H1N1 2009 Pandemic Analysis: Evaluation and Scenarios for Post-Pandemic Planning

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EXECUTIVE SUMMARY

BACKGROUND AND RESEARCH OBJECTIVES

The 2009 pH1N1 pandemic took the lives of 428 individuals and led to 8,678 hospitalizations in Canada. Despite these sobering numbers, it appears that as a result of existing pandemic preparation measures, Canadian health services were able to mitigate the effects of the virus and avoid a more serious public health crisis. However, it must be emphasized that pH1N1 proved to be generally mild and that, despite this, many issues emerged during the pandemic, raising questions about the capacity of the healthcare system and the appropriate level of intervention in such circumstances.

Since pH1N1, the notion of a pandemic is no longer as abstract as it once appeared, either for public health officials or for the general population. Using pH1N1 Canadian data as a baseline, this analysis seeks to inform post-pandemic public health discussions that focus on the evaluation of antiviral and vaccine interventions, considering several plausible hypothetical scenarios. Using empirically supported pandemic and economic mathematical models, the objectives of the research were to evaluate:

- The life and economic impact of pH1N1 in Canada;
- The effect of reported antiviral and vaccine interventions in mitigating the effects of the pandemic;
- The possible life and economic impacts of a similar influenza pandemic under several hypothetical cases. In particular:
    - If it occurred in the fall instead of in the spring,
    - If its effects were moderate or severe, rather than mild,
    - If antiviral agents were not used or if their use were widespread.

METHODS AND APPROACH

The approach employed an age-dependent Susceptible-Exposed-Infected-Recovered pandemic model, coupled with a macroeconomic model to estimate life and economic impacts. The life impacts evaluated included the attack rate, hospitalizations, and deaths; the economic analysis examined the effect of the pandemic on absenteeism and direct health costs. Healthcare resource use included only those costs directly related to the treatment of pH1N1 cases and took into account GP visits, emergency department visits, and hospitalizations. Absenteeism was assumed to be proportional to the number of infectious individuals and any hospitalizations that occurred among the employed.

Given the interest in understanding the full potential impact of pH1N1 in Canada, the analysis evaluated the following scenarios:

- Pandemic pH1N1, with and without each combination of reported antiviral and vaccine intervention used;
- Spring-start moderate and severe pandemics, with and without vaccination and antiviral interventions (where antiviral use could be either at 2009 levels or more widespread); and
- Fall-start moderate and severe pandemics, with and without vaccination and antiviral interventions (where antiviral use could be either at 2009 levels or more widespread)

These scenarios allowed for the contributions of antiviral and vaccine use to be reconciled and they investigated different pandemic severity and timing assumptions, in combination with possible increased antiviral use. Each moderate and severe pandemic scenario used the same attack rate, based on that of pH1N1 had there been no interventions. Conversely, age-dependent hospitalization and case fatality ratios were scaled on the basis of historical precedents; thus, moderate pandemic scenarios were scaled to the average 1957/58 pandemic case fatality ratio, and severe pandemic scenarios were scaled to the lower estimates of the 1918 pandemic.

The outcome analysis was performed from an aggregate Canadian healthcare payer perspective, using the cost-utility measures of the cost of quality-adjusted life years (QALYs) gained and the incremental cost effectiveness ratio (ICER). For this analysis, the cost effectiveness analysis of an intervention included the costs of the intervention, as well as the healthcare cost savings resulting from a given intervention.

As part of the substantiation and validation process, an independent group of recognized Canadian and international infectious disease experts, medical experts and virologists was formed as the Pandemic Research Advisory Committee (PRAC). The members of the committee were consulted throughout this study by way of four workshops that focused upon the assumptions, face validity and internal validity of the model and the results that were being generated.

RESULTS AT A GLANCE: PANDEMIC H1N1 ANALYSIS

With relatively low reported antiviral treatment intervention (approximately 6.2% of people with influenza received antiviral treatment) and the arrival of vaccine in late October 2009, the Public Health Agency of Canada attributes 8,678 hospitalizations and 428 mortalities to pH1N1 by April 24th 2010. By calibrating the pandemic simulation model to reported data, the analysis estimated:

- The pH1N1 attack rate of approximately 15%;
- 12,680 QALYs lost;
- Direct healthcare costs of $58 million; and
- The indirect economic production impact due to pandemic-induced absenteeism of $1.6 billion or 0.1% of gross domestic product (GDP).

Without the reported use of antivirals and vaccine during 2009, the analysis indicated that the pandemic impact of pH1N1 would have been approximately:

- Twice as large in terms of hospitalizations and GDP impacts;
- Almost three times as great in terms of hospitalization costs and QALYs; and
- Almost four times as large in terms of deaths.

Disentangling the relative contributions of antivirals and vaccines has been a challenge given their joint use in a highly dynamic process such as a pandemic. In terms of hospitalizations, antivirals would have independently accounted for 7.6% of the cases saved and vaccines for 85.4%. The balance of 7.0% is reflective of the synergistic use of both antivirals and vaccines together. In terms of deaths, antivirals would have independently accounted for 55.1% of the cases saved and vaccines for 65.0%. The excess of 20.1% reflects the common ability of both interventions to prevent death.

On its own, antiviral use was considered very cost-effective at an estimated $2,002 cost for each QALY gained. Once healthcare costs saved were taken into account, rather than a net cost per QALY, antivirals resulted in a net savings of $1,077 for each QALY gained. That is, antiviral use paid for itself in terms of healthcare costs saved.

During the period of pH1N1, a reported 50.4 million doses of vaccine were purchased, of which approximately 14.6 million were estimated to have been used. On its own, vaccine use was estimated to have an incremental cost-effectiveness ratio (ICER) of $2,076 cost per QALY gained when the cost of vaccine not used was excluded. With respect to the total amount of vaccine which had been purchased, an ICER of $17,317 cost per QALY gained had been estimated. Both measures indicate that vaccines can also be considered very cost effective. As a caveat however, sensitivity analysis conducted showed that the results were highly sensitive to the timing of the vaccine rollout. If the vaccine was administered later than estimated in the analysis, or at a slower rate than modelled, the benefits attributable to vaccine materially diminished. Detailed information about the actual vaccination rollout was unavailable.

Due to the absence of data, distribution costs were not incorporated into the cost effectiveness measures. While the inclusion of such costs would reduce the cost-effectiveness, the exclusion was not expected to change the general conclusions of the cost-effectiveness analysis. Assuming a $50,000 ICER threshold (which is approximately one-third of the World Health Organization recommendation), the distribution costs of antivirals would have to exceed $650 million ($1,000 per prescription), and the distribution costs for vaccines would have to exceed $614 million ($42 per dose used) before their cost effectiveness measures would begin to be questioned.

RESULTS AT A GLANCE: SPRING/FALL, MODERATE/SEVERE PANDEMIC ANALYSIS

Examination of the possible impacts if pH1N1 had a different severity or timing, under the assumption that the applied antiviral and vaccine levels do not change, yielded the following results:

- A moderately severe spring pandemic was estimated to result in approximately four times the hospitalizations and thirteen times the mortalities of pH1N1. Vaccines were estimated to arrive 4 weeks before the potential pandemic peak;
- A severe spring pandemic was estimated to result in approximately 27 times the hospitalizations and 75 times the mortalities of pH1N1. Vaccines were estimated to arrive 4 weeks before the potential pandemic peak;
- A moderately severe fall pandemic was estimated to result in 10 times the hospitalizations and 32 times the mortalities of pH1N1. Vaccines were estimated to arrive 12 weeks after the potential pandemic peak;
- A severe fall pandemic was estimated to result in 72 times the hospitalizations and over 200 times the mortalities of pH1N1. Vaccines were estimated to arrive 14 weeks after the potential pandemic peak.

These scenario results reveal how much worse the experience of a pandemic could have been if the severity or timing of a pandemic had been different. For example, if antiviral and vaccine interventions remained the same, a moderate pandemic in the spring would be expected to result in approximately 38,781 hospitalizations, 5,582 mortalities, 121,961 QALYs lost, direct healthcare costs of $235 million and GDP impact from absenteeism of $2.6 billion (0.15% of GDP). A moderate pandemic in the fall would be expected to result in approximately 88,206 hospitalizations, 13,453 mortalities, 280,658 QALYs lost, direct healthcare costs of $529 million and GDP impact from absenteeism of $4.3 billion (0.26% of GDP).

