2.1
Ottawa–Gatineau	8.9	0.2	14.7	0.7	17.6	0.4	29.4	1.4
Kingston	14.5	1.3	17.2	2.6	29.0	2.4	34.5	5.3
Peterborough	15.5	1.6	18.0	3.0	30.9	3.1	36.1	6.1
Oshawa	14.8	0.8	19.1	2.0	29.4	1.5	38.2	4.0
Toronto	3.7	0.1	9.8	0.2	7.2	0.1	19.3	0.4
Hamilton	11.7	0.4	17.0	1.2	23.2	0.8	34.0	2.4
St. Catharines–Niagara	13.6	0.7	17.8	1.8	27.2	1.4	35.7	3.6
Windsor	16.0	0.9	20.3	2.3	31.8	1.8	40.7	4.5
Kitchener–Cambridge–Waterloo	12.8	0.6	17.3	1.6	25.5	1.1	34.6	3.1
Brantford	16.9	1.6	19.9	3.2	33.7	3.2	39.8	6.4
Guelph	15.6	1.4	18.4	2.9	31.2	2.8	36.8	5.9
London	12.8	0.6	17.1	1.5	25.3	1.1	34.3	3.1

Barrie	16.7	1.3	20.2	2.9	33.4	2.6	40.4	5.8
Greater Sudbury	15.1	1.3	18.0	2.7	30.2	2.6	36.1	5.5
Thunder Bay	15.4	1.6	17.8	3.0	30.8	3.0	35.9	6.1
Winnipeg	11.4	0.4	16.6	1.2	22.6	0.8	33.2	2.3
Regina	14.4	1.0	17.5	2.4	28.8	2.1	35.1	4.7
Saskatoon	13.7	0.9	17.0	2.1	27.3	1.7	34.1	4.2
Calgary	8.7	0.2	14.2	0.7	17.1	0.4	28.4	1.4
Edmonton	8.9	0.2	14.4	0.7	17.5	0.5	28.7	1.5
Kelowna	14.8	1.2	17.7	2.6	29.6	2.4	35.6	5.2
Abbotsford–Mission	16.6	1.4	19.9	2.9	33.1	2.7	39.8	5.9
Vancouver	6.2	0.1	12.3	0.4	1.2	0.2	24.5	0.8
Victoria	11.2	0.6	14.4	1.5	22.4	1.2	28.9	3.1

*R_0 = basic reproductive rate; HR = hospitalization rate (as a percentage of symptomatic cases)

Appendix 26. Peak acute-care hospital demand, as percentage of capacity, by CMA and disease scenario

Results presented reflect the average value across five simulations. Confidence intervals were not included due to a very small degree of variance across simulations, which suggests that the timing of an outbreak — as it relates to school terms — has only a small impact on overall pandemic burden. . Table 26.1 presents percent reductions as a result of inter-wave vaccination, by CMA and disease scenario. Table 26.2 presents ICU admission proportions, by CMA and disease scenario.

Table 26.1 Predicted number of ICU admissions by CMA, disease scenario and vaccination status.

Census Metropolitan Area	Scenario											
	Ro=1.65; HR=0.4%*			Ro=1.80; HR=0.4%%			Ro=1.65; HR=1.0%			Ro=1.80; HR=1.0%		
	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)
St. John's	3.6	0.4	88.9%	4.6	0.8	82.6%	7.3	0.8	89.0%	9.2	1.5	83.7%
Halifax	4.8	0.3	93.8%	6.1	0.9	85.2%	9.7	0.7	92.8%	12.2	1.8	85.2%
Moncton	3.6	0.4	88.9%	4.5	0.8	82.2%	7.2	0.9	87.5%	9.1	1.5	83.5%
Saint John	4.3	0.5	88.4%	5.4	0.9	83.3%	8.5	1.1	87.1%	10.7	1.8	83.2%
Saguenay	3.8	0.4	89.5%	4.8	0.8	83.3%	7.7	0.9	88.3%	9.7	1.6	83.5%
Sherbrooke	3.6	0.4	88.9%	4.5	0.7	84.4%	7.1	0.7	90.1%	8.9	1.5	83.1%
Trois-Rivieres	3.8	0.5	86.8%	4.8	0.8	83.3%	7.6	0.9	88.2%	9.6	1.6	83.3%
Montreal	4.6	0.1	97.8%	7.9	0.2	97.5%	9	0.1	98.9%	15.8	0.5	96.8%
Quebec City	4.9	0.2	95.9%	6.1	0.7	88.5%	9.7	0.4	95.9%	12.3	1.3	89.4%
Ottawa–Gatineau	7.9	0.2	97.5%	10	0.8	92.0%	15.8	0.4	97.5%	20	1.5	92.5%
Kingston	6.8	0.8	88.2%	8.5	1.4	83.5%	13.6	1.6	88.2%	17.1	2.8	83.6%
Peterborough	5.8	0.8	86.2%	7.3	1.2	83.6%	11.7	1.5	87.2%	14.7	2.5	83.0%
Oshawa	15.2	1.1	92.8%	19.1	2.8	85.3%	30.3	2.2	92.7%	38.2	5.7	85.1%
Toronto	7.8	0.1	98.7%	16.4	0.4	97.6%	15.1	0.2	98.7%	32.7	0.7	97.9%
Hamilton	8.4	0.4	95.2%	10.5	1.2	88.6%	16.7	0.7	95.8%	21.1	2.3	89.1%
St. Catharine's–Niagara	12.8	0.9	93.0%	16.1	2.3	85.7%	25.5	1.8	92.9%	32.1	4.6	85.7%
Windsor	11.5	0.9	92.2%	14.5	2.2	84.8%	23	1.8	92.2%	29	4.5	84.5%

Kitchener–Cambridge–Waterloo	14.8	0.9	93.9%	18.6	2.5	86.6%	29.5	1.8	93.9%	37.1	5	86.5%
Brantford	15.3	1.9	87.6%	19.1	3.2	83.2%	60.5	3.8	93.7%	38.4	6.4	83.3%
Guelph	13.1	1.6	87.8%	16.4	2.7	83.5%	26.1	3.2	87.7%	32.8	5.5	83.2%
London	7.0	0.4	94.3%	8.9	1.2	86.5%	14.1	0.8	94.3%	17.7	2.4	86.4%
Barrie	12.2	1.3	89.3%	15.3	2.5	83.7%	24.2	2.6	89.3%	30.5	5.1	83.3%
Greater Sudbury	6.2	0.7	88.7%	7.8	1.3	83.3%	12.5	1.4	88.8%	15.7	2.6	83.4%
Thunder Bay	3.9	0.5	87.2%	4.9	0.8	83.7%	7.8	1	87.2%	9.8	1.6	83.7%
Winnipeg	5.6	0.2	96.4%	7	0.8	88.6%	11.2	0.5	95.5%	14.1	1.5	89.4%
Regina	5.1	0.5	90.2%	6.4	1.1	82.8%	10.2	1	90.2%	12.9	2.1	83.7%
Saskatoon	5.1	0.5	90.2%	6.4	1	84.4%	10.2	0.9	91.2%	12.8	2.1	83.6%
Calgary	7.7	0.2	97.4%	9.7	0.8	91.8%	15.4	0.4	97.4%	19.5	1.5	92.3%
Edmonton	6.8	0.2	97.1%	8.6	0.7	91.9%	13.6	0.4	97.1%	17.2	1.4	91.9%
Kelowna	7.9	0.9	88.6%	9.9	1.6	83.8%	15.8	1.7	89.2%	19.8	3.3	83.3%
Abbotsford–Mission	10.1	1.1	89.1%	12.7	2.1	83.5%	20.2	2.3	88.6%	25.4	4.2	83.5%
Vancouver	8.3	0.1	98.8%	11.6	0.6	94.8%	16.4	0.3	98.2%	23.3	1.1	95.3%
Victoria	5.6	0.4	92.9%	7.1	1.1	84.5%	11.3	0.8	92.9%	14.2	2.1	85.2%

*R_0 = basic reproductive rate; HR = hospitalization rate (as a percentage of symptomatic cases)

Table 26.2 Predicted proportion of ICU admissions (per 10,000 population) by CMA, disease scenario and vaccination status.

Census Metropolitan Area	Scenario							
	Ro=1.65; HR=0.4%		Ro=1.80; HR=0.4%%		Ro=1.65; HR=1.0%		Ro=1.80; HR=1.0%	
	No Vaccination	25% Pre-vaccination	No Vaccination	25% Pre-vaccination	No Vaccination	25% Pre-vaccination	No Vaccination	25% Pre-vaccination
St. John's	3.1	0.3	3.8	0.5	6.2	0.5	7.5	1.1
Halifax	2.8	0.1	3.7	0.4	5.7	0.3	7.5	0.7
Moncton	3.5	0.4	4.2	0.6	7.1	0.6	8.4	1.4
Saint John	3.8	0.4	4.3	0.7	7.4	0.7	8.7	1.4
Saguenay	3.4	0.3	3.9	0.6	6.7	0.6	7.9	1.2
Sherbrooke	3.3	0.2	4.0	0.5	6.6	0.5	8.0	1.1
Trois-Rivieres	3.4	0.3	4.0	0.6	6.7	0.6	7.9	1.3
Montreal	1.0	0.0	2.5	0.1	2.0	0.0	4.9	0.1
Quebec City	2.5	0.1	3.6	0.2	4.9	0.2	7.3	0.5
Ottawa–Gatineau	2.0	0.0	3.4	0.2	4.0	0.1	6.8	0.3
Kingston	3.4	0.3	4.1	0.6	6.9	0.6	8.1	1.3
Peterborough	3.6	0.3	4.2	0.8	7.3	0.8	8.5	1.4
Oshawa	3.4	0.2	4.4	0.4	6.7	0.3	8.7	0.9
Toronto	0.8	0.0	2.2	0.0	1.6	0.0	4.4	0.1
Hamilton	2.7	0.1	4.0	0.3	5.3	0.2	7.9	0.5
St. Catharines–Niagara	3.3	0.2	4.3	0.4	6.5	0.3	8.5	0.8
Windsor	3.7	0.2	4.7	0.5	7.4	0.4	9.4	1.0
Kitchener–Cambridge–Waterloo	2.9	0.1	3.9	0.3	5.7	0.3	7.8	0.7
Brantford	3.8	0.4	4.4	0.7	7.5	0.7	8.9	1.4
Guelph	3.5	0.4	4.2	0.6	7.1	0.6	8.4	1.3
London	2.9	0.1	4.0	0.3	5.8	0.3	7.9	0.7
Barrie	3.8	0.3	4.6	0.6	7.6	0.6	9.3	1.3

Greater Sudbury	3.5	0.3	4.2	0.6	7.2	0.6	8.5	1.3
Thunder Bay	3.7	0.3	4.3	0.7	7.4	0.7	8.6	1.5
Winnipeg	2.6	0.1	3.8	0.3	5.2	0.2	7.7	0.5
Regina	3.2	0.2	3.8	0.5	6.4	0.5	7.7	1.0
Saskatoon	3.0	0.2	3.8	0.5	6.1	0.4	7.5	0.9
Calgary	1.9	0.0	3.2	0.2	3.8	0.1	6.3	0.3
Edmonton	2.0	0.1	3.2	0.2	3.9	0.1	6.4	0.3
Kelowna	3.5	0.3	4.2	0.6	7.1	0.6	8.6	1.2
Abbotsford–Mission	3.6	0.3	4.3	0.6	7.3	0.6	8.7	1.3
Vancouver	1.5	0.0	3.0	0.1	2.8	0.1	5.9	0.2
Victoria	2.8	0.1	3.6	0.4	5.5	0.3	7.2	0.7

Appendix 27. Cases of ICU admission, by CMA and disease scenario

Results presented reflect the average value across five simulations. Confidence intervals were not included due to a very small degree of variance across simulations, which suggests that the timing of an outbreak — as it relates to school terms — has only a small impact on overall pandemic burden.

Census Metropolitan Area	Scenario											
	Ro=1.65; HR=0.4%*			Ro=1.80; HR=0.4%%			Ro=1.65; HR=1.0%			Ro=1.80; HR=1.0%		
	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)
St. John's	61	5	91.8%	74	10	86.5%	122	9	92.6%	148	21	85.8%
Halifax	111	5	95.5%	145	14	90.3%	221	11	95.0%	291	28	90.4%
Moncton	49	5	89.8%	58	9	84.5%	99	9	90.9%	116	19	83.6%
Saint John	48	5	89.6%	55	9	83.6%	95	9	90.5%	111	18	83.8%
Saguenay	53	4	92.5%	62	10	83.9%	106	9	91.5%	125	19	84.8%
Sherbrooke	66	5	92.4%	80	11	86.3%	133	10	92.5%	161	22	86.3%
Trois-Rivieres	51	4	92.2%	60	9	85.0%	101	9	91.1%	120	19	84.2%
Montreal	393	6	98.5%	942	22	97.7%	766	13	98.3%	1864	43	97.7%
Quebec City	188	6	96.8%	278	18	93.5%	373	12	96.8%	557	36	93.5%
Ottawa–Gatineau	253	6	97.6%	425	20	95.3%	498	13	97.4%	848	40	95.3%
Kingston	55	5	90.9%	65	10	84.6%	110	9	91.8%	130	20	84.6%
Peterborough	43	4	90.7%	50	9	82.0%	87	9	89.7%	101	17	83.2%
Oshawa	120	6	95.0%	155	16	89.7%	239	12	95.0%	311	32	89.7%
Toronto	456	7	98.5%	1239	24	98.1%	883	14	98.4%	2437	47	98.1%
Hamilton	195	7	96.4%	285	19	93.3%	385	13	96.6%	571	38	93.3%
St. Catharine's–Niagara	128	6	95.3%	167	16	90.4%	254	12	95.3%	335	33	90.1%
Windsor	118	7	94.1%	150	17	88.7%	235	13	94.5%	301	33	89.0%

Kitchener–Cambridge–Waterloo	138	6	95.7%	186	16	91.4%	274	12	95.6%	373	33	91.2%
Brantford	51	5	90.2%	60	10	83.3%	102	10	90.2%	120	19	84.2%
Guelph	50	5	90.0%	59	9	84.7%	100	9	91.0%	118	19	83.9%
London	139	6	95.7%	188	16	91.5%	276	12	95.7%	376	33	91.2%
Barrie	72	6	91.7%	86	12	86.0%	143	11	92.3%	173	25	85.5%
Greater Sudbury	57	5	91.2%	68	10	85.3%	115	10	91.3%	137	21	84.7%
Thunder Bay	45	4	91.1%	52	9	82.7%	90	9	90.0%	105	18	82.9%
Winnipeg	191	6	96.9%	281	19	93.2%	378	13	96.6%	561	37	93.4%
Regina	67	5	92.5%	81	11	86.4%	134	10	92.5%	163	22	86.5%
Saskatoon	79	5	93.7%	98	12	87.8%	158	10	93.7%	196	24	87.8%
Calgary	232	6	97.4%	385	19	95.1%	457	12	97.4%	770	37	95.2%
Edmonton	228	6	97.4%	374	19	94.9%	449	12	97.3%	748	37	95.1%
Kelowna	63	5	92.1%	76	11	85.5%	128	10	92.2%	154	22	85.7%
Abbotsford–Mission	62	5	91.9%	74	11	85.1%	124	10	91.9%	148	22	85.1%
Vancouver	336	6	98.2%	683	21	96.9%	659	13	98.0%	1359	43	96.8%
Victoria	97	5	94.8%	125	13	89.6%	194	10	94.8%	251	26	89.6%

*R_0 = basic reproductive rate; HR = hospitalization rate (as a percentage of symptomatic cases)

Appendix 28. Peak ICU demand, as percentage of capacity, by CMA and disease scenario

Results presented reflect the average value across five simulations. Confidence intervals were not included due to a very small degree of variance across simulations, which suggests that the timing of an outbreak — as it relates to school terms — has only a small impact on overall pandemic burden.

Census Metropolitan Area	Scenario											
	Ro=1.65; HR=0.4%*			Ro=1.80; HR=0.4%%			Ro=1.65; HR=1.0%			Ro=1.80; HR=1.0%		
	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)
St. John's	15.1	1.4	90.7%	18.8	3.1	83.5%	30.3	2.9	90.4%	37.7	6.2	83.6%
Halifax	26.2	1.6	93.9%	32.5	4.3	86.8%	52.5	3.1	94.1%	65.3	8.6	86.8%
Moncton	25.1	2.9	88.4%	31.1	5.3	83.0%	50.2	5.7	88.6%	62.4	10.7	82.9%
Saint John	22.8	2.7	88.2%	28.3	4.8	83.0%	45.5	5.4	88.1%	56.6	9.7	82.9%
Saguenay	14.1	1.5	89.4%	17.5	3.0	82.9%	28.2	3.0	89.4%	35.1	6.0	82.9%
Sherbrooke	12.3	1.2	90.2%	15.3	2.5	83.7%	24.6	2.3	90.7%	30.6	5.0	83.7%
Trois-Rivieres	11.0	1.2	89.1%	13.6	2.3	83.1%	22.0	2.4	89.1%	27.3	4.7	82.8%
Montreal	9.7	0.1	99.0%	19.9	0.5	97.5%	18.9	0.3	98.4%	39.7	1.0	97.5%
Quebec City	13.0	0.5	96.2%	16.2	1.5	90.7%	26.0	0.9	96.5%	32.4	2.9	91.0%
Ottawa–Gatineau	49.8	1.2	97.6%	65.6	4.2	93.6%	98.6	2.4	97.6%	131.3	8.3	93.7%
Kingston	16.1	1.7	89.4%	20.0	3.4	83.0%	32.2	3.4	89.4%	40.1	6.8	83.0%
Peterborough	35.2	4.3	87.8%	43.7	7.5	82.8%	70.5	8.6	87.8%	87.6	15.1	82.8%
Oshawa	82.7	5.3	93.6%	102.7	14.1	86.3%	164.9	10.5	93.6%	205.3	28.2	86.3%
Toronto	28.7	0.3	99.0%	70.4	1.3	98.2%	55.5	0.7	98.7%	139.3	2.6	98.1%
Hamilton	33.2	1.2	96.4%	41.2	3.9	90.5%	66.3	11.6	82.5%	82.6	7.7	90.7%
St. Catharine's–Niagara	97.9	5.8	94.1%	121.5	16.0	86.8%	195.7	7.5	96.2%	243.4	32.0	86.9%
Windsor	54.6	3.8	93.0%	67.8	9.7	85.7%	108.8	7.5	93.1%	135.5	19.4	85.7%

Kitchener–Cambridge–Waterloo	68.4	3.5	94.9%	84.9	10.2	88.0%	136.6	7.0	94.9%	170.2	20.3	88.1%
Brantford	67.8	7.8	88.5%	84.2	14.4	82.9%	135.4	15.6	88.5%	168.5	28.9	82.8%
Guelph	45.2	5.1	88.7%	56.1	9.5	83.1%	90.2	10.2	88.7%	112.3	19.2	82.9%
London	28.7	1.5	94.8%	35.7	4.3	88.0%	57.4	2.9	94.9%	71.5	8.6	88.0%
Barrie	70.1	6.8	90.3%	87.0	14.4	83.4%	139.7	13.6	90.3%	174.0	28.9	83.4%
Greater Sudbury	50.0	5.3	89.4%	62.1	10.5	83.1%	100.1	10.6	89.4%	124.4	21.1	83.0%
Thunder Bay	31.3	3.8	87.9%	38.7	6.6	82.9%	62.5	7.8	87.5%	77.7	13.4	82.8%
Winnipeg	23.0	0.8	96.5%	28.5	2.7	90.5%	45.8	1.6	96.5%	57.1	5.3	90.7%
Regina	35.1	3.2	90.9%	43.5	7.0	83.9%	70.1	6.4	90.9%	87.2	14.1	83.8%
Saskatoon	37.8	3.0	92.1%	47.0	7.2	84.7%	75.6	6.0	92.1%	94.2	14.4	84.7%
Calgary	28.2	0.7	97.5%	36.9	2.4	93.5%	55.9	1.4	97.5%	74.0	4.8	93.5%
Edmonton	26.9	0.7	97.4%	34.9	2.4	93.1%	53.4	1.3	97.6%	70.0	4.7	93.3%
Kelowna	41.7	4.2	89.9%	51.8	8.6	83.4%	85.5	8.3	90.3%	103.8	17.3	83.3%
Abbotsford–Mission	79.1	8.1	89.8%	98.3	16.4	83.3%	157.8	16.2	89.7%	196.6	33.0	83.2%
Vancouver	52.7	0.9	98.3%	85.2	3.3	96.1%	103.6	1.7	98.4%	170.9	6.5	96.2%
Victoria	62.0	4.0	93.5%	76.9	10.6	86.2%	124.3	8.0	93.6%	154.5	21.2	86.3%

*R_0 = basic reproductive rate; HR = hospitalization rate (as a percentage of symptomatic cases)

Appendix 29. Total influenza-related mortality, by CMA and disease scenario

Results presented reflect the average value across five simulations. Confidence intervals were not included due to a very small degree of variance across simulations, which suggests that the timing of an outbreak — as it relates to school terms — has only a small impact on overall pandemic burden.