Under moderate or severe pandemic scenarios, it is unlikely that the level of antiviral use and vaccine uptake would remain the same as that reported during pH1N1. The timing of vaccine distribution, relative to the peak of a pandemic, is a key parameter that is not fully under control of healthcare authorities. For instance, results of pandemic modeling indicated that vaccines would likely arrive prior to the peak of a spring pandemic but after the peak of a fall pandemic. This consideration underlines the importance of antivirals in controlling a pandemic before a targeted vaccine can be made available.

To investigate the impact of greater antiviral use, an additional scenario was analyzed, in which 50% of the sick population received treatment (consistent with the Canadian Pandemic Influenza Plan) and 5% of the population (i.e., all healthcare workers and emergency service providers in the Canadian population) received post-exposure prophylaxis. Regardless of whether the pandemic arrived in Canada in the spring or fall, widespread antiviral use would have significant incremental benefits for either a moderate or a severe pandemic, with 30,059 to 229,650 additional hospitalizations prevented, 4,331 to 33,945 deaths averted, 94,485 to 779,784 QALYs saved, $182 million to $1.2 billion in healthcare costs saved and $2.0 billion to $6.2 billion GDP saved. ICER analysis of this widespread antiviral use scenario indicates that, rather than a net cost per QALY, antivirals can result in a net savings of approximately $1,000 per QALY gained.

The importance and role of an antiviral strategy is further emphasized by the fall pandemic results, where mass vaccination was estimated to arrive well beyond the potential pandemic peaks. In those cases, the use of antivirals was estimated to account for almost the entire intervention benefit.

CONCLUSIONS

The present research is focused on making broad conclusions about the effectiveness of antiviral and vaccine use by providing general scenario analysis to inform policy discussions in the aftermath of the pH1N1 pandemic. The research is oriented towards population health management and future risk mitigation issues, as they relate to Canadian life and economic effects of pH1N1. The work demonstrates how such effects could have changed under different severity and timing scenarios.

The analysis suggests that the joint use of antiviral and vaccine intervention played a pivotal role in blunting the potential negative impacts of pH1N1. Without the reported use of antivirals and vaccine during 2009, pH1N1 impacts could have been at least twice as large. The analysis revealed that antivirals played a therapeutic role for the sick, whereas vaccination served as the primary means by which infection could be prevented. These interventions appear to have been very cost effective, both independently and as part of a joint intervention effort.

The pandemic severity and timing analysis demonstrated how much worse the 2009/2010 pandemic experience could have been. A moderate to severe spring pandemic could result in 13 to 75 times greater mortality than was seen with pH1N1, assuming the same levels of antivirals and vaccines were used. A moderate to severe fall pandemic could result in 32 to over 200 times this level of mortality. The relative mildness of the pH1N1 experience raises three key issues for consideration, further discussion and research.

First, public health interventions are significantly dependent on the cooperation of healthcare workers, emergency service providers and the public, as well as on the perception of risk among these individuals. Arguably, the perception of risk waxed and waned throughout pH1N1, which may have resulted in sporadic capacity and expectation management issues, with an overall reduction in antiviral use and vaccine uptake. The degree to which

the recent pandemic experience has influenced the public's perception of future pandemic risk remains unknown, a potentially important issue for the policymakers and public health authorities to consider.

Second, the pandemic timing analysis demonstrated the consequences of current vaccine manufacturing and approval processes. The analysis strongly suggested that under the current vaccine distribution timelines, a vaccine would be unlikely to arrive before the first peak of a pandemic. This delay could result in significant and serious consequences for the health and welfare of a population.

Third, analyses of pandemic severity and timing emphasized the important role of a widespread antiviral strategy, given the availability of antivirals prior to a mass-vaccination effort and their therapeutic properties in individuals who have not yet developed immunity to the pandemic virus. On its own, widespread antiviral use can significantly diminish hospitalization and death rates. This approach is cost effective to the point of generating positive value for the healthcare system, and it can reduce absenteeism to help protect the productive capacity of the economy.

Modeling complex dynamic systems such as a pandemic has its limitations. A primary limitation is the quality and quantity of data available at the time of analysis. While updated data may change the specifics of the results, it is not expected to change the general conclusions made for population health management and future risk-mitigation purposes.

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1.1 BACKGROUND

1.1.1 pH1N1 Canadian Pandemic

The 2009 pH1N1 flu pandemic experience and the positive response by the Canadian healthcare system suggested that prior pandemic preparation, spurred by SARS and the threat of highly virulent influenza strains such as H5N1, was of value. However, from a population-based perspective, the pH1N1 was relatively mild. Despite this, many issues emerged as the pandemic unfolded revealing weaknesses in the pandemic preparedness plan, including: capacity issues among healthcare services, debates on the use of antivirals, antiviral policies, antiviral resistance and questions regarding the appropriate quantity, timing and distribution of the vaccine supply. These all became issues that the Canadian healthcare system and Canadian governments had to address and quickly remedy.

Pandemic Influenza and the Observed pH1N1 Pandemic

Pandemic influenza occurs when a new strain of the Type A virus is observed, against which humans have little or no immunity. The Canadian Pandemic Influenza Plan (CPIP) identified four major conditions necessary for a pandemic to occur, all of which the pH1N1 influenza A virus had satisfied. These included:

- The emergence of a new influenza A virus;
- A virulence capable of causing severe illness and death;
- A population with little immunity to the new virus; and
- Sustained human-to-human transmission of the virus.

The pH1N1 influenza outbreak that led to the 2009 pandemic began in Mexico in March 2009 (1). An estimated 11,357 suspected and 822 confirmed cases in Mexico were reported as of May 5, 2009 (2). By July over 94,000 confirmed cases were reported internationally. The first reported cases of acute respiratory illness in Canada were identified by public health officials in Nova Scotia on April 25th, 2009 when 4 individuals were confirmed to have had the novel human swine-origin influenza A (H1N1) virus (1). Within 13 days, 99 cases of pH1N1 were identified and associated with the cluster of Nova Scotia cases (1). All cases associated with the early Nova Scotia cluster were identified as being in close contact with a case or had travelled to Mexico. Over the next month the number of reported and suspected cases in Canada and world-wide began to increase and the virus was shown to be successfully transmissible from human-to-human. A phase 6 global pandemic was declared by the World Health Organization (WHO) on June 11, 2009 (3).

Canada experienced two waves of the pH1N1. The first occurred in the spring of 2009 and peaked on the 23rd week and the second occurred in the fall with a peak in the 44th week (4). During the first wave approximately 7,107 cases were confirmed in Canada (3). The number of positive pH1N1 cases reported during the second wave (August 30th 2009 to April 24th 2010) reached approximately 33,513 (5). However, from mid-June, regions stopped testing all suspected cases and as a result, the total number of positive pH1N1 cases is a significant underestimate of all actual cases. From April 12th 2009 to April 24th 2010 there were a total of 8,867 hospitalizations, 1,473 ICU admissions and 428 deaths due to pH1N1 (5). The number of hospitalizations, ICU admissions and deaths were significantly increased during the second wave: 82.3% of hospitalizations, 80.2% of ICU admissions and 82.0% of

deaths occurred in the second wave (5). Increased rates of hospitalizations, ICU admissions and death were observed among those with underlying medical conditions, pregnant woman and Aboriginals (5).

Based on the initial outbreak, the case fatality ratio (CFR) in Mexico was estimated to be 0.4% using data on confirmed and suspected cases up until the end of April 2009. Early estimates in Canada (up until the end of June) estimated the range of CFR between 0.0004% to 0.003% (6).

Antiviral Drugs

Antiviral drugs can be used to treat influenza Type A and Type B. The class of antiviral drugs approved for use in Canada are called neuraminidase inhibitors. They work by inhibiting the neuraminidase protein of the influenza virus thus preventing the release of the virus from infected cells. This prevents the virus from further replication by inhibiting or limiting the spread of the virus to healthy (susceptible or uninfected) cells in the respiratory tract (7).

The two types of neuraminidase inhibitors currently on the Canadian market are oseltamivir (Tamiflu®) and zanamivir (Relenza®). They are recommended for use as post-exposure prophylaxis after coming into contact with the virus or as treatment after contracting the infection. These antiviral drugs have been shown to work effectively when used as treatment or post-exposure prophylaxis for the seasonal flu (8; 9; 10; 11). However, their efficacy against unknown pandemic strains is uncertain (7). Further research is required on the resistance of antiviral drugs and it is unknown whether a pandemic virus could be resistant or become resistant to the drugs (7). Since beginning of pH1N1 13 cases in Canada were reported as being oseltamivir resistant to the pandemic strain (5).