Census Metropolitan Area	Scenario											
	Ro=1.65; HR=0.4%*			Ro=1.80; HR=0.4%%			Ro=1.65; HR=1.0%			Ro=1.80; HR=1.0%		
	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)	No Vaccination	25% Pre-vaccination	Reduction (%)
St. John's	36	2	94.4%	46	5	89.1%	71	5	93.0%	92	11	88.0%
Halifax	57	3	94.7%	82	7	91.5%	113	5	95.6%	164	13	92.1%
Moncton	30	2	93.3%	37	5	86.5%	60	5	91.7%	74	10	86.5%
Saint John	29	2	93.1%	36	5	86.1%	57	5	91.2%	71	10	85.9%
Saguenay	30	2	93.3%	38	5	86.8%	60	5	91.7%	77	10	87.0%
Sherbrooke	41	3	92.7%	53	6	88.7%	81	5	93.8%	105	12	88.6%
Trois-Rivieres	29	2	93.1%	36	5	86.1%	58	4	93.1%	73	10	86.3%
Montreal	185	3	98.4%	483	11	97.7%	359	7	98.1%	951	21	97.8%
Quebec City	98	3	96.9%	163	9	94.5%	193	6	96.9%	325	18	94.5%
Ottawa–Gatineau	126	3	97.6%	238	10	95.8%	246	6	97.6%	472	19	96.0%
Kingston	31	2	93.5%	39	5	87.2%	62	5	91.9%	79	10	87.3%
Peterborough	26	2	92.3%	31	5	83.9%	51	4	92.2%	63	9	85.7%
Oshawa	71	3	95.8%	100	9	91.0%	139	7	95.0%	199	17	91.5%
Toronto	199	3	98.5%	578	11	98.1%	385	7	98.2%	1130	22	98.1%
Hamilton	101	3	97.0%	167	9	94.6%	200	7	96.5%	332	19	94.3%
St. Catharine's–Niagara	66	3	95.5%	95	8	91.6%	130	6	95.4%	190	15	92.1%
Windsor	67	3	95.5%	94	9	90.4%	113	7	93.8%	187	17	90.9%

Kitchener–Cambridge–Waterloo	81	3	96.3%	120	9	92.5%	159	6	96.2%	240	17	92.9%
Brantford	34	3	91.2%	42	6	85.7%	68	6	91.2%	85	12	85.9%
Guelph	32	3	90.6%	40	5	87.5%	64	5	92.2%	80	11	86.3%
London	77	3	96.1%	116	8	93.1%	153	6	96.1%	231	17	92.6%
Barrie	44	3	93.2%	57	7	87.7%	87	6	93.1%	113	14	87.6%
Greater Sudbury	33	2	93.9%	42	5	88.1%	66	5	92.4%	84	11	86.9%
Thunder Bay	25	2	92.0%	31	4	87.1%	50	4	92.0%	62	9	85.5%
Winnipeg	100	3	97.0%	166	9	94.6%	198	6	97.0%	330	18	94.5%
Regina	45	3	93.3%	58	7	87.9%	89	6	93.3%	117	13	88.9%
Saskatoon	52	3	94.2%	69	7	89.9%	102	6	94.1%	139	14	89.9%
Calgary	127	3	97.6%	238	10	95.8%	249	7	97.2%	472	20	95.8%
Edmonton	124	3	97.6%	229	10	95.6%	243	6	97.5%	455	19	95.8%
Kelowna	35	2	94.3%	45	5	88.9%	70	5	92.9%	90	11	87.8%
Abbotsford–Mission	43	3	93.0%	54	7	87.0%	85	6	92.9%	109	14	87.2%
Vancouver	139	3	97.8%	315	9	97.1%	272	6	97.8%	624	18	97.1%
Victoria	45	2	95.6%	65	6	90.8%	90	4	95.6%	129	11	91.5%

*R_0 = basic reproductive rate; HR = hospitalization rate (as a percentage of symptomatic cases)

Appendix 30. Sensitivity analysis of demographic and health system predictors of elevated pandemic burden and hospital-resource stress

Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

Characteristic	Scenario	Symptomatic cases		Hospitalizations		ICU cases		Peak acute care demand (%)		Peak ICU demand (%)		Deaths	
		Correlation (R)	r^2	Correlation (R)	r^2	Correlation (R)	r^2	Correlation (R)	r^2	Correlation (R)	r^2	Correlation (R)	r^2
% Infants	1	0.2486	0.0618	0.2763	0.0763	0.2535	0.0643	0.2944	0.0866	0.0802	0.0064	0.3558	0.1266
	2	0.2103	0.0442	0.2265	0.0513	0.2117	0.0448	0.3083	0.9500	0.0933	0.0087	0.2788	0.0777
	3	0.2495	0.0442	0.3607	0.0513	0.2540	0.0448	0.2920	0.0950	0.0756	0.0087	0.3552	0.0777
	4	0.2646	0.0700	0.4001	0.1601	0.3723	0.1386	0.0784	0.0061	0.0103	0.0001	0.6598	0.4353
	5	0.1358	0.0185	0.0577	0.0033	0.0527	0.0028	0.0903	0.0082	0.1120	0.0019	0.0640	0.0041
% Children	1	0.0537	0.0029	0.1143	0.1310	0.1022	0.0104	0.6761	0.4572	0.4955	0.2456	0.1718	0.0295
	2	0.0519	0.0027	0.0835	0.0070	0.0752	0.0057	0.6757	0.4566	0.4995	0.2495	0.1100	0.0121
	3	0.0531	0.0028	0.1702	0.0290	0.1023	0.0105	0.6735	0.3181	0.4915	0.2416	0.1581	0.0250
	4	0.0632	0.0040	0.4733	0.2240	0.5511	0.3037	0.4610	0.2125	0.4249	0.1805	0.6122	0.3748
	5	0.0000	0.0000	-0.0636	0.0040	-0.0584	0.0034	0.4061	0.1649	0.5129	0.0879	-0.0712	0.0052
% Young adults	1	0.1087	0.0118	0.0776	0.0060	0.0791	0.0063	-0.2222	0.0476	-0.0752	0.0057	0.0877	0.0077
	2	0.0658	0.0043	0.0499	0.0025	0.0508	0.0026	-0.2160	0.0466	-0.0683	0.0047	0.0625	0.0039
	3	0.1109	0.0123	0.0639	0.0041	0.0806	0.0065	-0.2194	0.0543	-0.0752	0.0057	0.0992	0.0098
	4	0.2297	0.0527	-0.0617	0.0038	-0.0837	0.0070	-0.2788	0.0778	-0.2043	0.0417	0.0473	0.0022
	5	0.1362	0.0186	0.2476	0.0613	0.2351	0.0553	0.1360	0.0185	-0.0646	0.0310	0.2754	0.0759
% Adults	1	0.3185	0.1014	0.3128	0.0979	0.3137	0.0984	-0.1279	0.0164	-0.3176	0.1009	0.3029	0.0918
	2	0.2999	0.0895	0.2985	0.0891	0.3013	0.0908	-0.0770	0.0059	-0.2483	0.0617	0.3046	0.0928
	3	0.3186	0.1015	0.2016	0.0406	0.3130	0.0980	-0.1321	0.0169	-0.3230	0.1043	0.3020	0.0912
	4	0.2208	0.0487	0.1777	0.0316	0.1621	0.0263	-0.3076	0.0946	-0.4029	0.1623	0.0245	0.0006
	5	0.1939	0.0376	0.0622	0.0039	0.0594	0.0035	-0.3690	0.1362	-0.2403	0.1793	0.0401	0.0016
% Seniors	1	-0.3774	0.1424	-0.3934	0.1547	-0.3924	0.1462	-0.2245	0.0503	-0.0512	0.0027	-0.4475	0.2002

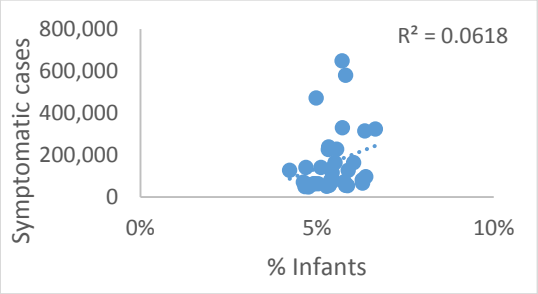
	2	-0.3230	0.1044	-0.3336	0.1130	-0.3276	0.1073	-0.2649	0.0702	-0.1073	0.0115	-0.3749	0.1406
	3	-0.3790	0.1436	-0.3645	0.1328	-0.3823	0.1469	-0.2215	0.0201	-0.0449	0.0020	-0.4471	0.1999
	4	-0.4130	0.1705	-0.4454	0.1984	-0.4586	0.2103	0.1129	0.0127	0.1572	0.0247	-0.5709	0.3260
	5	-0.2584	0.0668	-0.1990	0.0396	-0.1898	0.0360	-0.1238	0.0153	-0.1276	0.0004	-0.2020	0.0408
Acute care beds (per 10,000 population)	1	NA	NA	NA	NA	NA	NA	-0.8697	0.7564	-0.7044	0.4962	NA	NA
	2	NA	NA	NA	NA	NA	NA	-0.9077	0.8238	-0.7629	0.5820	NA	NA
	3	NA	NA	NA	NA	NA	NA	-0.8676	0.7527	-0.7012	0.4917	NA	NA
	4	NA	NA	NA	NA	NA	NA	-0.4628	0.2142	-0.3876	0.1502	NA	NA
	5	NA	NA	NA	NA	NA	NA	-0.9127	0.8330	-0.7709	0.4581	NA	NA
ICU beds (per 10,000 population)	1	NA	NA	NA	NA	NA	NA	-0.6592	0.4345	-0.8151	0.6644	NA	NA
	2	NA	NA	NA	NA	NA	NA	-0.6720	0.4515	-0.8502	0.7228	NA	NA
	3	NA	NA	NA	NA	NA	NA	-0.6599	0.2879	-0.8133	0.6614	NA	NA
	4	NA	NA	NA	NA	NA	NA	-0.3861	0.1491	-0.5742	0.3297	NA	NA
	5	NA	NA	NA	NA	NA	NA	-0.6969	0.4857	-0.8529	0.6470	NA	NA

Appendix 31. Sensitivity analysis scatter plots

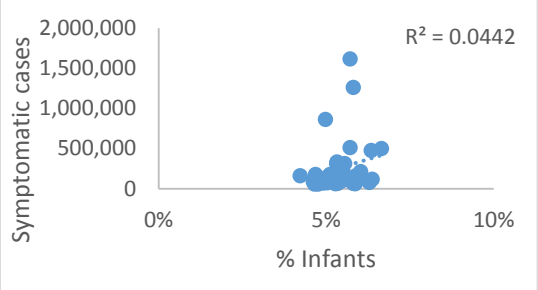
This appendix presents five unique scatterplots, and associated r^2 value, for each of the 34 associations between demographic and health system characteristics and pandemic outcomes tested.

Figure A31.1 Association between the percentage of the total population represented by infants and the overall number of symptomatic cases. Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C), Scenario 4 (D) and Scenario 5 (E).

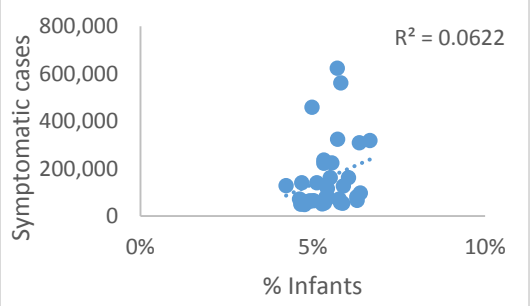
A)



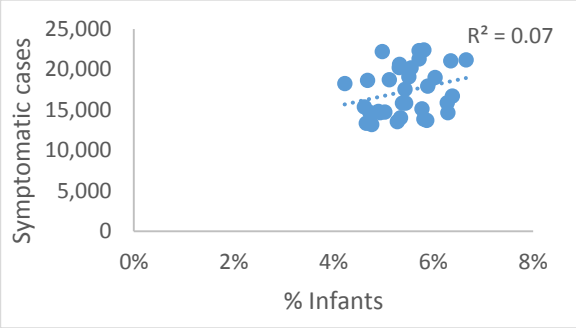
B)



C)



D)



E)

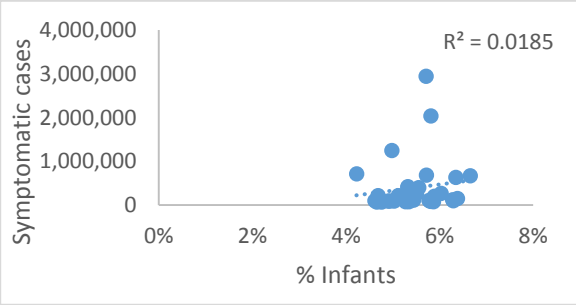
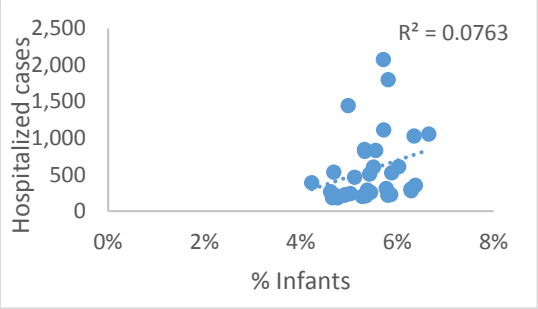
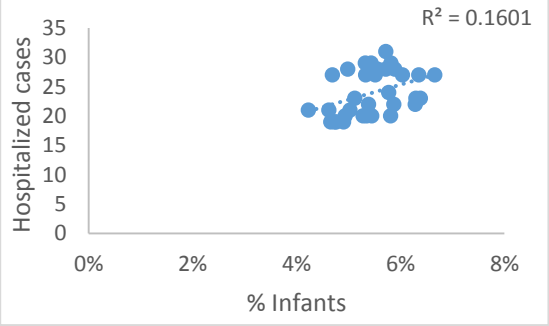


Figure A31.2 Association between the percentage of the total population represented by infants and the overall number of acute hospitalizations admissions. Negligible correlation in Scenario 1 (A), Scenario 2 (B) and Scenario 5 (E); mild correlation in Scenario 3 (C) and 4 (D). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

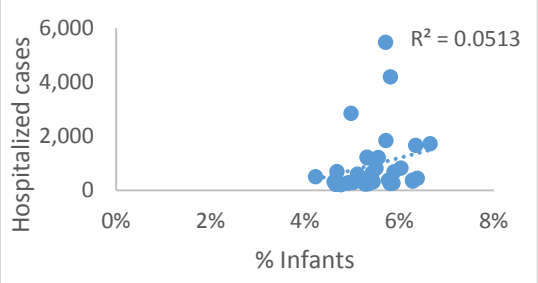
A)



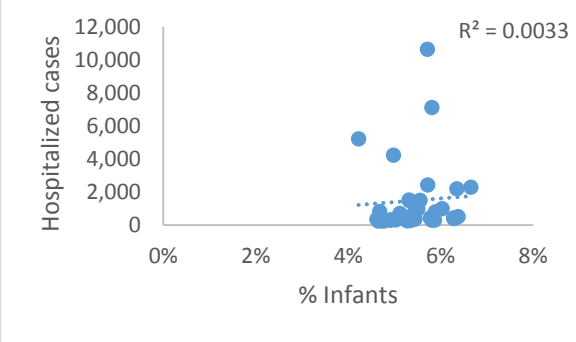
D)



B)



E)



C)