A description of their use for post-prophylaxis and for treatment as well as the dose regimens, and relative efficacies follows.

Post-Exposure Prophylaxis: Prophylaxis beginning immediately after exposure to the influenza virus in order to prevent or reduce symptoms, secondary complications and mortality. Recommended adult dosage is 1 pill a day for a duration of 10 days. The relative efficacy of post-exposure prophylaxis ranges from 35% to 94% (8; 11)

Treatment: Treatment beginning within 48 hours of symptom onset to reduce the duration and severity of symptoms and secondary complications (4). The recommended adult dosage is 2 pills a day for a duration of 5 days. Antivirals have been shown to reduce hospitalizations by 59% (10) , reduce symptom duration or patient recovery time by 30% (9), reduce the use of antimicrobial drugs by 63% and reduce the number of days of work lost by 1 day (7).

Vaccines

Canada's National Advisory Committee on Immunization (NACI) provides annual influenza vaccine use recommendations for high risk populations. The Pandemic Influenza Committee (PIC) with input from NACI provides recommendations on the development, production and use of pandemic vaccines as well as immunization priority groups. The aim of Canada's pandemic immunization program is to provide a safe and effective vaccine to all Canadians as quickly as possible by allocating, distributing and administering the vaccine to appropriate groups and monitoring the safety and effectiveness of vaccination programs (12).

In October 2009, the Government of Canada authorized the use of the adjuvant and non-adjuvant pH1N1 influenza vaccination. Various dose levels (adjuvant and non-adjuvant) of the pH1N1 vaccine have been recommended for children 6 months to 9 years, healthy children and adults ages 10 to 64, seniors 65 and over and pregnant women

(13). The vaccine was not approved for infants under the age of 6 months and was not recommended for those who had previous anaphylaxis to vaccine elements, hypersensitivity to eggs, current high fever, or Guillan-Barré Syndrome following a seasonal flu vaccination (13; 14).

1.1.2 Overview of Research Objectives

The focus of this research was to provide analysis that supports post pandemic debates on the importance of continued pandemic planning following the 2009 pH1N1 and to investigate a series of risk mitigation scenarios. In particular, through the lens of empirically support mathematical models, this study examined the impact of what had already occurred and how these outcomes could have changed with the adjustment of certain pandemic characteristics (such as the timing of the pandemic or a change in its severity). In this regard the objectives of the research were to evaluate:

(1) The life and economic impact of pH1N1 in Canada and the impact of reported antiviral and vaccine interventions;
(2) The possible life and economic impacts if pH1N1 was a spring or fall, moderate or severe pandemic, and the effect of the widespread use of antivirals.

The first objective evaluated the recent pH1N1 experience by simulating its life and economic impacts for the Canadian population using RiskAnalytica's Life at Risk® Infectious Disease model. The evaluation contrasted the potential impacts of different pandemic intervention scenarios including the use of antivirals and vaccines for the population using 2009 pH1N1 data adjusted for vaccine use as a base model. The second objective evaluated the life and economic impacts of pH1N1 under scenarios that consider its timing and severity. The following scenarios were considered:

1. While holding the pH1N1 start date constant, the pandemic was evaluated assuming a moderate and severe strain of the virus;
2. Assuming a start date of September 2009, the pandemic was evaluated assuming a moderate and severe strain of the virus; and
3. Both (1) and (2) were further evaluated assuming widespread use of antivirals and assuming no antiviral supply or distribution constraints.

2 METHODS

2.1 OUTCOME ANALYSIS

Both, the life and the economic evaluations were performed to estimate health outcomes and costs related to the use of antivirals and vaccine during pH1N1 and for other pandemic severity and timing scenarios. The evaluation was conducted against a baseline of the health outcomes and costs of the full potential of a pandemic scenario when antiviral and vaccine interventions were not used.

The target population was the entire population of Canada with the outcome analysis performed from an aggregate Canadian healthcare payer perspective using the cost-utility measures of the cost of Quality Adjusted Life Years gained (QALYs) and the incremental cost-effectiveness ratio (ICER). For this analysis, ICER adjusts the cost of QALYs gained for healthcare costs saved by virtue of the cost and implementation of the intervention evaluated.

QALYs are a measure of disease burden, that takes into account both the quantity and quality of life generated by healthcare interventions (15). QALYs lost per case of influenza due to morbidity and death were taken from Sanders *et al*. (16) in which the quality-adjusted life expectancy was discounted at 3% per year in the base case analysis (17).

Impacts upon Gross Domestic Product (GDP) were also calculated. GDP impacts were not used as part of the cost effectiveness results, rather this was provided so that other economic participants could gain an understanding of the potential effects of health interventions upon their welfare.

2.2 THE INFECTIOUS DISEASE MODEL

2.2.1 MODEL SUMMARY

The pandemic model was based upon the well-studied Susceptible-Exposed-Infectious-Recovered (SEIR) compartmental model (18). In a simple SEIR model, members of the susceptible population become 'exposed' (infected with the virus, but not yet infectious) at a rate proportional to the number of infectious individuals in the population and the rate of contact between individuals. After infection, people transition into the infectious state at a rate dependent upon the latent time of the virus. Finally, at a rate dependent upon the average infectious period and the case fatality rate, people either recover or die. In this model, asymptomatic cases were not distinguished and the infectious population referred to both symptomatic and asymptomatic cases.

The basic SEIR model was extended to include age groups, antiviral use, vaccination and hospitalizations. Contact rates between age groups were based on an extensive study of 8 European countries (19). Antiviral use incorporated into the model consisted of:

- Antiviral treatment for those who are hospitalized;
- Antiviral treatment for the public; and
- Post-exposure prophylaxis.

In addition, the model took into account the existing immunity to pH1N1 observed in the elderly (20; 21). Finally, a seasonal dependence on contact rates was introduced to account for the decline in the first wave during the summer of 2009. The detailed equations for the model can be found in Appendix C.

2.2.2 Model Parameters

There are two types of model parameters associated with infectious disease modelling. The first are parameters that deal strictly with the properties of the pandemic virus. In any SEIR-based model, these are the effective transmissibility of the virus, the duration of the infectious period, the age-dependent hospitalization rate, and the age-dependent case fatality rate. The second type is social parameters which are generally related to the response of the community to the pandemic. The social parameters in the model include the level of antiviral use, vaccination timing and uptake, and reduction in contacts during the summer months.

2.2.3 Geographies

The model simulated the pandemic across 12 regions in Canada. Each province, the Yukon, and the combination of the Northwest Territories and Nunavut were considered. In order to account for regional variations due to geography, demographic profiles, and variations in reporting policy, each region was allowed to have a slightly different effective transmissibility, average hospitalization rate, and average case fatality rate. For both the CHR and CFR, the relative age distribution remained the same across all regions. In addition, the time of the first infection arriving in each region, or equivalently, the number of initial cases at a common start time, was also allowed to vary between regions. As healthcare policy in Canada falls under provincial control, each region also had a different fraction of the population seeking antiviral treatment and vaccination.

2.2.4 Economic Model

A macroeconomic structural simulation model is coupled with the infectious disease model. The economic model is a version of the Klein Model (22; 23; 24; 25; 26; 27) and includes simulations of: the labour force by industry and employment status; wages; economic production (GDP); income and consumption taxation rates by government type; corporate profits; and demand for healthcare services and products.

Two different types of economic impacts were considered in this study. The first was the direct cost associated with vaccine and antiviral interventions. The second was the indirect cost to the economy driven by employee absenteeism. Direct health costs types included GP visits, emergency department visits, and hospitalization costs. All unit cost estimates were taken from Sander *et al*. (16). Indirect GDP impacts were computed from employee absenteeism only. The relationship between infections and total absenteeism was estimated from a Statistics Canada study (28) of the number of work hours lost due to pH1N1. The impact upon production due to absenteeism was then calculated using the friction cost method (29). This approach allowed for unemployment and other realistic circumstances to exist in productivity cost calculations because it distinguishes between a friction period, in which productivity loss occurs and a further period where a sick worker has been replaced (30). The impact of absenteeism on output was conducted using an aggregate production function with an output-hours elasticity of 0.6 for the period of absence (31).

For more information on the economic model, refer to the supplementary appendix titled *Life at Risk® Economic Framework*.