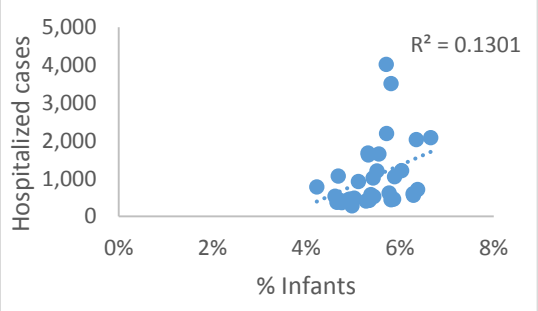
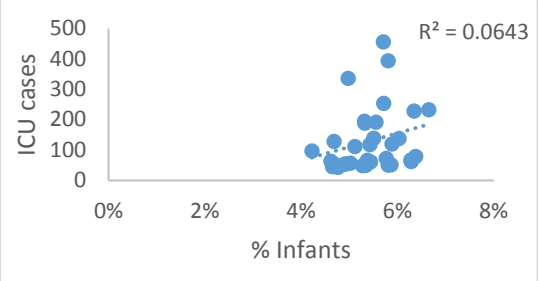
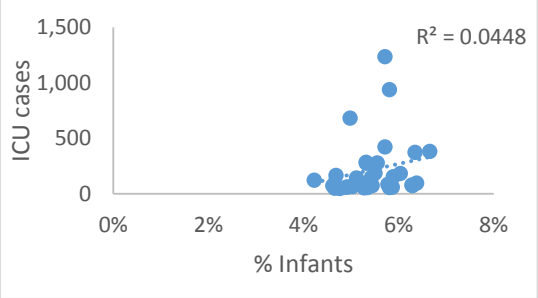


Figure A31.3 Association between the percentage of the total population represented by infants and the overall number of ICU admissions. Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C) and Scenario 5 (E); mild correlation in Scenario 4 (D). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

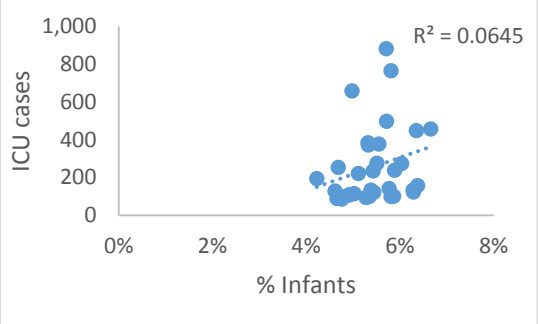
A)



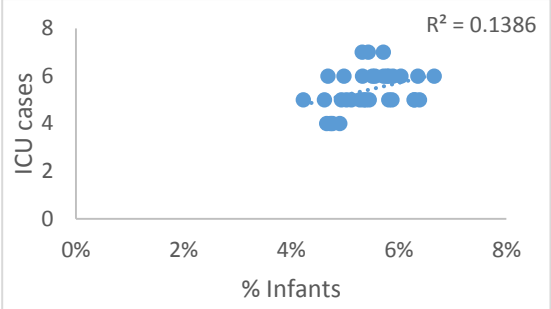
B)



C)



D)



E)

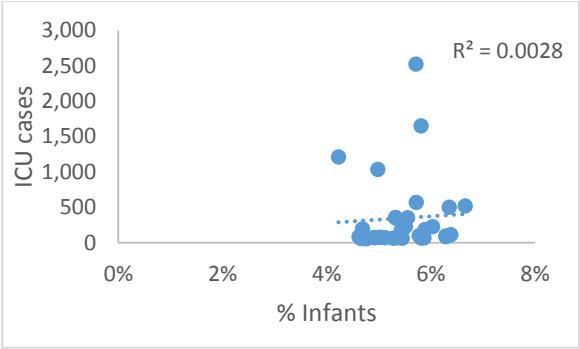
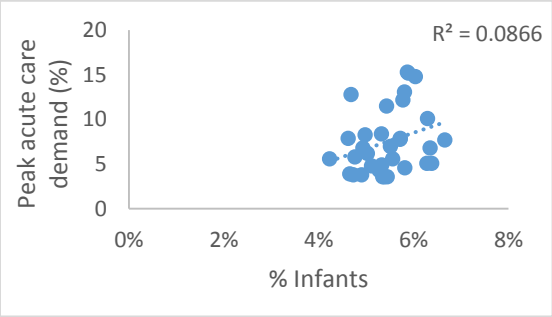
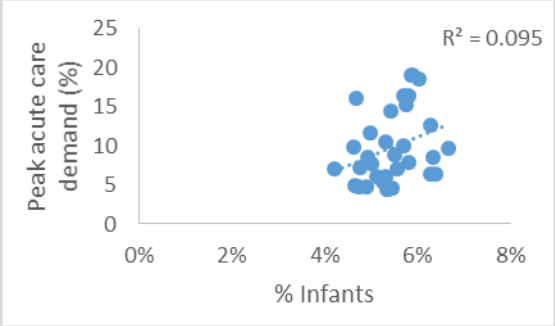


Figure A31.4 Association between the percentage of the total population represented by infants and the peak acute-care demand (as a percentage of total capacity). Negligible correlation in Scenario 1 (A), Scenario 3 (C), Scenario 4 (D) and Scenario 5 (E); mild correlation in Scenario 2 (B). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

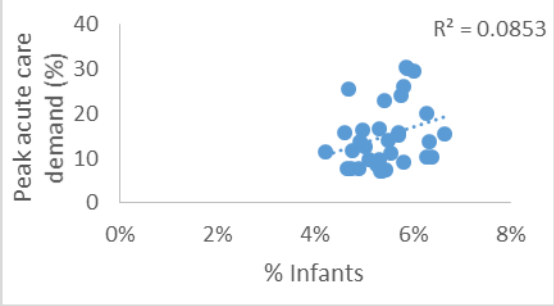
A)



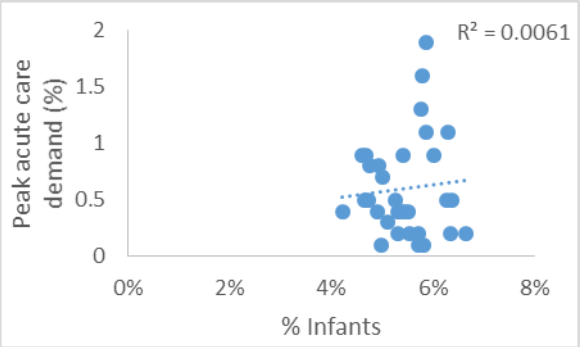
B)



C)



D)



E)

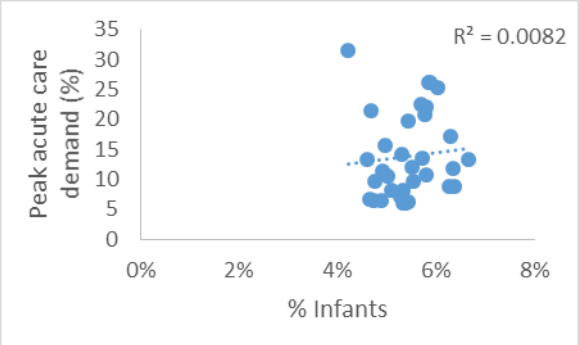
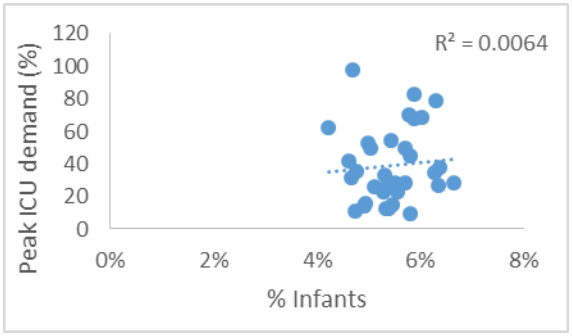
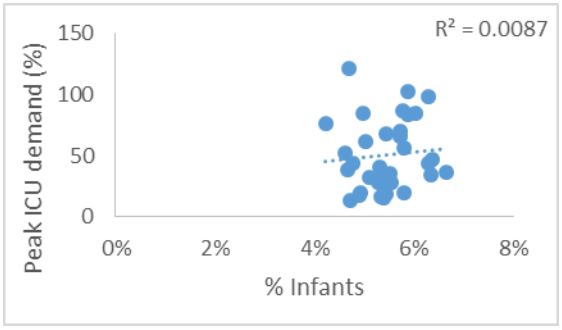


Figure A31.5 Association between the percentage of the total population represented by infants and the peak ICU demand (as a percentage of total capacity). Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C), Scenario 4 (D) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

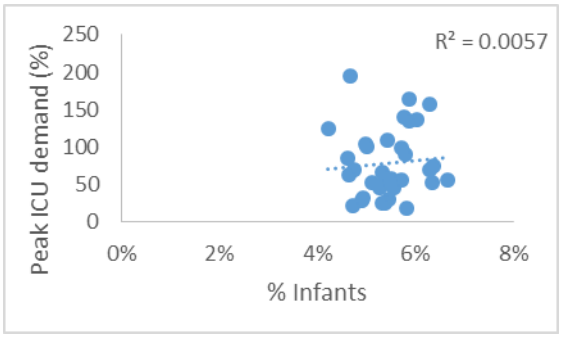
A)



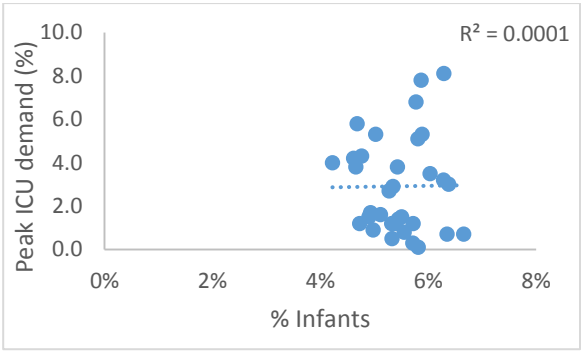
B)



C)



D)



E)

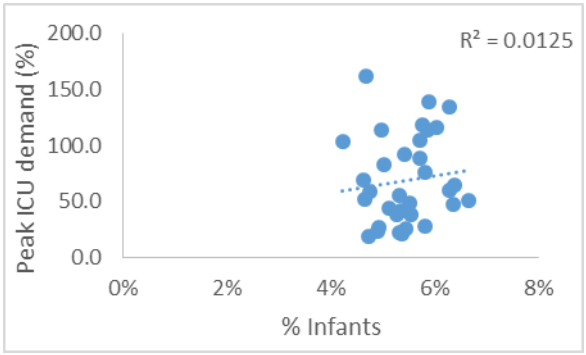
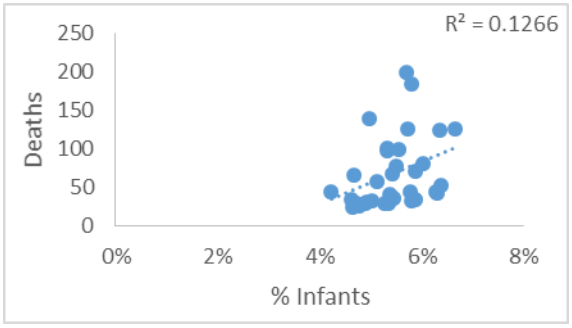
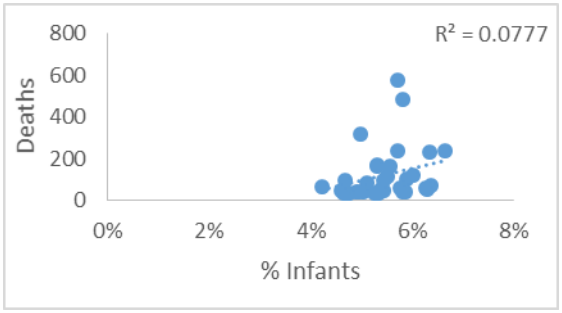


Figure A31.6 Association between the percentage of the total population represented by infants and total mortality. Negligible correlation in Scenario 2 (B) and Scenario 5 (E); mild correlation in Scenario 1 (A) Scenario 3 (C); moderate correlation in Scenario 4 (D). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

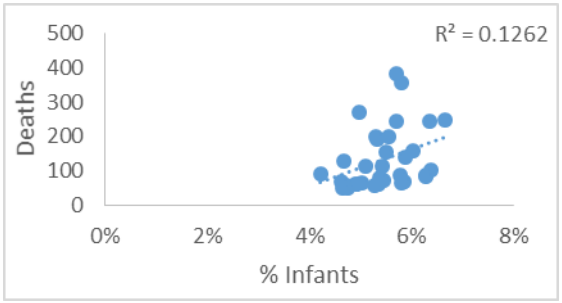
A)



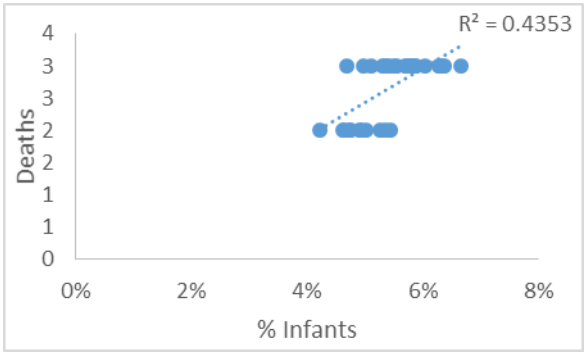
B)



C)



D)



E)

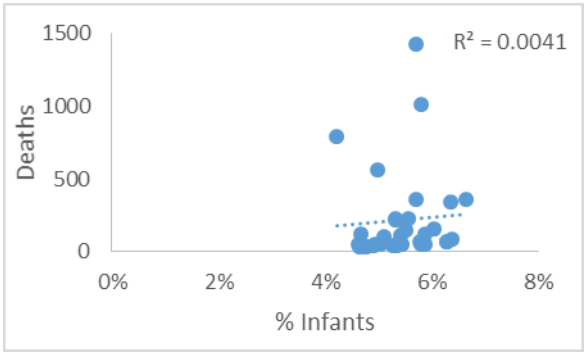
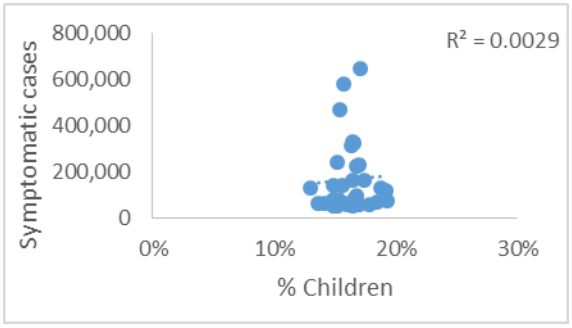
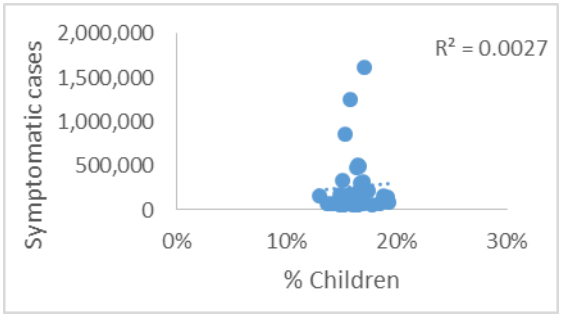


Figure A31.7 Association between the percentage of the total population represented by children and overall number of symptomatic cases. Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C), Scenario 4 (D) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

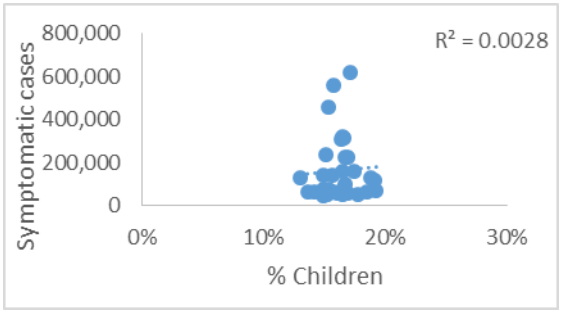
A)



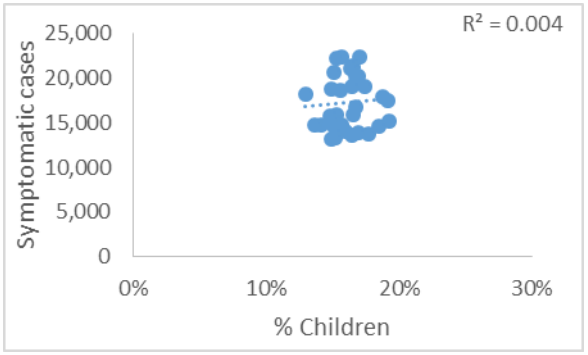
B)



C)



D)



E)

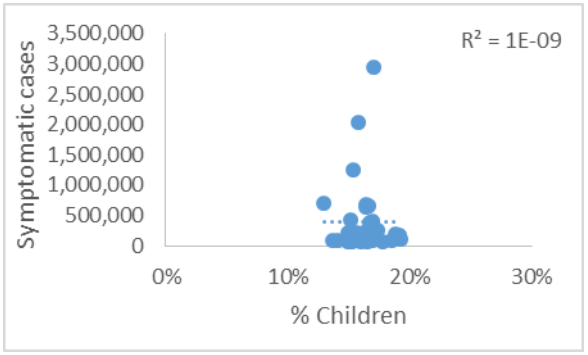
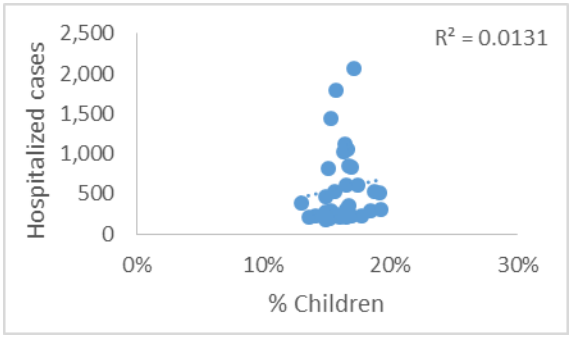
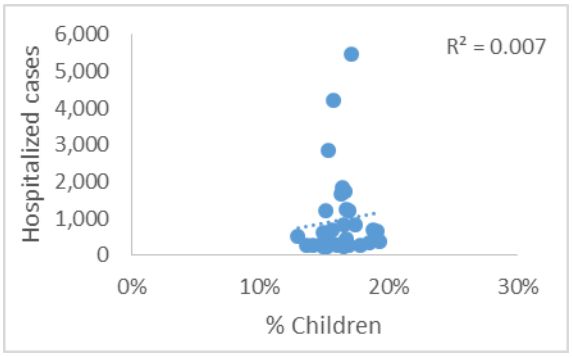


Figure A31.8 Association between the percentage of the total population represented by children and overall number of acute hospital admissions. Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C), and Scenario 5 (E); mild correlation in Scenario 4 (D). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