2.3 PH1N1 IN CANADA

The pH1N1 base model consisted of the best-fit match of the observed hospitalizations, mortalities and early confirmed cases to the infectious disease model. During the fitting procedure, both vaccines and antivirals were incorporated into the model as reported across Canada. Ontario age-dependent hospitalization and mortality reports were used to determine the age-profile of the case hospitalization rate and the case fatality rate. The data used to fit the model are provided in Appendix B. A complete list of assumptions and other data used in the model can be found in Appendix F.

The fitting procedure consisted of:

1. Fitting Ontario aggregate results to determine an initial estimate of the average pH1N1 parameters;
2. Based upon the initial average results from Ontario from step 1, adding age-dependence to the hospitalization and mortality rates and performing an age-dependent fit;
3. Using the age-dependent hospitalization and mortality rates from Ontario, the model was fit to the rest of the regions using their age-independent hospitalizations and mortalities.

In order to model the observed antiviral use, the model determined the fraction of population that would seek antiviral treatment when they become ill. No prophylaxis use was considered during the fitting procedure. It was assumed that vaccines become widely available at the end of October 2009 and become effective by providing full protection in 2 weeks time. Estimates of the total fraction of the population vaccinated were available from provincial ministries of health, but detailed information about who actually received vaccinations was not available. Therefore, it was assumed that the age and sex distribution of those who received vaccinations was similar to the seasonal vaccination distributions. This does not necessarily agree with the suggested vaccination priority lists from the Public Health Agency of Canada, but was the best estimate available. In addition, a reduction in contacts during the summer months was incorporated into the fits to drive the two wave behaviour.

In summary:

- For Ontario, there were a total of 20 parameters:
    - The initial number of infections;
    - The confirmation rate (fraction of total cases positively identified);
    - The infectiousness;
    - The average infectious duration;
    - The fraction of the population over 55 who were immune;
    - The summer contact rate adjustment for adults and children;
    - The fraction of population eligible for antiviral treatment;
    - The age-dependent hospitalization rate in 6 age-groups; and
    - The age-dependent mortality rate in 6 age-groups.
- For remaining regions 7 parameters were fit:
    - The initial number of infections;
    - The hospitalization rate adjustment;
    - The mortality rate adjustment;
    - The overall contact rate adjustment;
    - The summer contact rate adjustment for adults and children; and
    - The fraction of population eligible for antiviral treatment.

Once the base model was calibrated to the Canadian observations, it was possible to remove the antiviral and vaccination interventions to determine their effects, both in terms of life and economics, on the evolution of the pandemic. The three scenarios investigated were:

1. **No Intervention:** Neither antivirals nor vaccines were used in the model.
2. **Antiviral Use Only:** Only antivirals were used at same levels seen during the pH1N1.
3. **Vaccination Only:** No antivirals were used, but vaccines became available at the same time as observed, and had the same uptake observed in 2009

2.4 PANDEMIC POTENTIALS

There was general consensus that the pH1N1 in 2009 was quite mild in terms of the number of cases with relatively few deaths (32; 33; 34). In addition, the pandemic arrived in two waves with the spring wave having significantly fewer infections than the fall wave. This allowed early identification of the virus and a considerable length of time was available prior to the fall wave peaking. The total mortalities associated with pH1N1 were quite small with some regions reporting fewer total influenza-related deaths than during a regular flu season (35; 36; 37). In this regard, the severity of the 2009 pandemic was very mild. These points are important to remember when developing response plans for future pandemics. Basing the assumptions of future plans solely upon the observations of 2009 may lead to a false sense of security. If the pandemic had broken out in late summer or early fall and directly proceeded into the large fall wave, vaccines may not have been available until well past the peak, or if the pandemic had been much more severe, there could have been considerably more deaths.

In order to quantify the impact of other potential pandemics, four unrealized pandemic scenarios were modelled to investigate the consequences of pandemics of different timings and severities. Using the "No Intervention" pandemic of pH1N1 in Canada from the first part of this study, the mortality and hospitalization rates were increased, while maintaining the same no-intervention attack rate, to model a moderate pandemic with a CFR of 0.16% and severe pandemic with a CFR of 1.4%. For both the moderate and severe pandemics, each was started in April (as observed in Canada), and late in the summer such that there were the same number of infections on September 1st, as there were on May 1st. In each case, it was assumed that the antiviral and vaccine uptake rates remain the same as what was observed in Canada.

For each pandemic, five scenarios were applied:

- No vaccine and no antiviral use;
- Vaccination but no antiviral use;
- Wide-spread antiviral use, but no vaccine;
- Both wide-spread antiviral use and vaccine; and
- Limited antiviral use and vaccine based upon the 2009 observed interventions.

Widespread antiviral use is defined as:

- 50% of the people who become ill would seek treatment; and
- 5% of the population was eligible for post-exposure prophylaxis.

The 5% eligible for post-exposure prophylaxis corresponds to the approximate number of healthcare and emergency service providers in Canada.

By starting a pandemic in the late summer, a pandemic with a single strong wave develops in a manner consistent with the spring pandemic models with no model changes required other than the date of first infection. The observed two wave spring pandemic was modelled by assuming a change in contact rates during the summer months. As this does not occur in our model for a pandemic starting in the fall, there is only a strong single wave. The conclusions regarding the fall pandemic would apply to any pandemic that has a single wave regardless of the time of year.

2.5 MODEL VALIDATION AND COLLABORATION WITH SUBJECT MATTER EXPERTS

2.5.1 ROLE OF THE PANDEMIC RESEARCH ADVISORY COMMITTEE (PRAC)

In order to substantiate and validate the model and its assumptions, an independent group of recognized Canadian and international infectious disease experts, medical experts and virologists forming the Pandemic Research Advisory Committee (PRAC) was consulted throughout this study. The role of PRAC was to provide advice and recommendations regarding data inputs, pandemic severity assumptions, antiviral use assumptions, and to examine and review the reasonableness of the simulation results.

For the objectives of this project, PRAC participated in four workshops in which they:

- Reviewed the scope and objectives of this project;
- Reviewed and provided feedback and direction on the preliminary parameters and model assumptions;
- Reviewed and provided feedback on the reasonableness of the preliminary model outcomes; and
- Reviewed and confirmed the final model results, input data and assumptions.

2.5.2 ROLE OF THE PANDEMIC ADVISORY COMMITTEE (PAC)

In addition to the PRAC, a group of frontline healthcare workers and emergency service providers was established. This group, known as the Pandemic Advisory Committee (PAC), was consulted throughout this study. The key task of the PAC was to assist in the development of the project by ensuring that the perspective of the healthcare and emergency service provider communities was reflected in the project. The expertise from PAC provided on-the-ground knowledge of frontline health and emergency care under pandemic scenarios to ensure that the model assumptions and findings provide for a reasonable representation of what has happened and what could have happened under various scenarios of the pH1N1.

Throughout this engagement PAC participated in two workshops in which they:

- Were introduced to the overall project framework and strategy, the general methodology and model development;
- Reviewed the scope and objectives of this project; and
- Reviewed the model outcomes for reasonableness and relevance.

3 RESULTS

3.1 OBJECTIVE 1: PH1N1 IN CANADA

3.1.1 PH1N1 CHARACTERISTICS

The results for the pandemic fit for all of Canada are shown in Figure 1. The model fit was shown to perform well in matching the reported hospitalizations and mortalities from across Canada. The detailed age-dependent results from Ontario and the provincial fit results are presented in Appendix E.

Figure 2 shows the age-dependent case hospitalization and mortality rates determined from the Ontario data. The case hospitalization rate for young children was significantly higher than the rest of the population. However, this is expected as fevers pose a high risk for children if the cause is bacterial and health practitioners may err on the side of caution. The low mortality rate among children reflects the fact that, even through the hospitalization rate for children may be high, those who are hospitalized are typically able to recover at higher rates than the adult population.