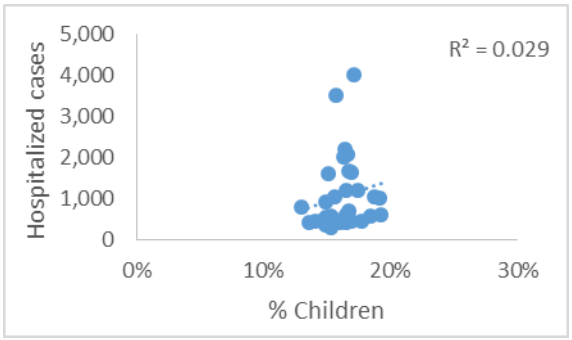
A)



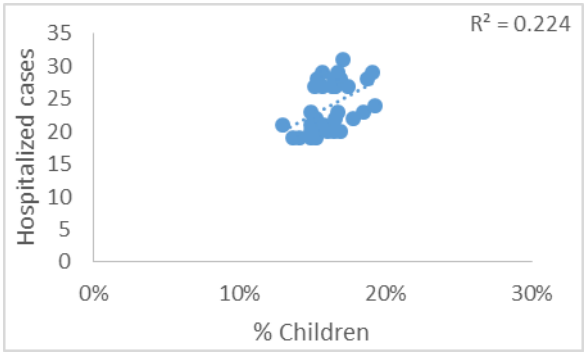
B)



C)



D)



E)

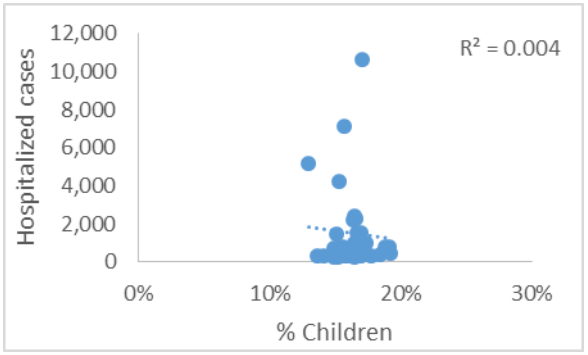
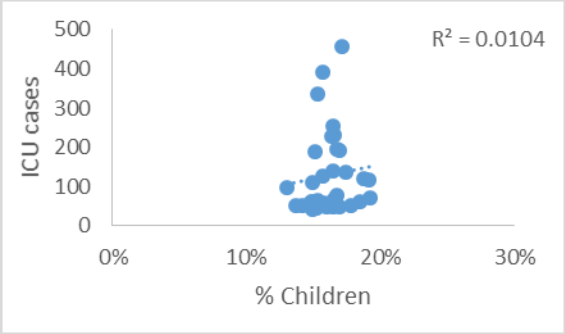
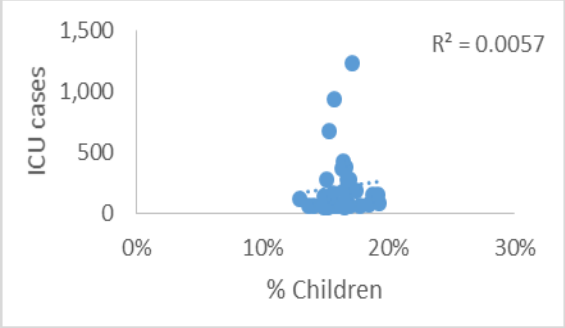


Figure A31.9 Association between the percentage of the total population represented by children and overall number of ICU admissions. Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C), and Scenario 5 (E); moderate correlation in Scenario 4 (D). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

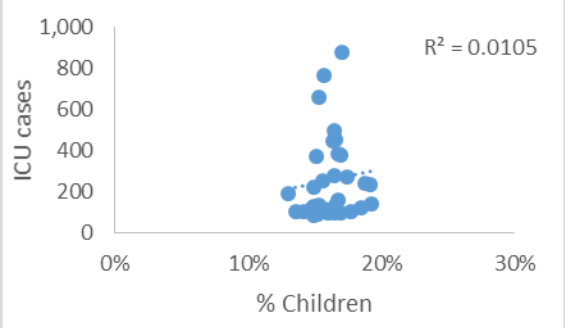
A)



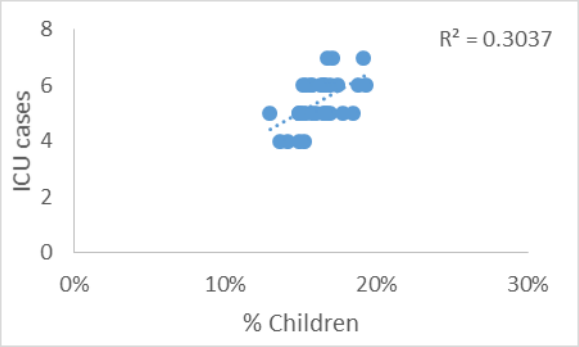
B)



C)



D)



E)

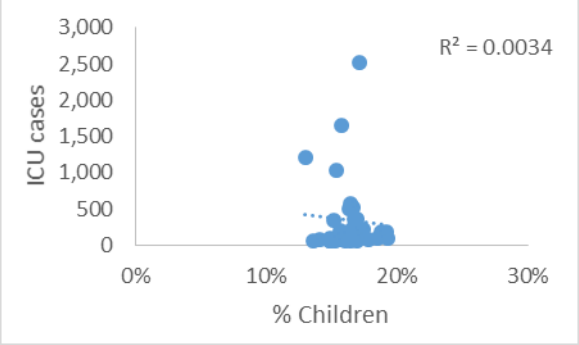
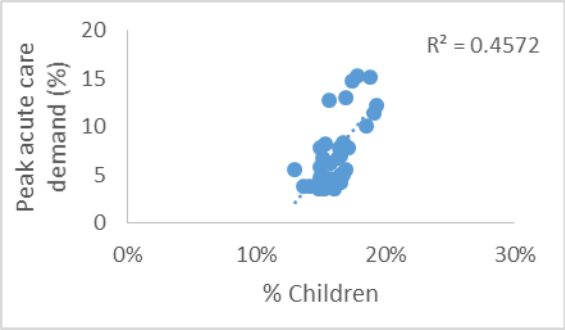
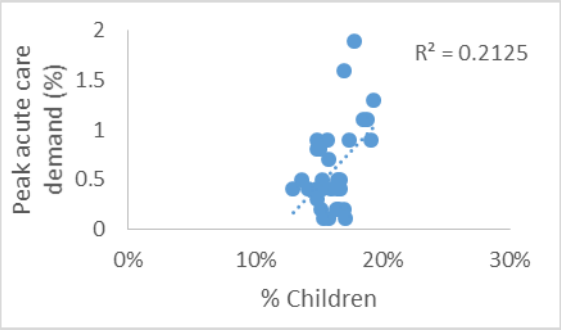


Figure A31.10 Association between the percentage of the total population represented by children and peak acute-care demand (as percentage of total capacity). Weak correlation in Scenario 4 (D) and Scenario 5 (E); moderate correlation in Scenario 1 (A), Scenario 2 (B) and Scenario 3 (C). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

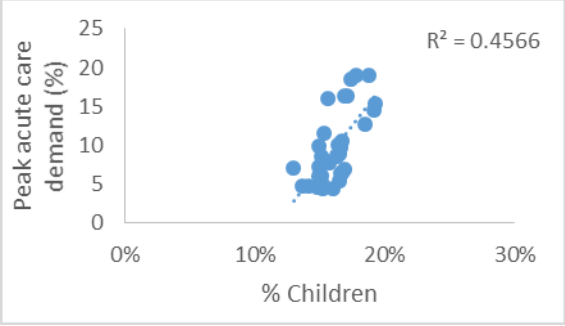
A)



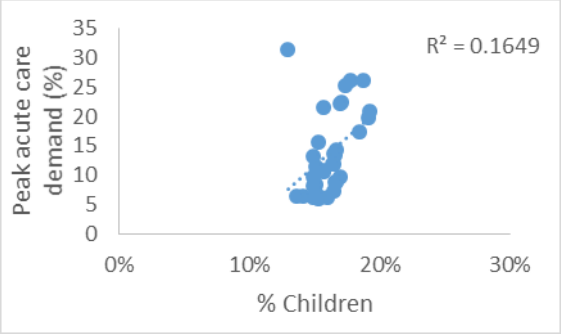
D)



B)



E)



C)

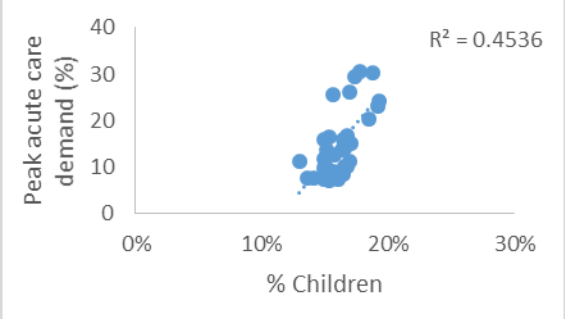
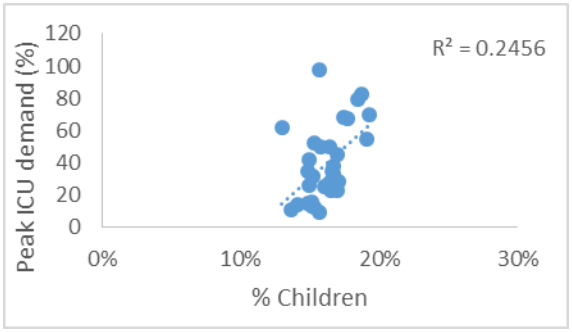
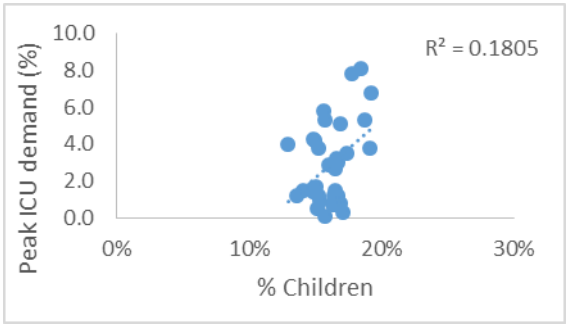


Figure A31.11 Association between the percentage of the total population represented by children and peak ICU demand (as percentage of total capacity). Weak correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C) and Scenario 4 (D); moderate correlation in Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

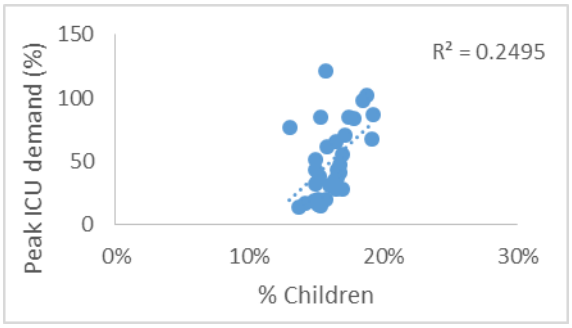
A)



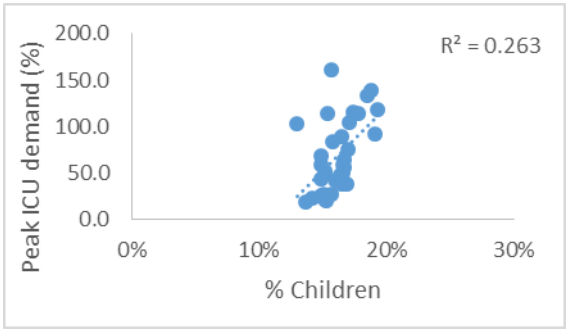
D)



B)



E)



C)

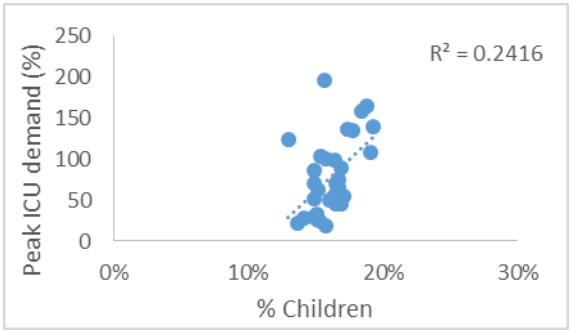
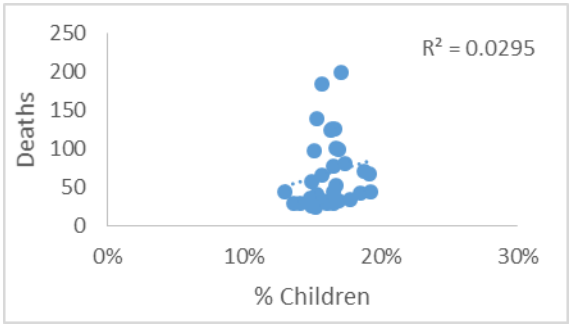
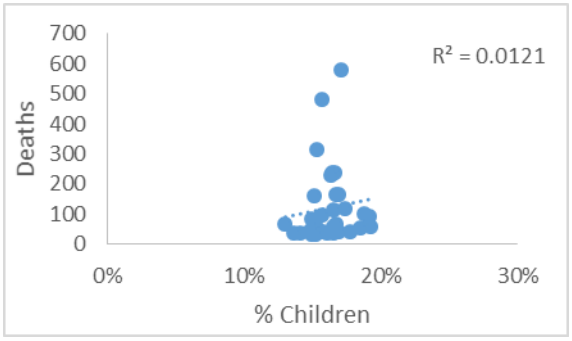


Figure A31.12 Association between the percentage of the total population represented by children and overall mortality. Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C) and Scenario 5 (E); moderate correlation in Scenario 4 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

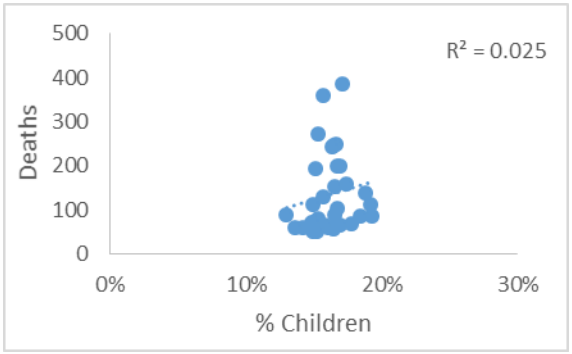
A)



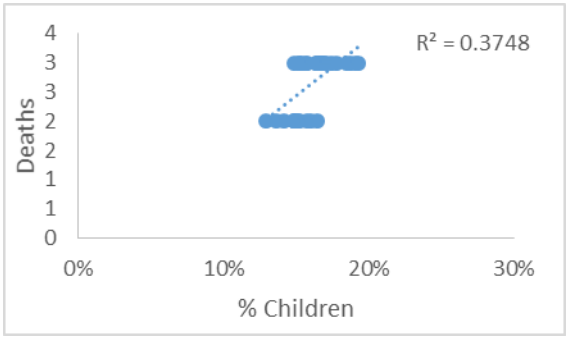
B)



C)



D)



E)

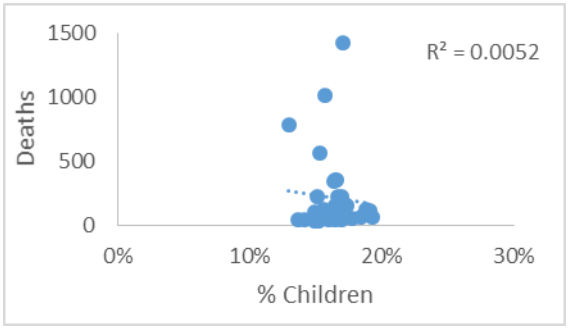
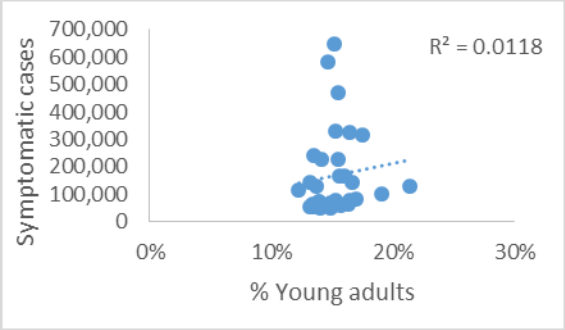
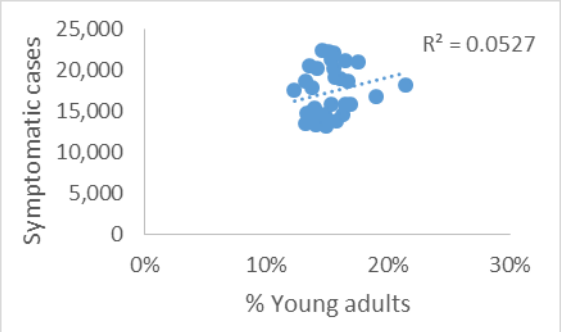


Figure A31.13 Association between the percentage of the total population represented by young adults and overall number of symptomatic cases. Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C), Scenario 4 (D) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

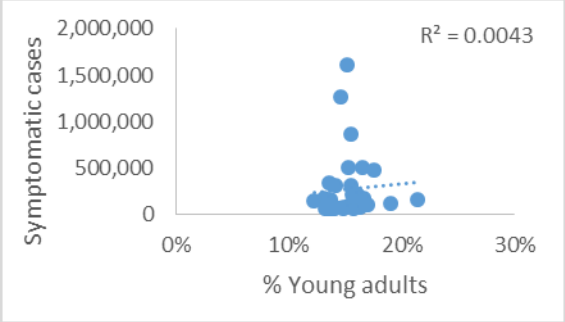
A)



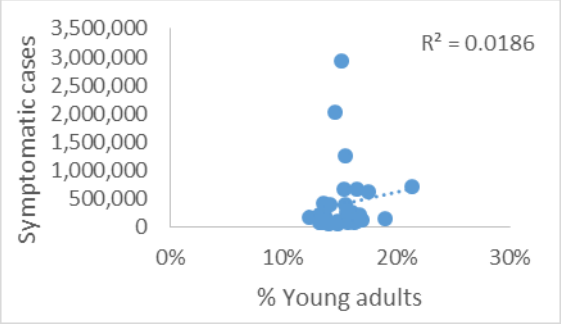
D)



B)



E)



C)

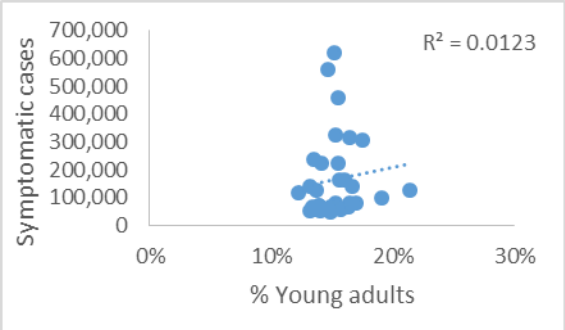
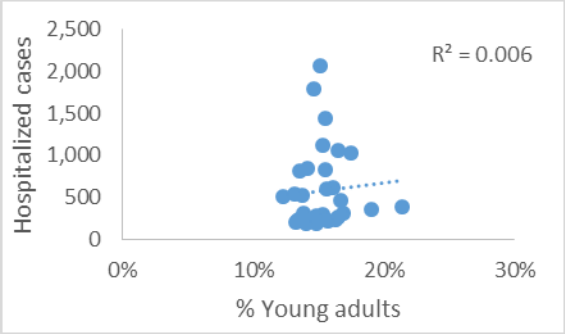
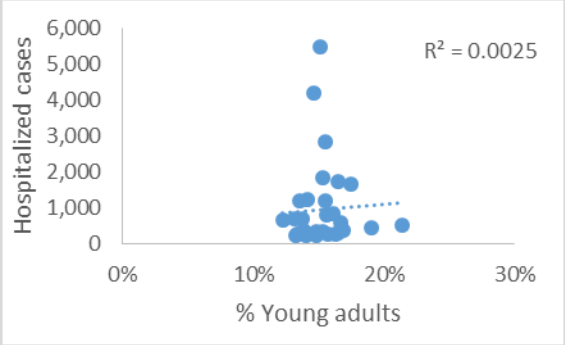


Figure A31.14 Association between the percentage of the total population represented by young adults and overall number of acute hospital admissions. Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C), Scenario 4 (D) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

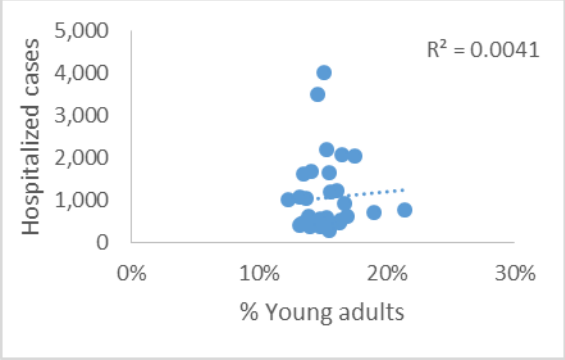
A)



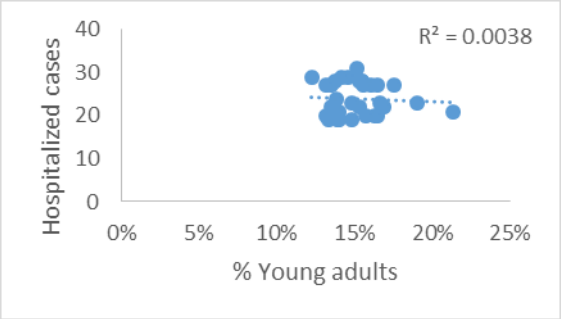
B)



C)



D)



E)

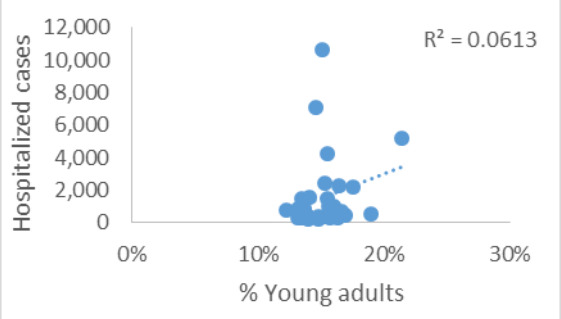
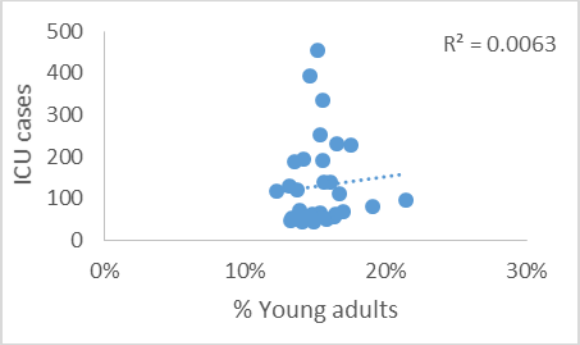
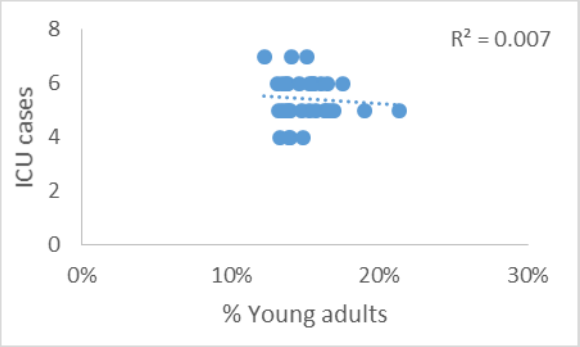


Figure A31.15 Association between the percentage of the total population represented by young adults and overall number of ICU admissions. Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C), Scenario 4 (D) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

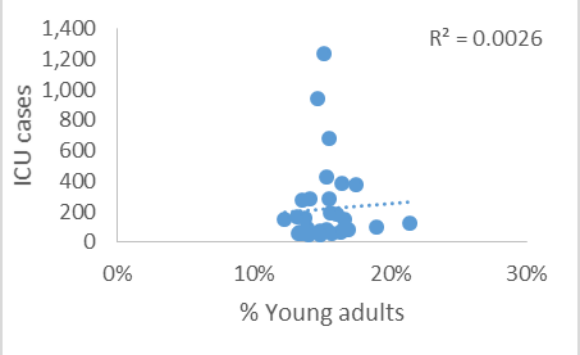
A)



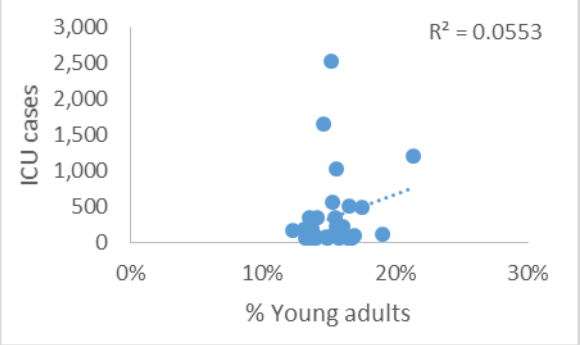
D)



B)



E)



C)

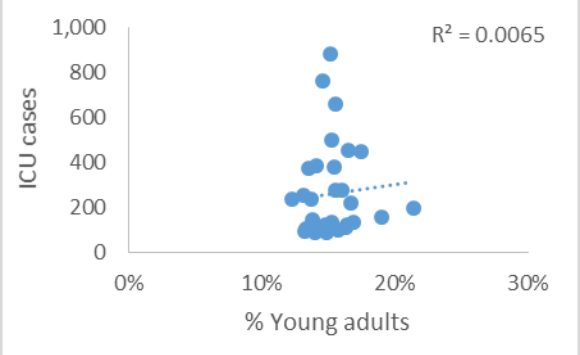
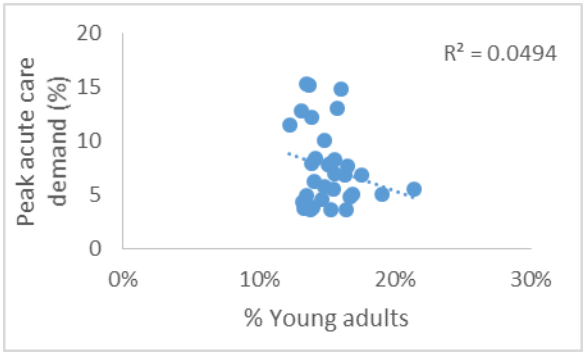
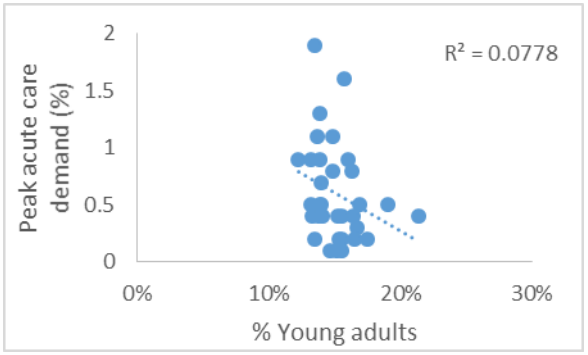


Figure A31.16 Association between the percentage of the total population represented by young adults and peak acute-care demand (as a percentage of total capacity). Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C), Scenario 4 (D) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

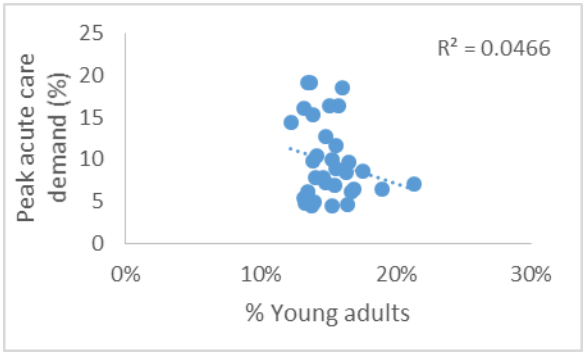
A)



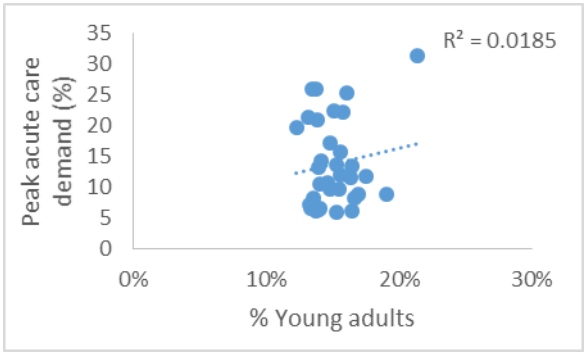
D)



B)



E)



C)

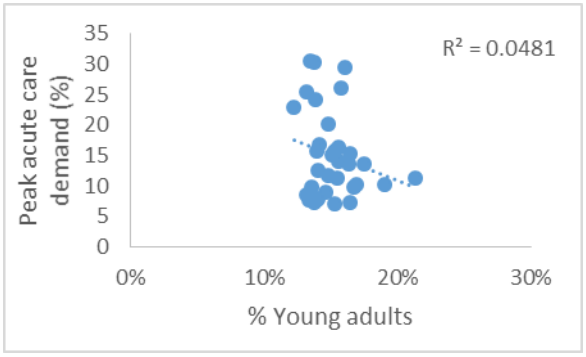
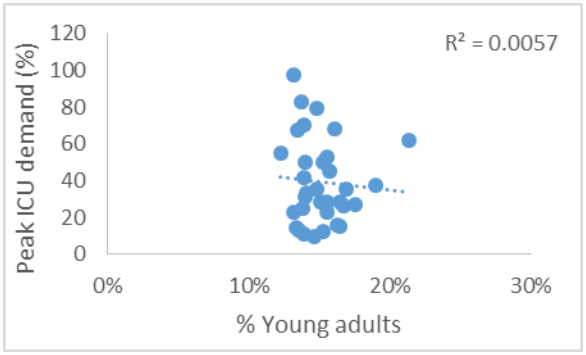
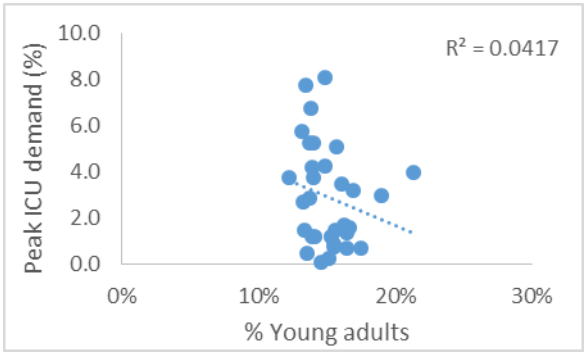


Figure A31.17 Association between the percentage of the total population represented by young adults and peak ICU demand (as a percentage of total capacity). Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C), Scenario 4 (D) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

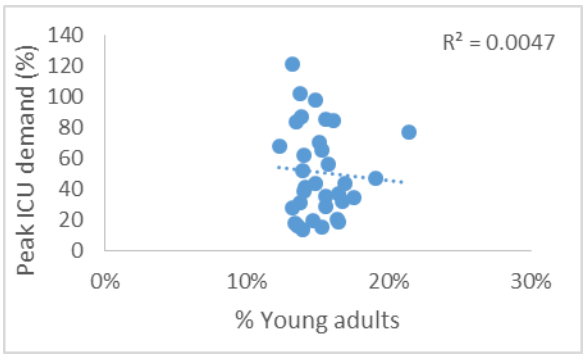
A)



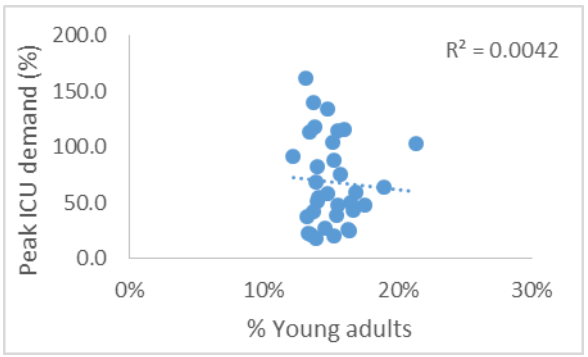
D)



B)



E)



C)

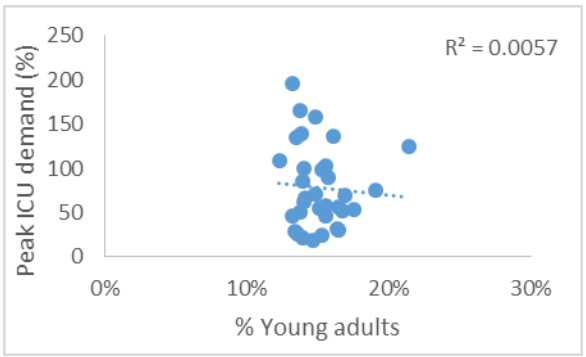
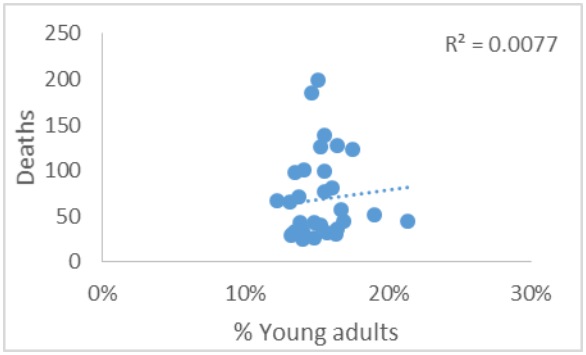
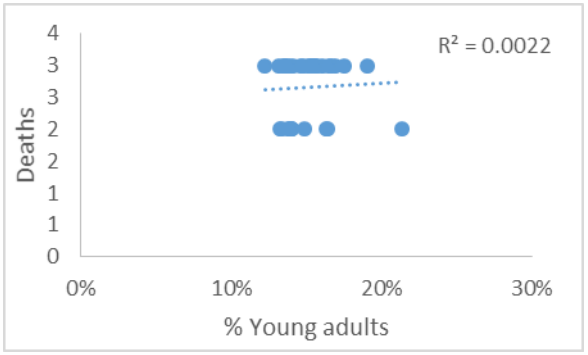


Figure A31.18 Association between the percentage of the total population represented by young adults and total mortality. Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C), Scenario 4 (D) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

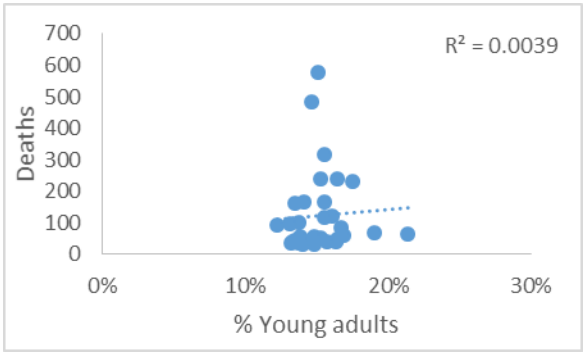
A)



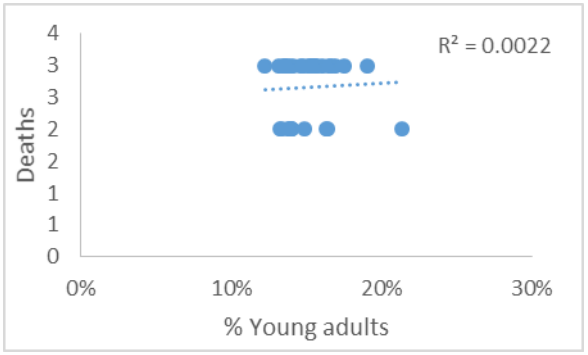
D)



B)



E)



C)

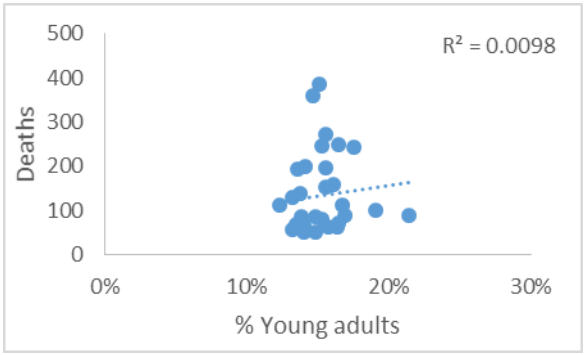
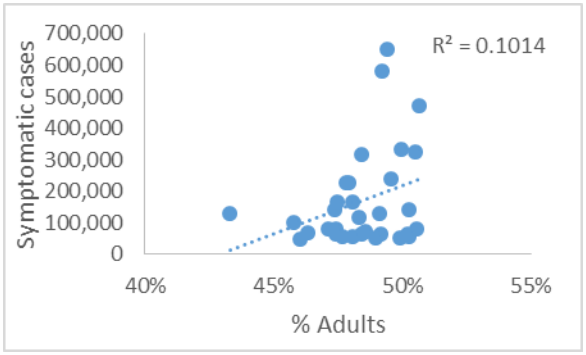
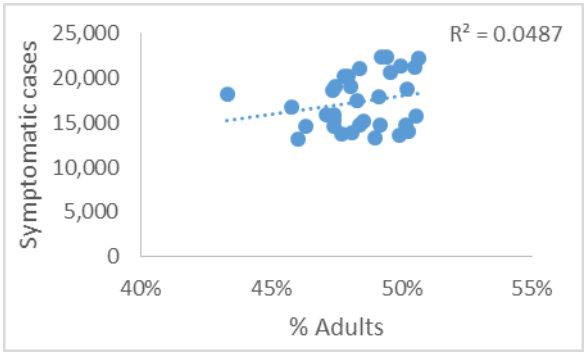