Not surprisingly, both case hospitalization rates (except for children as previously discussed) and case mortality rates were highest among the elderly. It is important to note that these are a measure of consequences once a patient is ill, and do not reflect the likelihood of a person contracting the virus in the first place. Figure 3 shows the age-dependent attack rate for Ontario based on the model fit. The much lower attack rate among the elderly hides their much higher risk of death once infected in the confirmed mortality data. In Ontario, there were twice as

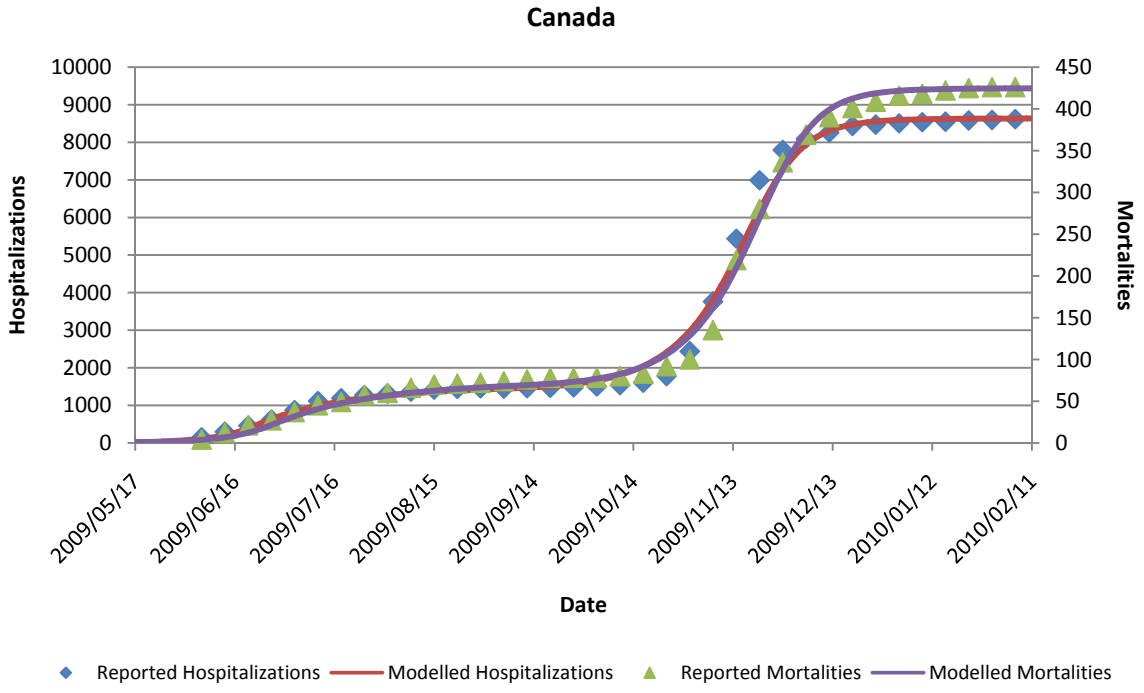

Figure 1: Comparison of reported and modeled hospitalizations (left-hand axis) and mortality (right-hand axis) in Canada

many deaths for people between 45 and 65 years of age than for people over 65 years old (62 compared to 31), even though the CFR for the 65+ age group was over 7 times greater.

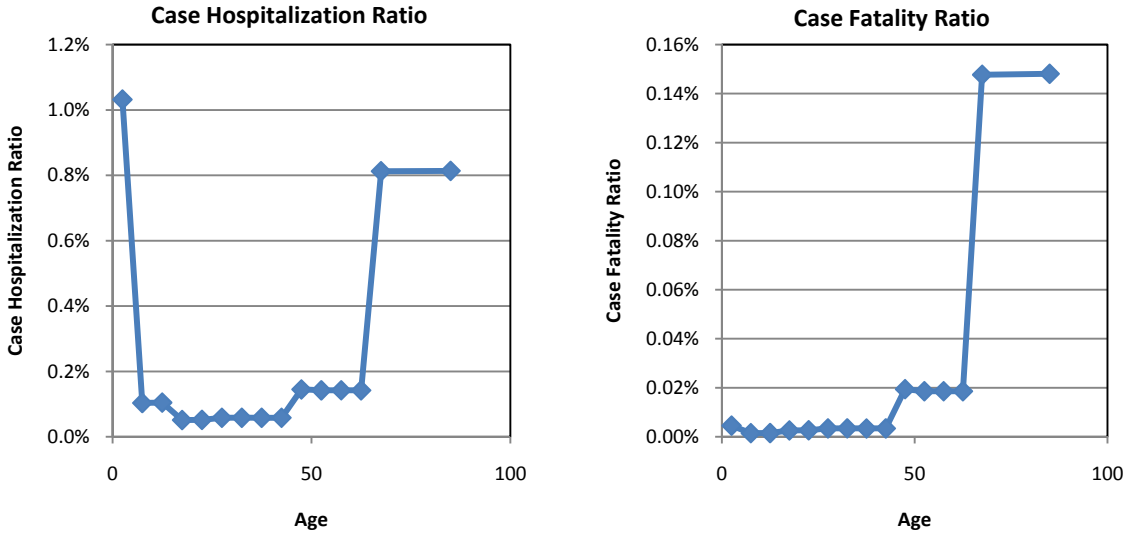

Figure 2: Case hospitalization ratio (left) and case mortality ratio (right) for H1N1 in Ontario

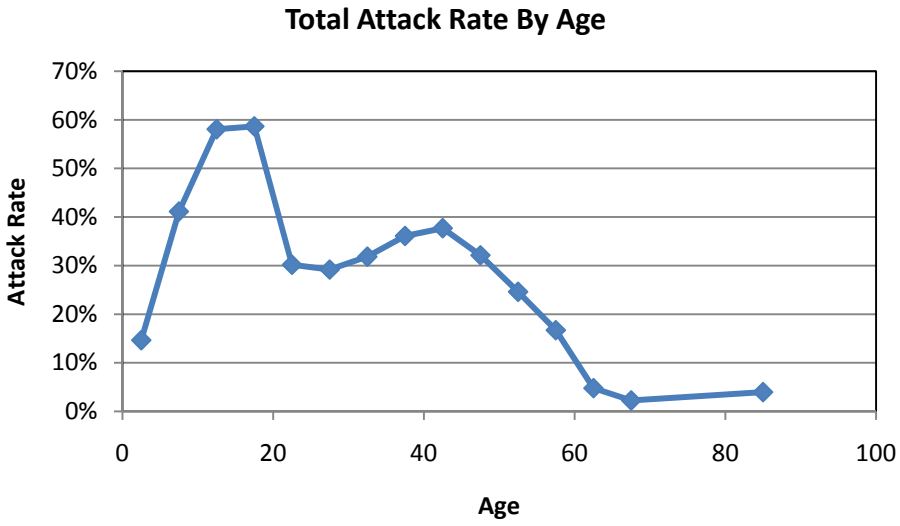

Figure 3: Age-dependent attack rate based upon the fit and contact rates from Mossong *et al.* (2008) **(19)**

3.1.2 Life and Economic Impact of pH1N1

In Canada, there were 8,678 reported hospitalizations and 428 reported deaths attributed to pH1N1 by April 24th, 2010. Calibrating the pandemic simulation model to the time- and age-dependent data, the analysis estimated a pH1N1 attack rate of approximately 15%, 12,680 QALYs lost, and direct healthcare costs of $58 million (Table 1). It was estimated that approximated 6.2% of those ill received antiviral treatment. The economic impact of pH1N1 was estimated to be about $1.7 billion, or 0.1% of the Canadian GDP (Table 4). This compares with other estimates of the economic impact of single wave moderate pandemics which range from 0.1% to 1.5% of GDP (31). This estimate was strictly due to additional absenteeism due to illness, as well as any deaths among the employed and did not include any economic benefit which may have arisen due to pH1N1 displacing the regular seasonal flu.

Once the model was calibrated to the observations in 2009, the vaccine and antiviral interventions were selectively turned off to measure their impact. Figure 4 highlights the impact of vaccines and antivirals upon the infectious population in Canada. Approximately three weeks after vaccines became available the generation of pandemic infections began to diminish. The three week timeframe was a result of the combination of delay between vaccination and protection, and the time required to administer the vaccine to a sufficient fraction of the population. However, even in the scenarios without vaccines, the pandemic peaks naturally about 1 month after vaccines would have been available. As a result, vaccines were estimated to have decreased the time of the peak by approximately 10 days. The impact on the total attack rate still remained significant, reducing it from 28% with no intervention to 17% in the vaccination only scenario.