Figure A31.19 Association between the percentage of the total population represented by adults and total symptomatic cases. Negligible correlation in Scenario 2 (B), Scenario 4 (D) and Scenario 5 (E); weak correlation in Scenario 1 (A) and Scenario 3 (C). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

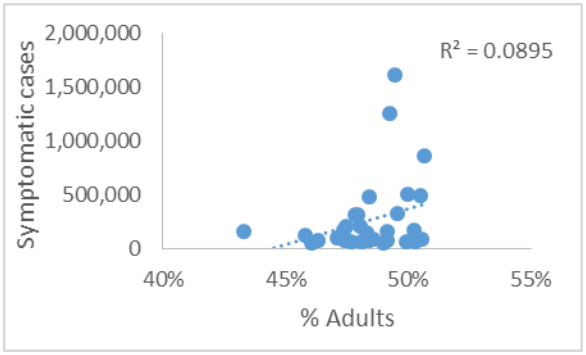
A)



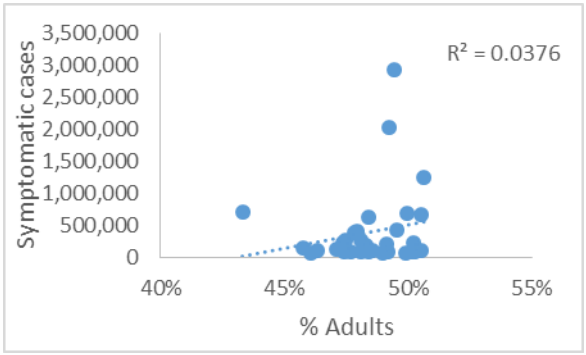
D)



B)



E)



C)

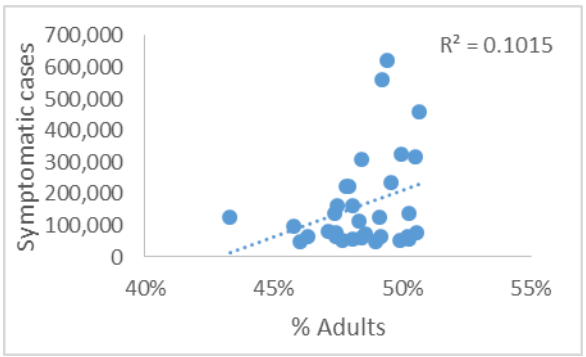
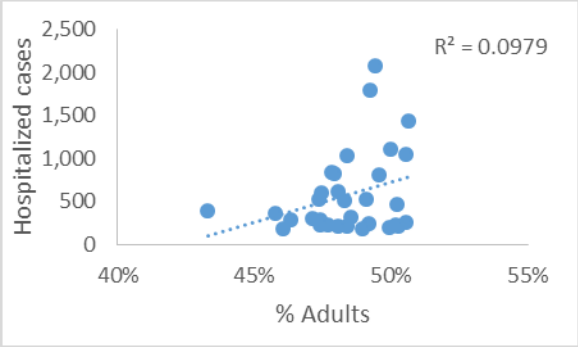
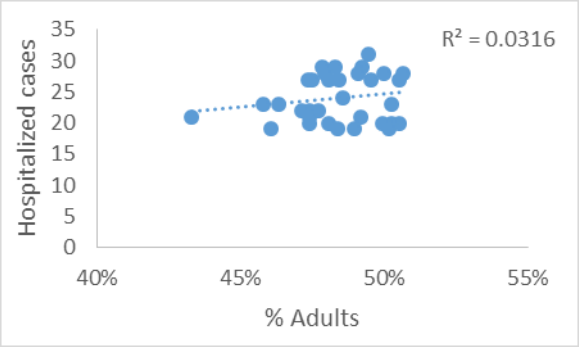


Figure A31.20 Association between the percentage of the total population represented by adults and total acute hospital admissions. Negligible correlation in Scenario 2 (B), Scenario 3 (C), Scenario 4 (D) and Scenario 5 (E); weak correlation in Scenario 1 (A). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

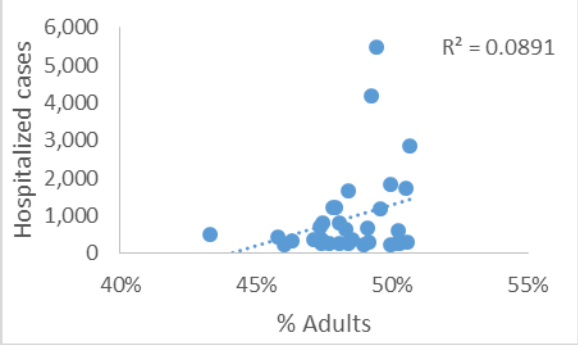
A)



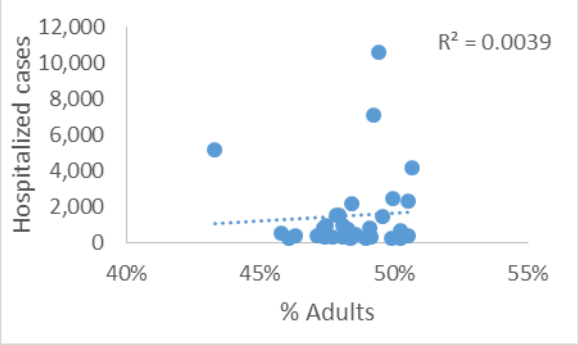
D)



B)



E)



C)

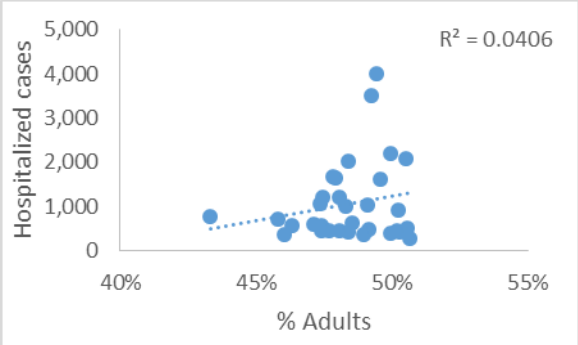
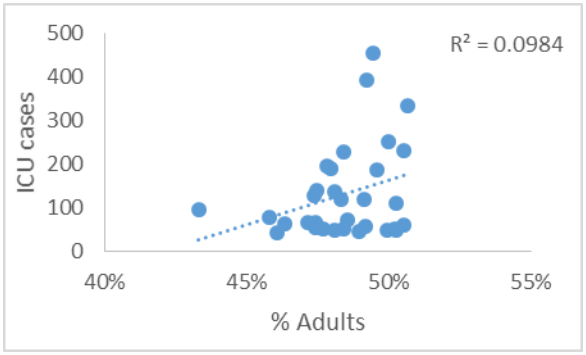
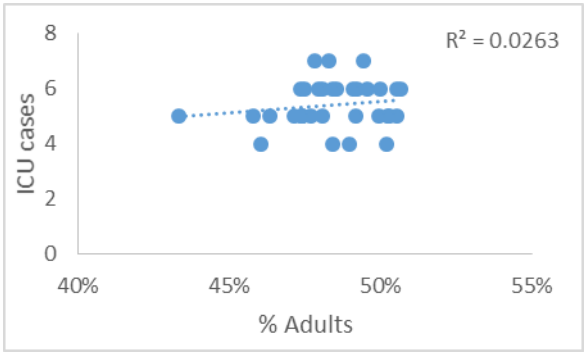


Figure A31.21 Association between the percentage of the total population represented by adults and total ICU admissions. Negligible correlation in Scenario 4 (D) and Scenario 5 (E); weak correlation in Scenario 1 (A). Scenario 2 (B) and Scenario 3 (C). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

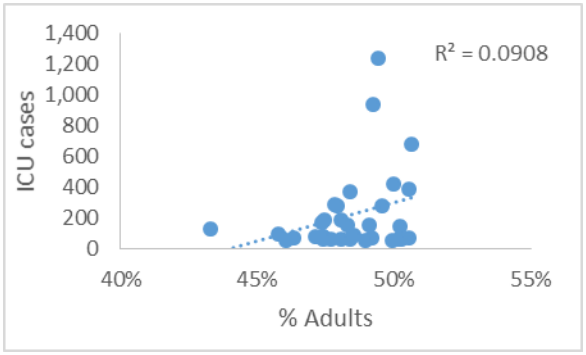
A)



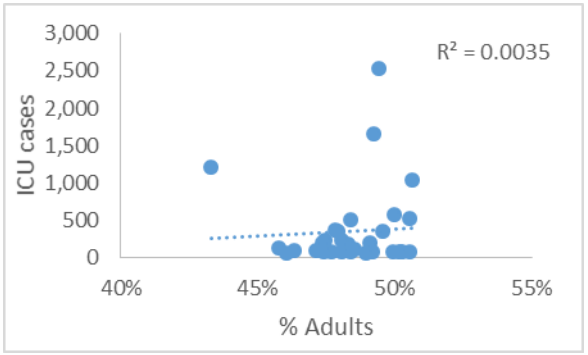
D)



B)



E)



C)

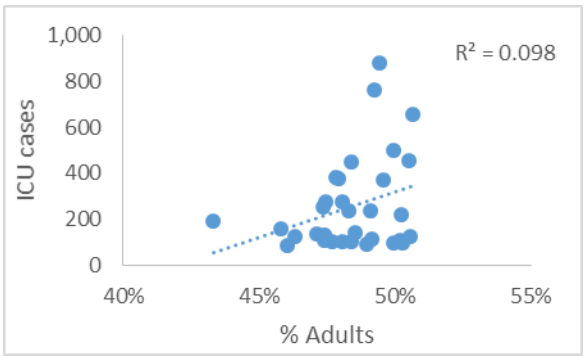
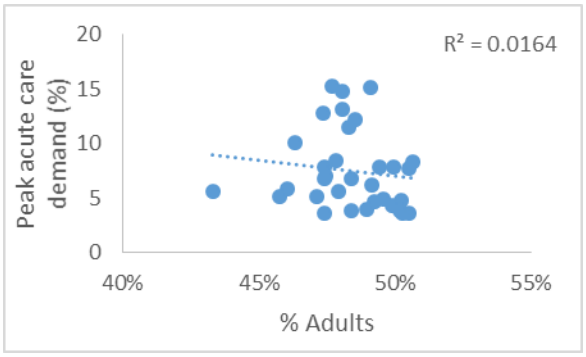
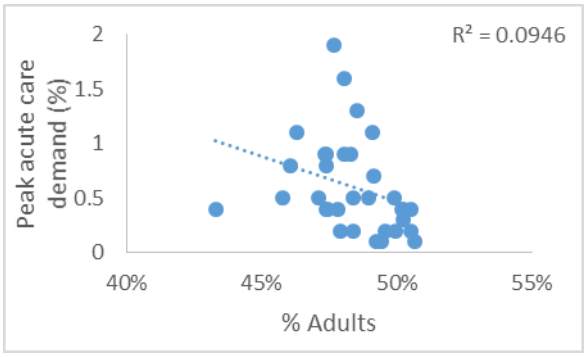


Figure A31.22 Association between the percentage of the total population represented by adults and peak acute-care demand (as a percentage of total capacity). Negligible correlation in Scenario 1 (A), Scenario 2 (B) and Scenario 3 (C); weak correlation in Scenario 4 (D) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

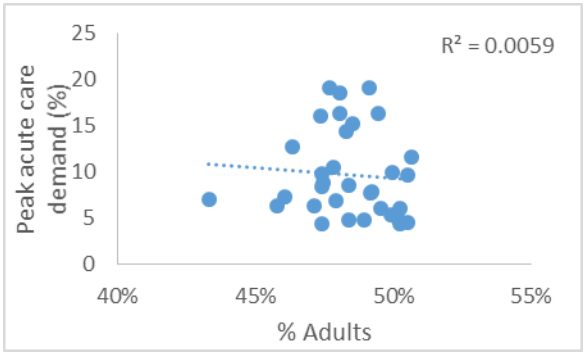
A)



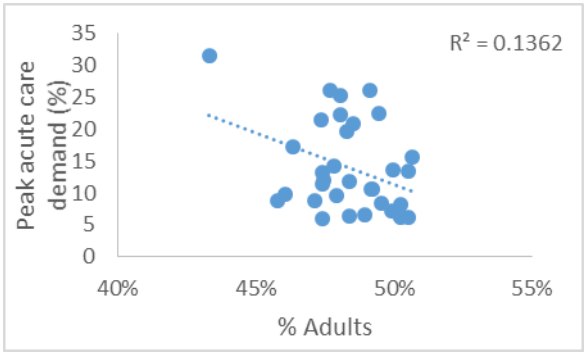
D)



B)



E)



C)

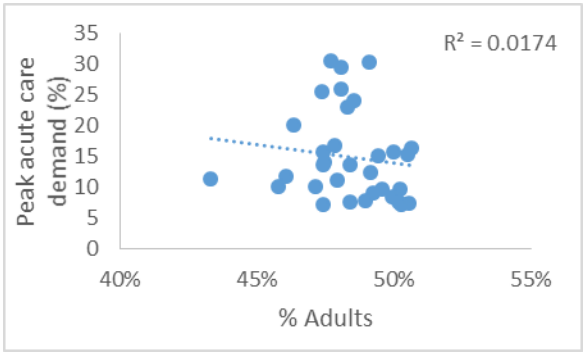
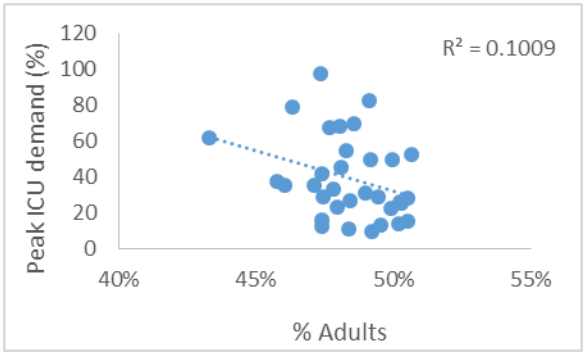
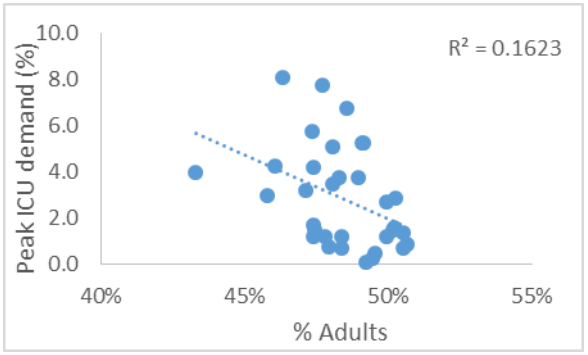


Figure A31.23 Association between the percentage of the total population represented by adults and peak ICU demand (as a percentage of total capacity). Negligible correlation in Scenario 2 (B) and Scenario 5 (E); weak correlation in Scenario 1 (A), Scenario 3 (C) and Scenario 4 (D). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

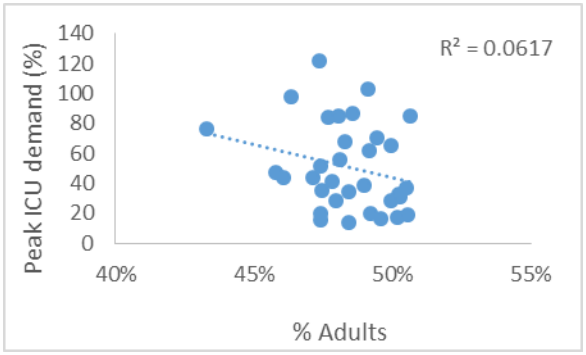
A)



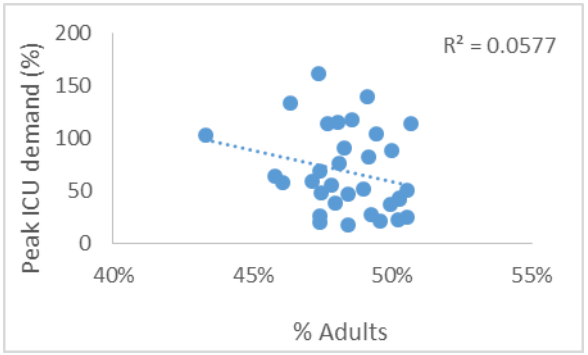
D)



B)



E)



C)

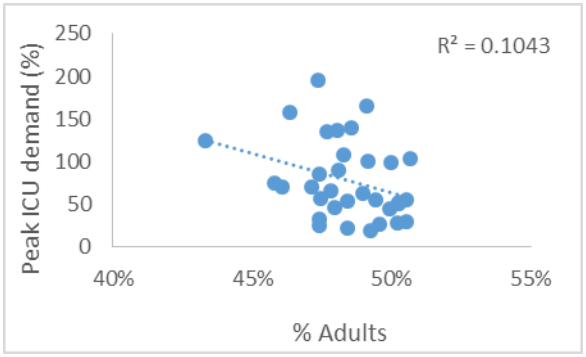
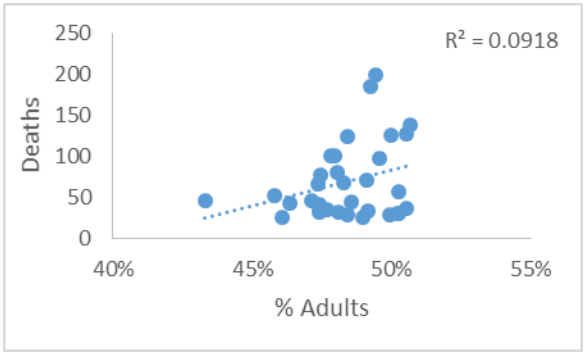
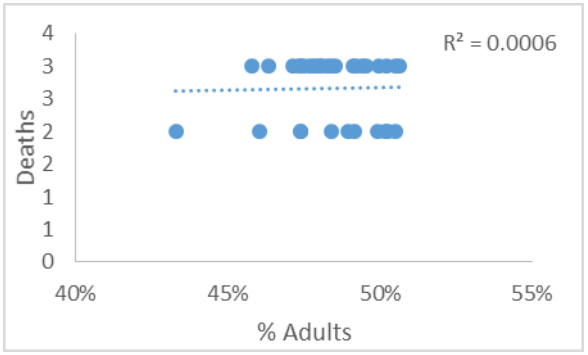


Figure A31.24 Association between the percentage of the total population represented by adults and total mortality. Negligible correlation in Scenario 4 (D) and Scenario 5 (E); weak correlation in Scenario 1 (A), Scenario 2 (B) and Scenario 3 (C). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