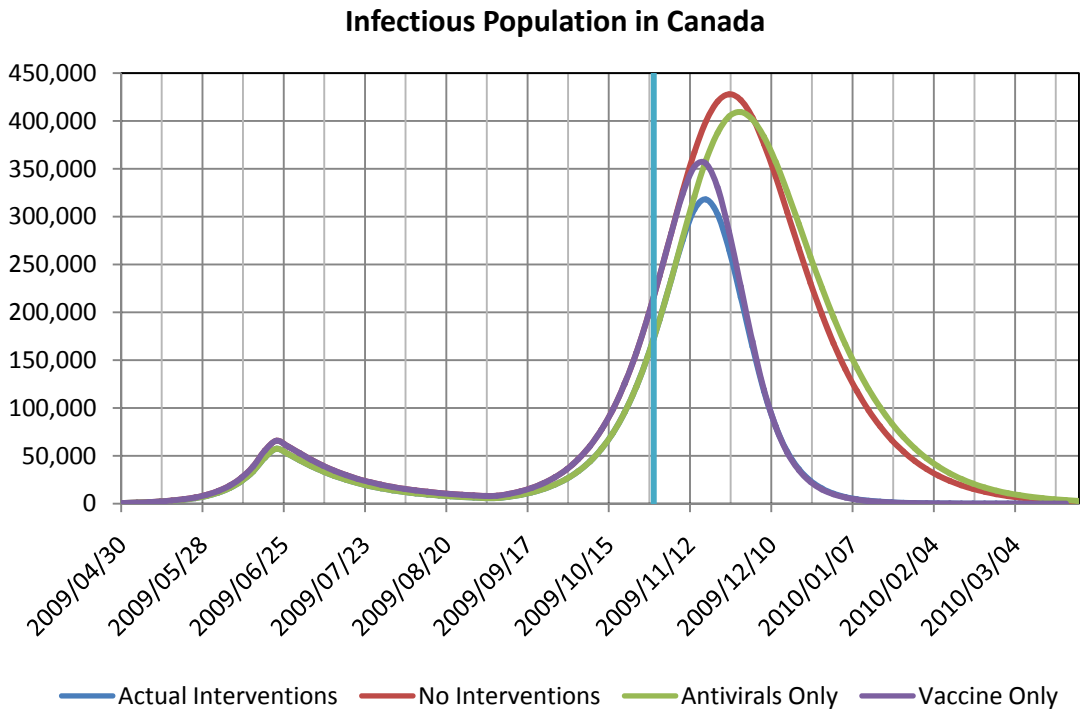

Figure 4: The infectious population in Canada under the actual antiviral and vaccine interventions and under scenarios where antivirals and/or vaccines are removed. The vertical line indicates when vaccines become available.

Scenario	Attack Rate	Hospitalizations	Mortalities	QALYs Lost
As observed (Modelled)	15% (-46%)	8,636 (-55%)	425 (-74%)	12,680 (-69%)
Reported vaccine use only	17% (-39%)	10,196 (-47%)	853 (-48%)	21,619 (-47%)
Limited antiviral use only	27% (-4%)	18,543 (-4%)	975 (-41%)	27,675 (-32%)
No antiviral or vaccine use	28%	19,353	1,649	40,410

Table 1: The life impacts of pH1N1 in Canada. The quantities in brackets are the percentage changes from the no intervention scenario. Note that the "As Observed" scenario presents the modelled results so the hospitalizations and mortalities differ slightly from the reported totals. QALYs are discounted at 3%.

Scenario	QALYs Morbidity	QALYs Mortality	Total QALYs
As observed	4,922	7,758	12,680
Reported vaccine use only	5,812	15,807	21,619
Limited antiviral use only	10,651	17,024	27,675
No antiviral or vaccine use	11,108	29,302	40,410

Table 2: The breakdown of quality adjusted life years lost due to morbidity and mortality. The mortality QALYs are discounted at 3%.

Scenario	Cost of Office Visits ($m)	Cost of ED visits ($m)	Cost of Hosp. ($m)	Total Cost ($m)
As observed	$9.4	$3.7	$45.2	$58.3
Reported vaccine use only	$11.2	$4.4	$71.1	$86.6
Limited antiviral use only	$20.3	$8.0	$97.0	$125.2
No antiviral or vaccine use	$21.2	$8.3	$134.9	$164.4

Table 3: The breakdown of healthcare costs due to office visits, emergency department visits, and hospitalizations. All costs are in 2009 dollars.

Scenario	Cost of Vaccine Used ($m)	Cost of Vaccine Not Used ($m)	Cost of Antivirals Used ($m)	Annualized Lost GDP ($m)	Annualized Lost GDP (%)
As observed (Modelled)	$117	$286	$12	$1,660 (-49%)	0.10% (-50%)
Reported vaccine use only	$117	$286	$0	$1,945 (-41%)	0.12% (-40%)
Limited antiviral use only	$0	$0	$25	$3,106 (-5%)	0.18% (-10%)
No antiviral or vaccine use	$0	$0	$0	$3,280	0.20%

Table 4: The intervention costs and indirect economic losses due to pH1N1. The quantities in brackets are the percentage changes from the no intervention scenario. All costs are in 2009 dollars.

Without the reported use of antivirals and vaccine during pH1N1, the analysis indicated that the pandemic impact of pH1N1 would have been approximately twice in terms of hospitalizations and GDP impacts; almost three times in terms of hospitalization costs and QALYs; and almost four times in terms of deaths. Table 1 shows the key life impact of vaccine and antiviral interventions.

Scenario	QALYs Gained	Cost of Intervention ($m)	Healthcare Costs Saved ($m)	Gross ICER ($/QALY)	Net ICER ($/QALY)
As observed (Modelled)	27,730	$129	$106	$4,644	$817
Reported vaccine use only	18,792	$117	$78	$6,216	$2,076
Limited antiviral use only	12,736	$25	$39	$2,002	-$1,077

Table 5: Cost effectiveness of the interventions for pH1N1 *excluding* the cost of unused vaccine. The gross ICER does not include the healthcare costs saved while the net ICER does. A negative ICER means a savings per QALY gained. All costs are in 2009 dollars.

Scenario	QALYs Gained	Cost of Intervention ($m)	Healthcare Costs Saved ($m)	Gross ICER ($/QALY)	Net ICER ($/QALY)
As observed (Modelled)	27,730	$415	$106	$14,972	$11,145
Reported vaccine use only	18,792	$403	$78	$21,456	$17,317
Limited antiviral use only	12,736	$25	$39	$2,002	-$1,077

Table 6: Cost effectiveness *including* the cost of unused vaccine. The gross ICER does not include the healthcare costs saved while the net ICER does. A negative ICER means a savings per QALY gained. All costs are in 2009 dollars.

Assessing the relative contributions of antivirals and vaccines is not possible given their joint use in a highly dynamic process such as a pandemic. In terms of hospitalizations, antivirals used on their own would have independently accounted for 7.6% of the cases saved and vaccines for 85.4%. The balance of 7.0% was reflective of the synergistic use of both antivirals and vaccines together. The primary driver of the synergy is that antivirals act to slow down the pandemic so that when vaccines are available, fewer people have been infected. In terms of deaths, antivirals would have independently accounted for 55.1% of the cases saved and vaccines for 65.0%. The excess of 20.1% was reflective of the common ability of both interventions to prevent death. Neither vaccines nor antivirals alone appear to be the optimal solution to mitigate the consequences of a pandemic similar to the one seen in 2009.

The QALYs lost are due to short term morbidity during the duration of the illness, and lost life years due to deaths. Table 2 shows the contribution to the total QALY impact due to morbidity and mortality where the QALYs due to mortality are discounted at 3%. It is evident that mortality contributed between 61% and 73% of the total QALY impact. While possible longer term complications from a hospitalization that recovers had not been taken into account, we expect that it would not significantly change the significance of mortality in driving the bulk of the QALY impacts.

In order to calculate the cost-effectiveness of the interventions, the healthcare costs due to the pandemic are required. There were three primary costs considered: GP visits, emergency department visits, and hospitalizations. The average unit costs used were from Sander *et al.* (16) but adjusted to 2009 dollars using a deflator of 2.8% provided by the Conference Board of Canada (38). In 2009 dollars, the costs of a doctor office visit and emergency department visit were $38.02 and $58.66 respectively. The average cost of a hospitalization without antiviral use was $6,972 per stay and it was estimated that this cost was reduced by 25% to $5,229 when antivirals are used. The breakdown of healthcare costs in each intervention scenario is given in Table 3. The costs required to implement each intervention scenario are given in Table 4.