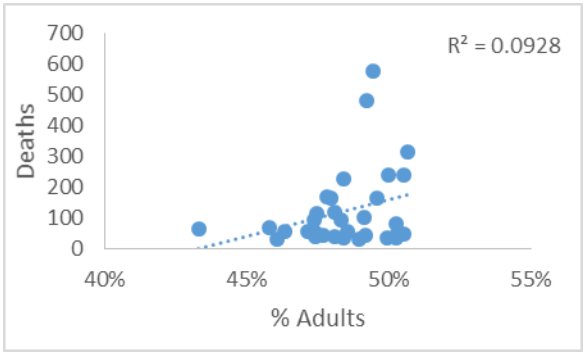
A)



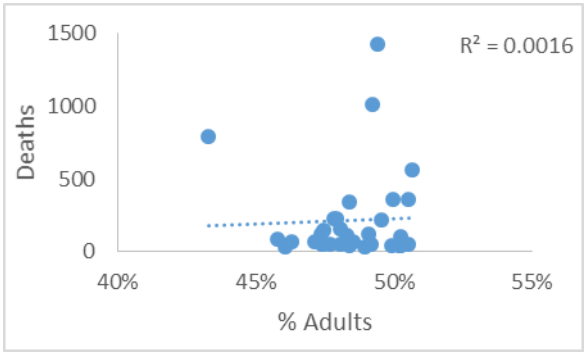
D)



B)



E)



C)

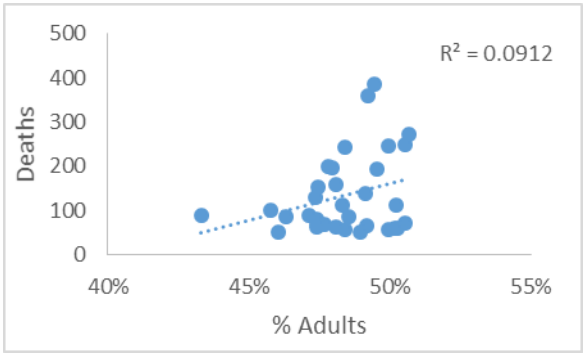
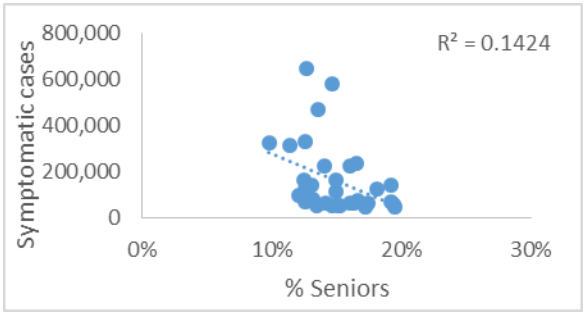
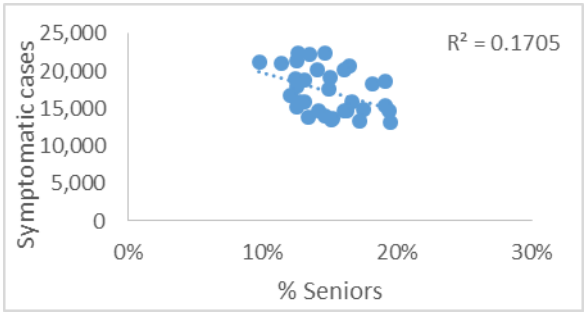


Figure A31.25 Association between the percentage of the total population represented by seniors and total symptomatic cases. Negligible correlation in Scenario 5 (E); weak correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C) and Scenario 4 (D). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

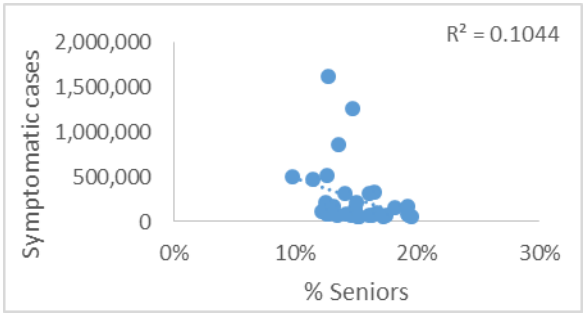
A)



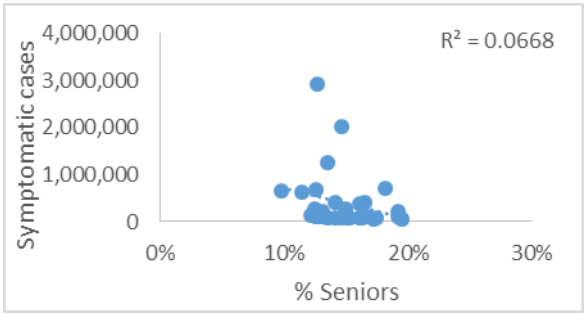
D)



B)



E)



C)

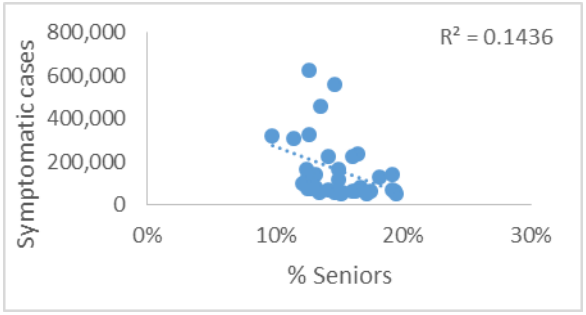
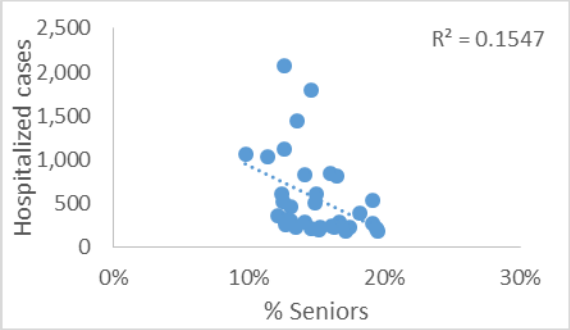
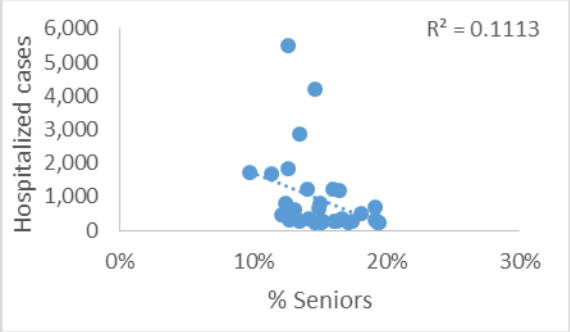


Figure A31.26 Association between the percentage of the total population represented by seniors and total acute hospital admissions. Negligible correlation in Scenario 5 (E); weak correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C) and Scenario 4 (D). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

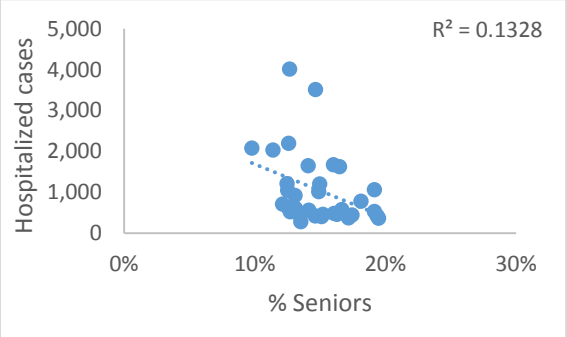
A)



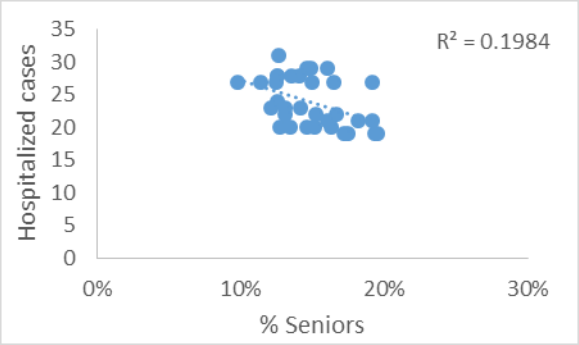
B)



C)



D)



E)

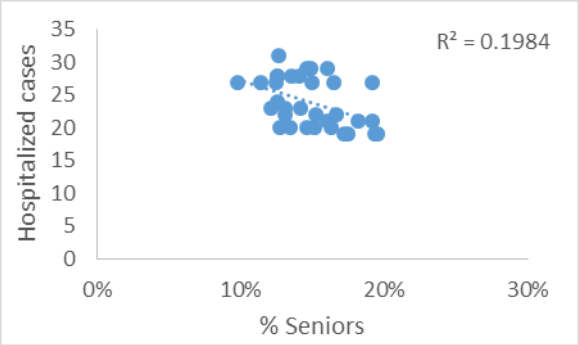
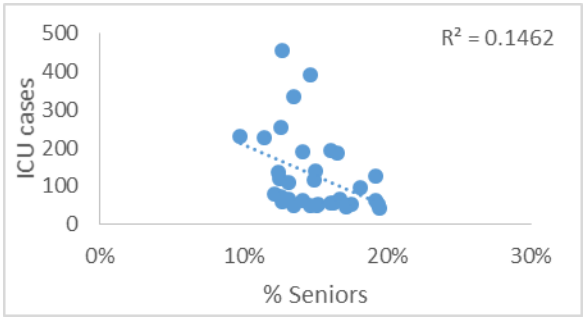
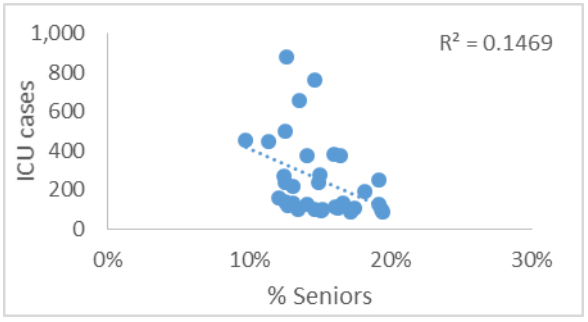


Figure A31.27 Association between the percentage of the total population represented by seniors and total ICU admissions. Negligible correlation in Scenario 5 (E); weak correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C) and Scenario 4 (D). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

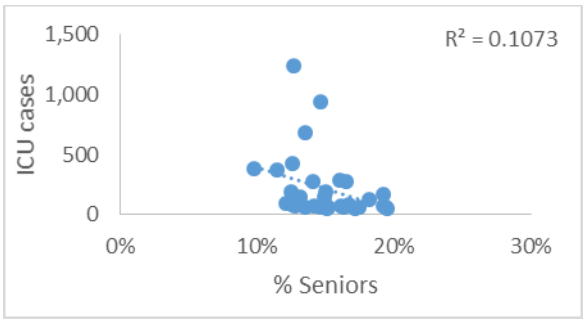
A)



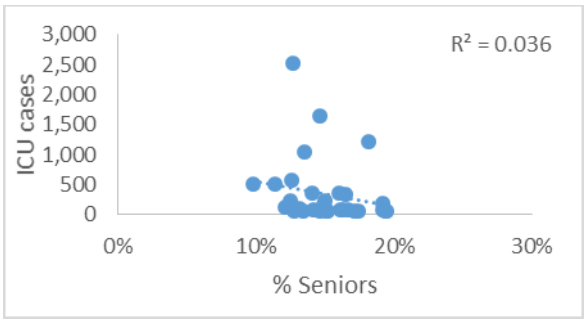
D)



B)



E)



C)

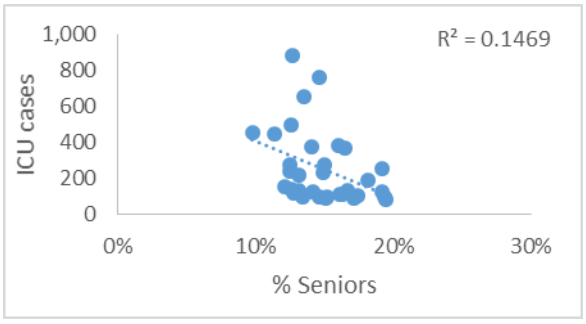
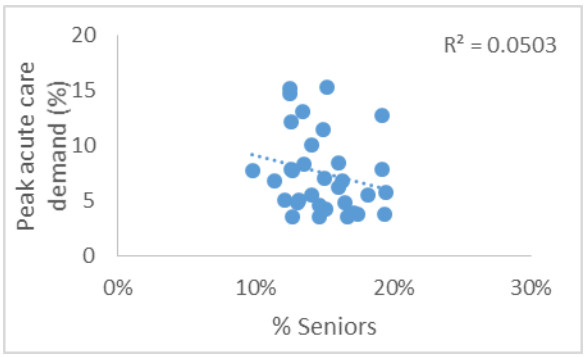
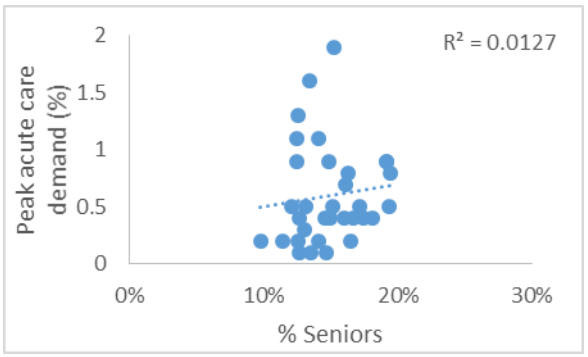


Figure A31.28 Association between the percentage of the total population represented by seniors and peak acute-care demand (as a percentage of total capacity). Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C), Scenario 4 (E) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

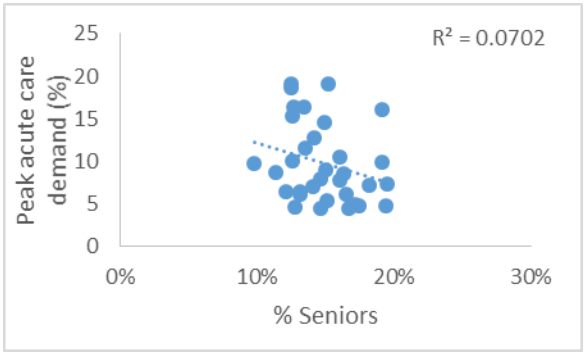
A)



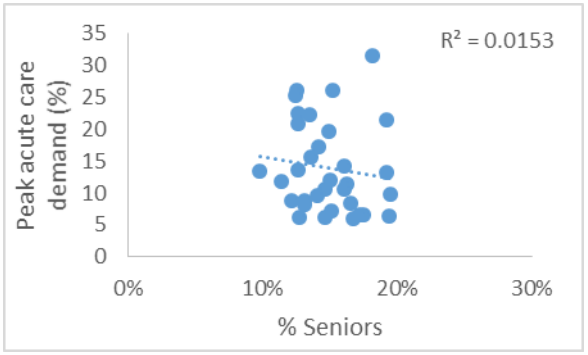
D)



B)



E)



C)

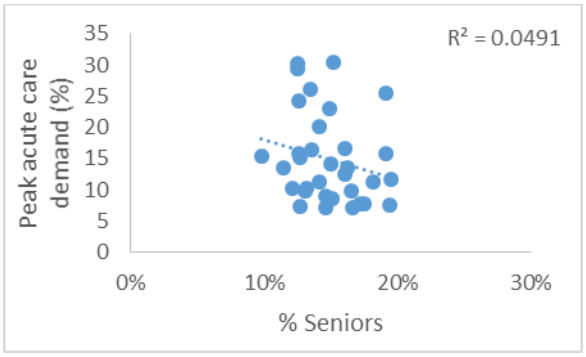
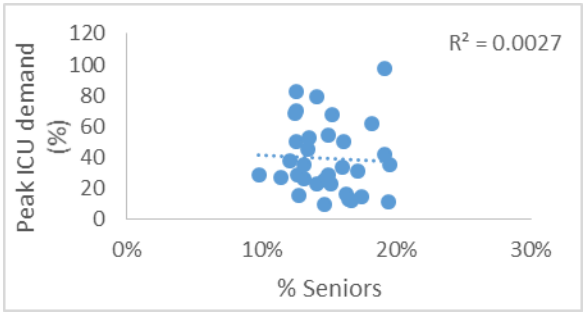
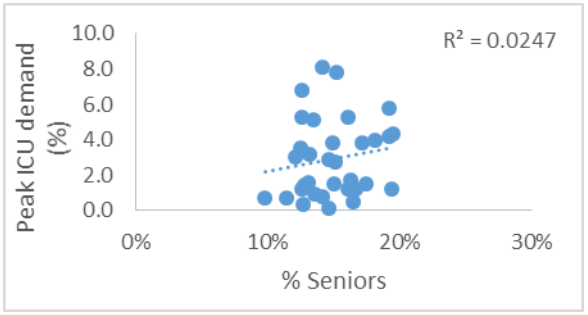


Figure A31.29 Association between the percentage of the total population represented by seniors and peak ICU demand (as a percentage of total capacity). Negligible correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C), Scenario 4 (E) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

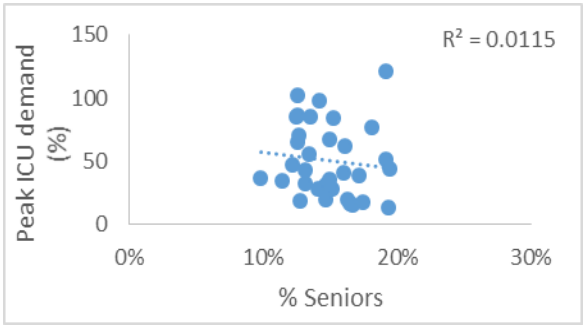
A)



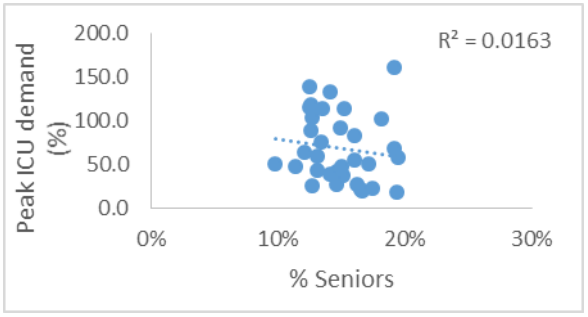
D)



B)



E)



C)