Table 5 and Table 6 show the cost-effectiveness of the interventions in each scenario under two potential definitions where the cost of unused vaccines is either excluded or included respectively. The antiviral only scenario is the same under both definitions and was considered very cost-effective at an estimated $2,000 cost for each QALY gained. Once healthcare costs saved were taken into account, rather than a net cost per QALY, there is a net $1,077 gain for each QALY gained. That is, it is generally concluded that antiviral use essentially pays for itself in terms of healthcare costs saved.

During pH1N1, a reported 50.4 million doses of vaccine were purchased, of which approximately 14.6 million were estimated to have been used. On its own and excluding the vaccine unused, the vaccination program was estimated to have a net ICER of $2,076 cost per QALY gained. If the cost of unused vaccine is included, the cost-effectiveness obviously drops but still remains very cost-effective with an estimated net ICER of $17,317 cost per QALY gained. As a caveat however, as discussed in more detail in Section 3.1.3, the results are highly sensitive to the timing of vaccine rollout.

Due to the absence of data, distribution costs were not incorporated into the cost-effectiveness measures. While the inclusion of such costs would reduce cost-effectiveness, the exclusion is not expected to change the general findings of the cost-effectiveness analysis. Under a $50,000 ICER threshold (which is approximately one third of WHO recommendations), the distribution costs of antivirals would have to exceed $650 million ($1,000 per prescription), and vaccines would have to exceed $614 million ($42 per dose distributed) before their respective cost effectiveness measures would begin to be questioned.

GDP impact estimates ranged between 0.1% with the reported antiviral and vaccine use interventions, to 0.2% when the effect of those interventions were taken out. GDP modeling is a highly dynamic process, in which effects can compound as time passes, which do not line up neatly with calendar periods. It is therefore difficult to claim a precise estimate of what the impact of the pandemic would have had in a single year. Rather, what is reported is the average impact over a twelve month period using the results for 2009 through to 2013.

These results indicate that, with respect to historical pandemic severities, the pH1N1 was exceptionally mild in terms of the number of hospitalizations and mortality. Also, the total attack rate with the observed interventions was relatively low at 15% and was within the range observed due to seasonal flu (39). However, from the perspective of quality adjusted life years, it was much more severe than a typical seasonal flu with over 12,000 QALYs lost due to pH1N1. A rough estimate of the QALYs lost due to seasonal flu in Canada under widespread vaccination, based upon 2.5 times the 1,134 QALYs lost in Ontario under universal immunization programs (16), yields only 2,835 QALYs lost. The significant difference is due to the impact of pH1N1 on younger members of the population unlike seasonal influenza that typically strikes the elderly.

3.1.3 Sensitivity To Vaccination Assumptions

There is considerable uncertainty in the actual rollout of vaccination and the fit results were shown to be sensitive to the vaccination timing. If instead of using October 30th, 2009 as the vaccine use start date, it was assumed that vaccines were available 2 weeks later (mid-November), the significance of vaccines is reduced. Note that this was not simply taking the “No Intervention” pandemic from the previous section and applying vaccination at different times. This involved completely re-parameterizing the pandemic. Figure 5 shows the significant impact that shifting the vaccine rollout had on the conclusions. The impact of vaccines was significantly reduced because they were assumed to arrive after the pandemic had peaked. This was expected since the model must fit the observed

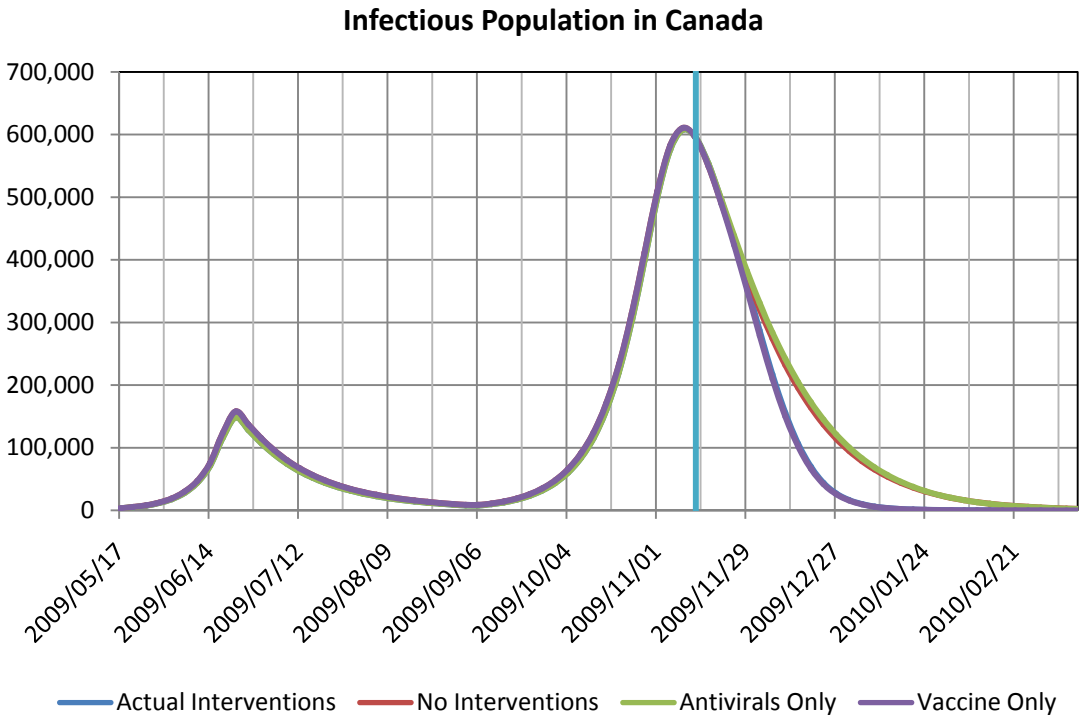

Figure 5: Infectious population in Canada if vaccines started mid-November

levelling off of the hospitalizations and mortality in November without the aid of vaccines. As a result, the observed model peaks naturally in mid-November around the time vaccines become available.

The importance of reliable vaccination data to accurately determine the actual pH1N1 trajectory is clearly visible. Unfortunately, only limited estimates of aggregate vaccination rates were available and therefore assumptions must be made. The more likely scenario, with a vaccine use start date at the end of October, was the case used for the analysis. If more detailed vaccination data become available, it may be worthwhile to repeat the analysis though the overall conclusions are not expected to change.

3.2 PANDEMIC POTENTIAL

Four different potential pandemic possibilities were considered. The first two started at the same time as the observed pandemic, but were assumed to have a greater severity. The final two maintain the same parameters as the first pair but were shifted to a fall start time. The details of the adjustments are provided in Section 2.4.

3.2.1 POTENTIAL LIFE AND ECONOMIC IMPACT OF A PH1N1-LIKE PANDEMIC: SPRING START

If the pandemic pH1N1 virus had a higher virulence resulting in a moderate or severe pandemic and the antiviral and vaccine usage remained the same as what was observed in 2009, the analysis showed that:

- A moderate pandemic would result in approximately four times the hospitalizations and almost 10 times the mortality of pH1N1;

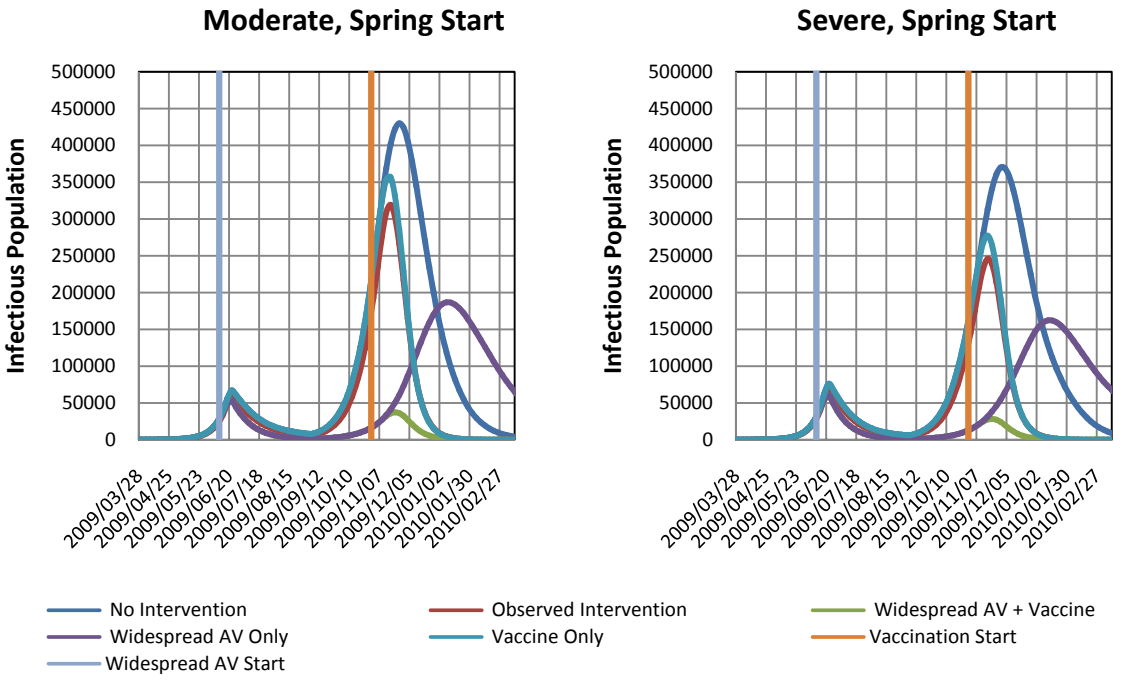

Figure 6: The infectious population in Canada under a moderate (left) and severe (right) pandemic which start in the spring.