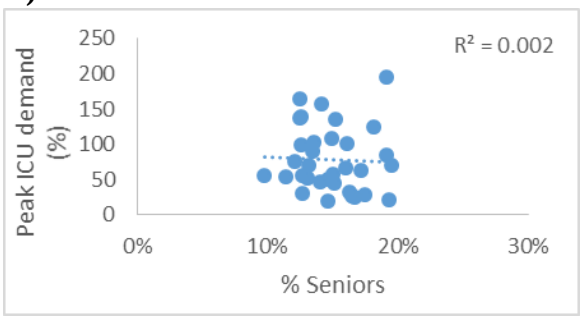
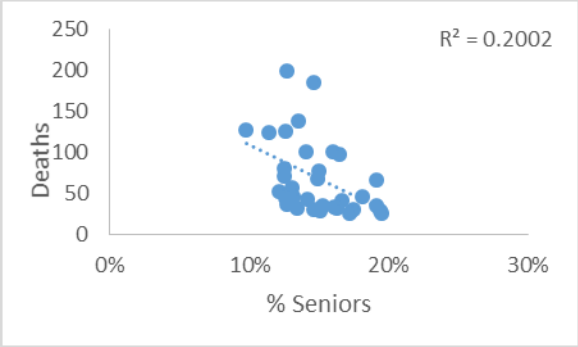
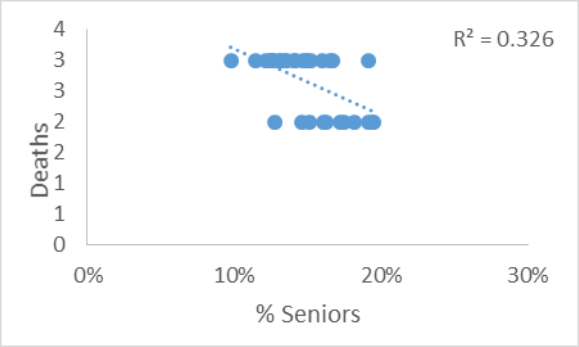


Figure A31.30 Association between the percentage of the total population represented by seniors and total mortality. Negligible correlation in Scenario 5 (E); weak correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C) and Scenario 4 (D). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

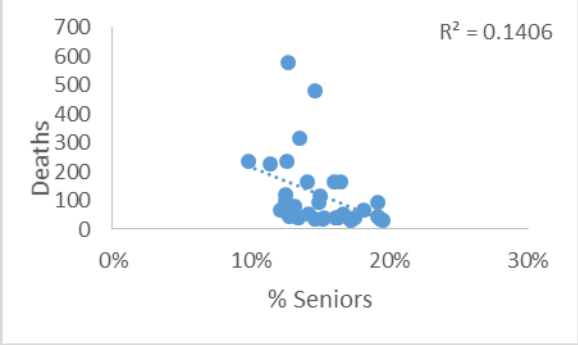
A)



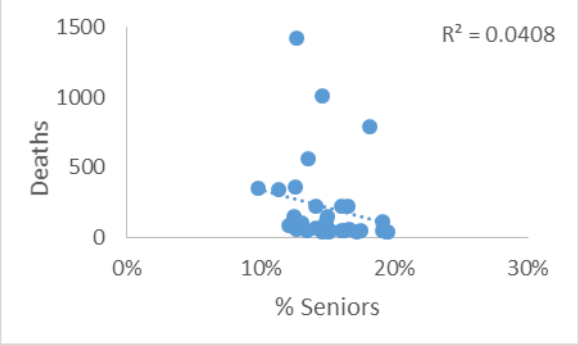
D)



B)



E)



C)

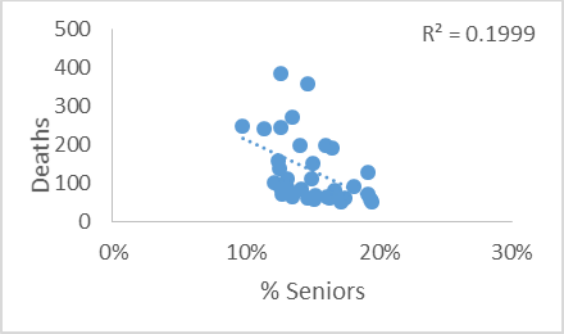
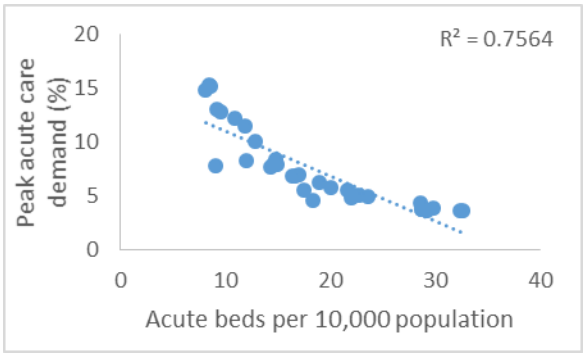
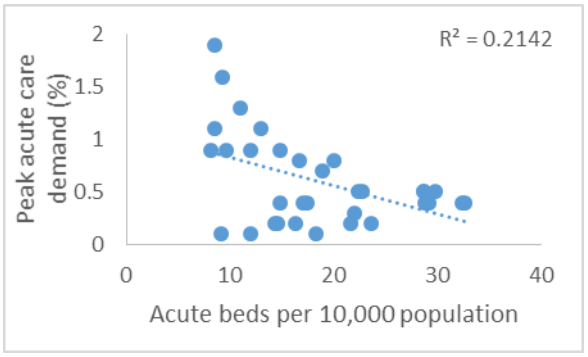


Figure A31.31 Association between the number of acute-care hospital beds per 10,000 population and peak acute-care demand (as a percentage of total capacity). Weak correlation in Scenario 4 (D); strong correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

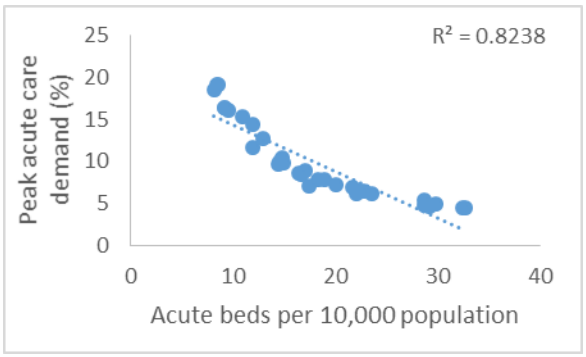
A)



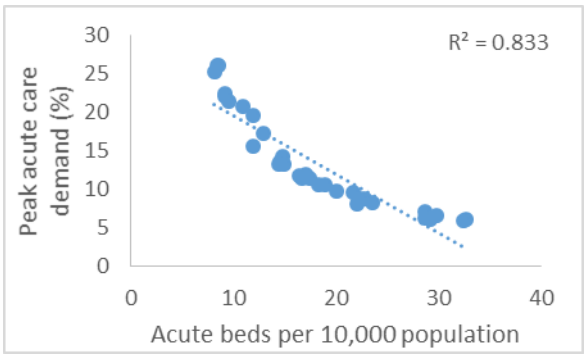
D)



B)



E)



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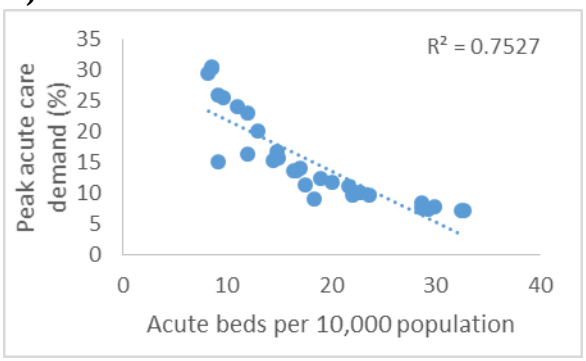
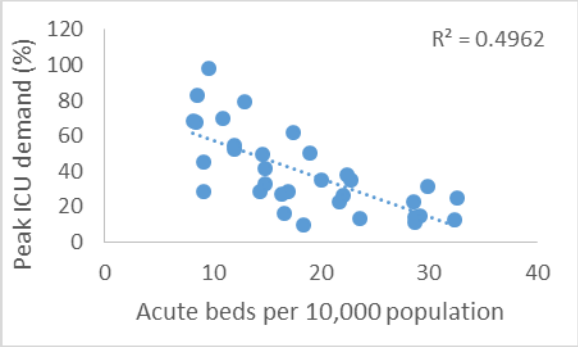
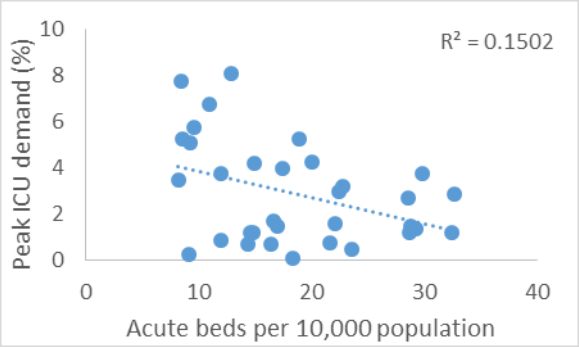


Figure A31.32 Association between the number of acute-care hospital beds per 10,000 population and peak ICU demand (as a percentage of total capacity). Weak correlation in Scenario 4 (D); strong correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

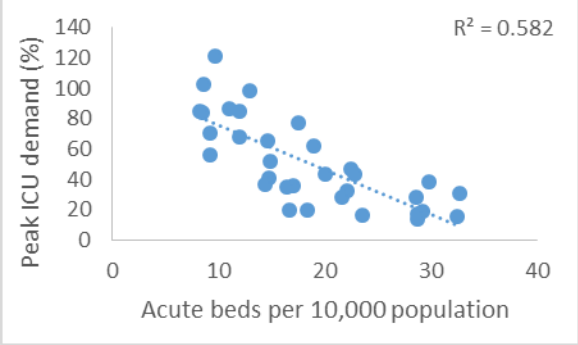
A)



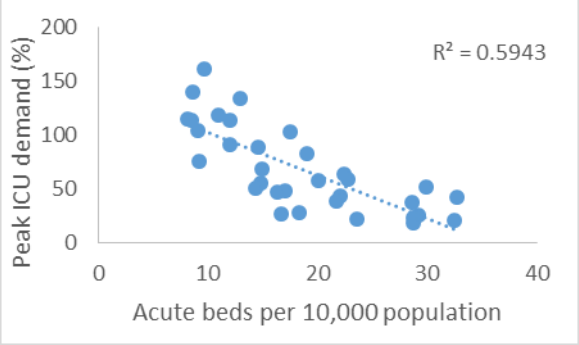
D)



B)



E)



C)

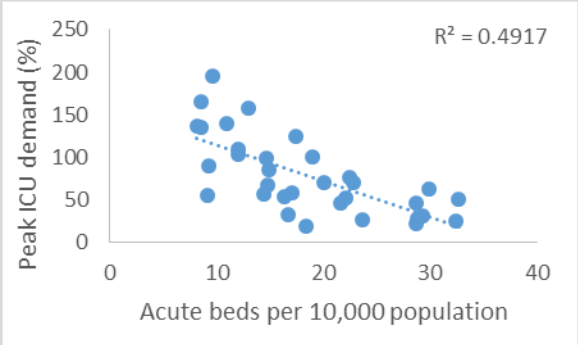
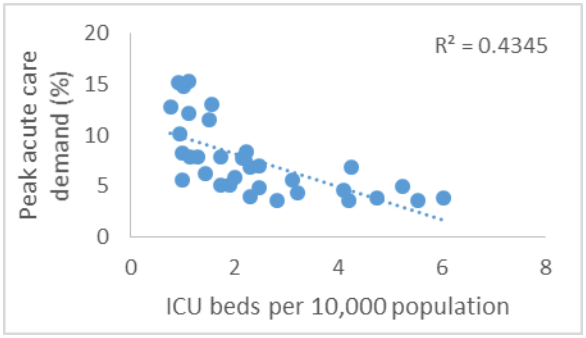
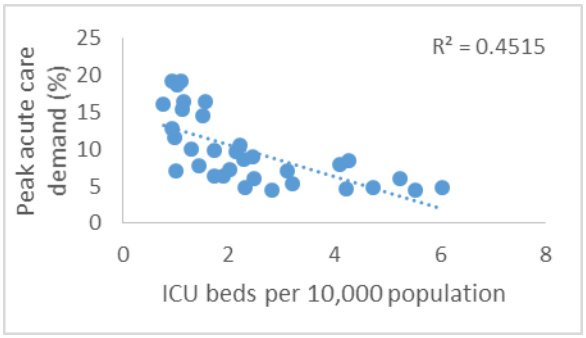


Figure A31.33 Association between the number of ICU beds per 10,000 population and peak acute-care demand (as a percentage of total capacity). Weak correlation in Scenario 4 (D); moderate correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

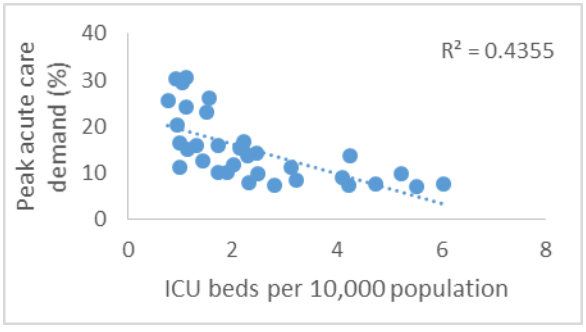
A)



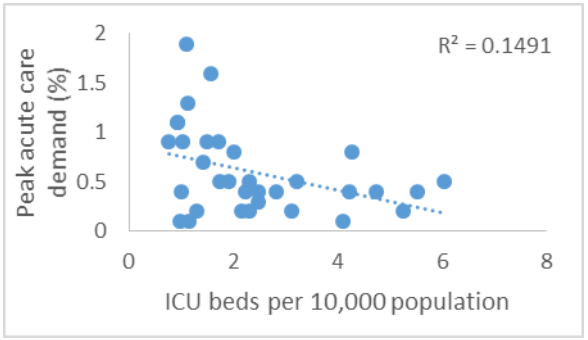
B)



C)



D)



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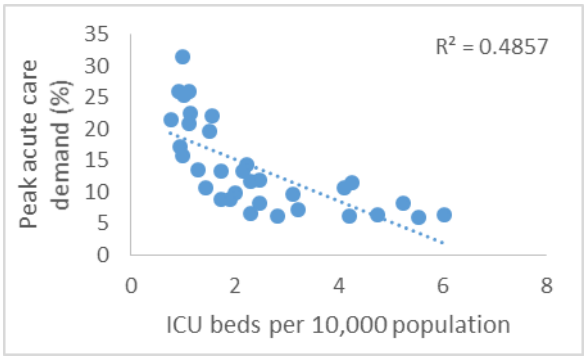
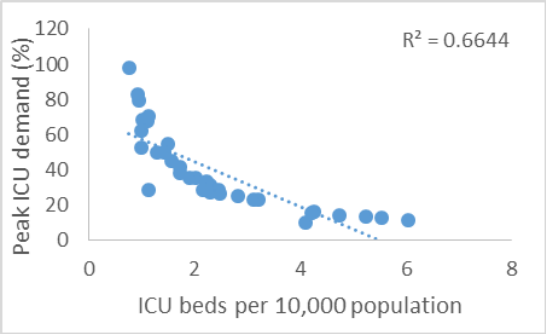
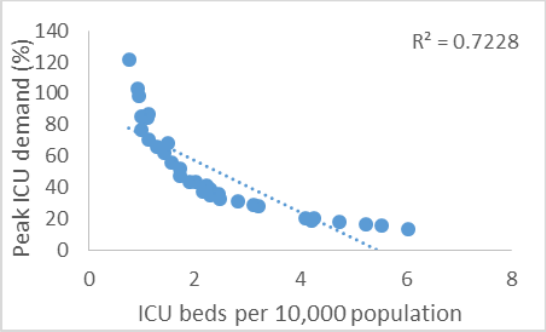


Figure A31.34 Association between the number of ICU beds per 10,000 population and peak ICU demand (as a percentage of total capacity). Moderate correlation in Scenario 4 (D); strong correlation in Scenario 1 (A), Scenario 2 (B), Scenario 3 (C) and Scenario 5 (E). Scenario 1: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 2 R_0 = 1.80, hospitalization rate = 0.4%; no intervention; pre-existing immunity in place; Scenario 3: R_0 = 1.65, hospitalization rate = 1.0%; no intervention; pre-existing immunity in place; Scenario 4: R_0 = 1.65, hospitalization rate = 0.4%; 25% pre-vaccination; pre-existing immunity in place; Scenario 5: R_0 = 1.65, hospitalization rate = 0.4%; no intervention; no pre-existing immunity.

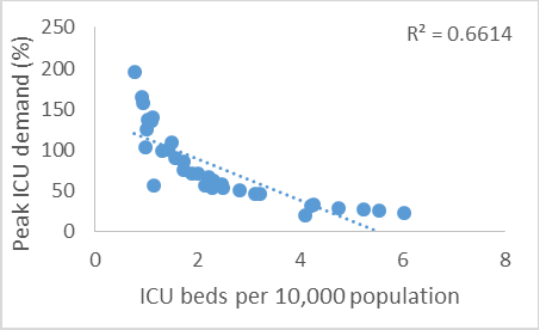
A)



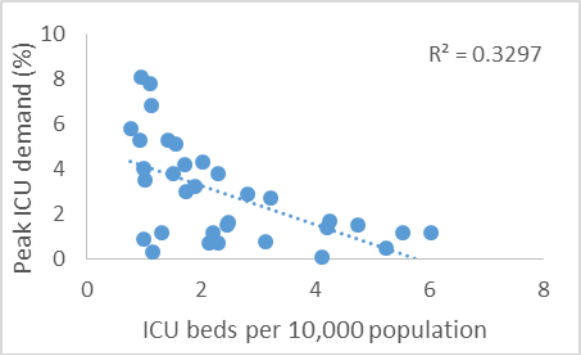
B)



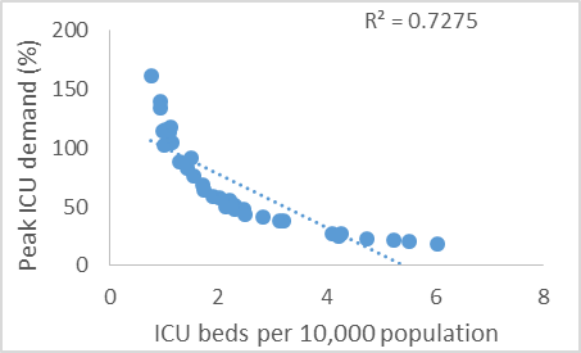
C)



D)



E)



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