- A severe pandemic would result in approximately twenty seven times the reported hospitalizations and seventy five times the reported mortality of pH1N1;
- In both cases, vaccines would arrive about 4 weeks before the potential pandemic peak;

These scenario results reveal how much worse the experience of a pandemic could have been if the severity had been different. If antiviral and vaccine interventions remained the same, a spring moderate pandemic was expected to result in approximately 39,000 hospitalizations, 5,600 mortalities, 122,000 QALYs lost, direct healthcare costs of $235 million, and a GDP impact from absenteeism of $2.6 billion or 0.15% of GDP. The detailed outcome results of each moderate spring pandemic scenario are presented in Table 8 through Table 9 and severe spring pandemic scenario results are available in Table 10 through Table 12.

GDP percentage impact estimates of a moderate spring pandemic ranged between 0.15% with the reported antiviral and vaccine use interventions, to 0.35% when the effect of those interventions were taken out. This compares well with other estimates of the economic impact of single wave moderate pandemics which range from 0.1% to 1.5% of GDP (31).

GDP percentage impact estimates of a severe spring pandemic ranged between 0.5% with the reported antiviral and vaccine use interventions, to 1.5% when no interventions were used. Again, this aligns well with other estimates for single wave severe pandemics which range from 0.4% to 3.1% of GDP (31).

Under moderate or severe pandemic scenarios, it is unlikely that the level of antiviral use would remain the same as that reported during pH1N1. To investigate the impact of a greater level of antivirals for treatment and for some post-exposure prophylaxis use, a widespread antiviral scenario was defined by the PRAC and evaluated.

Under this scenario, 50% of sick receive treatment, an assumption consistent with the Canadian Pandemic Influenza Plan, and 5% of the population receive post-exposure prophylaxis.

The results indicated that increasing the use of antivirals to a widespread use from the limited use seen during 2009 had significant incremental benefits when faced with either a moderate or severe pandemic. Under the moderate spring pandemic scenario, the widespread use of antivirals was estimated to incrementally increase the joint benefits of antivirals with vaccine resulting in:

- A further reduction in attack rate from 15% to 3%;
- Hospitalization reduction from 56% to 90% (an additional 30,059 prevented);
- Mortality reduction from 70% to 93% (an additional 4,331 saved);
- QALY saved increased from 68% to 93% (an additional 94,485 saved);
- Healthcare cost savings improved by $182 million; and
- GDP impact reduction from 44% to 90% (additional $2 billion of GDP);

Excluding the cost of vaccinations unused, the gross cost per QALY saved was $517 with a net gain of $1,239 per QALY saved when health costs savings are included.

Similarly, under the severe pandemic scenario, the widespread use of antivirals could incrementally increase the joint benefits of antivirals with vaccine with:

- A further reduction in attack rate from 12% to 3%;
- Hospitalization reduction from 62% to 91% (an additional 178,984 prevented);
- Mortality reduction from 75% to 94% (an additional 24,180 saved);
- QALY saved increased from 74% to 94% (an additional 575,101 saved);
- Healthcare cost savings improve by $972 million; and
- GDP impact reduction from 67% to 92% (additional $6.2 billion of GDP);

Again, if the costs of vaccinations not used are excluded, the gross cost per QALY saved was $65 and after the savings due to reduced healthcare costs are included, there would be a net gain of $1,460 per QALY saved. If vaccines were not used, antivirals would still be cost effective in both the moderate and severe spring pandemics with net savings per QALY gained.

Under a moderate and severe pandemic starting at the same time as the observed pH1N1, both vaccines and widespread antiviral use play important roles. As in the observed pH1N1, there exists a synergy between the two where their combined impact is greater than the sum of their individual impacts. For the moderate and severe pandemic, vaccines alone reduced hospitalizations by 47% and 55% respectively. Widespread antivirals by themselves reduced hospitalizations by 39% in both cases. The use of both widespread antivirals and vaccines reduced total hospitalizations by 90% and 91% for the moderate and severe pandemic respectively. By effectively slowing down the pandemic, the widespread use of antivirals allowed vaccines to have a bigger impact once they are available. This can be seen in Figure 6 where the pandemic profiles with widespread antiviral use peak later and at a lower level than the corresponding scenarios without widespread antiviral use.

Scenario	Attack Rate	Hospitalizations	Mortalities	QALYs Lost
Widespread antiviral use and reported vaccine use	3% (-88%)	8,722 (-90%)	1,251 (-93%)	27,476 (-93%)
Limited antiviral treatment use and reported vaccine use	15% (-48%)	38,781 (-56%)	5,582 (-70%)	121,961 (-68%)
Reported vaccine use only	17% (-40%)	46,746 (-47%)	9,486 (-49%)	205,349 (-47%)
Widespread antiviral use only	19% (-32%)	53,901 (-39%)	8,128 (-56%)	170,125 (-56%)
No antiviral or vaccine use	28%	87,933	18,456	384,722

Table 7: Life impact of the *moderate spring* pandemic. The quantities in brackets are the percentage changes from the no intervention scenario.

Scenario	Direct Healthcare Costs ($m)	Vaccine Used ($m)	Antivirals Used ($m)	Annualized Lost GDP ($m)	Annualized Lost GDP (%)
Widespread antiviral use and reported vaccine use	$53 (-92%)	$117	$68	$585 (-90%)	0.03% (-90%)
Limited antiviral treatment use and reported vaccine use	$235 (-65%)	$117	$13	$2,595 (-55%)	0.15% (-55%)
Reported vaccine use only	$364 (-47%)	$117	$0	$3,343 (-43%)	0.20% (-43%)
Widespread antiviral use only	$326 (-52%)	$0	$329	$3,005 (-48%)	0.18% (-48%)
No antiviral or vaccine use	$680	$0	$0	$5,822	0.35%

Table 8: Economic impact of the *moderate spring* pandemic. The quantities in brackets are the percentage changes from the no intervention scenario. All costs are in 2009 dollars.

Scenario	QALYs Gained	Cost of Intervention used ($m)	Healthcare Costs Saved ($m)	Gross ICER ($/QALY)	Net ICER ($/QALY))
Widespread antiviral use and reported vaccine use	357,247	$185	$627	$517	-$1,239
Limited antiviral treatment use and reported vaccine use	262,762	$130	$445	$494	-$1,200
Reported vaccine use only	179,373	$117	$316	$651	-$1,112
Widespread antiviral use only	214,597	$329	$355	$1,532	-$120

Table 9: Cost effectiveness of interventions during the *moderate spring* pandemic excluding the cost of vaccine not used. Negative ICER values indicate a net savings per QALY gained. All costs are in 2009 dollars.

Despite the impacts of vaccine and antiviral interventions in reducing the hospitalizations and mortalities, under the assumed severe pandemic in the best intervention scenario, there were still over 7,500 deaths in Canada and over 50,000 hospitalizations estimated.

It is important to note that the same vaccination uptake rate was assumed for all pandemic severities. In reality, the vaccine update may be significantly greater in a severe pandemic which would likely act to increase the benefits of the interventions. Notwithstanding, even under the limited uptake assumption of vaccines used in the scenarios, the results indicated that the ICER of vaccine only increased from a net cost of $2,076 per QALY gained (assuming cost of vaccine used only) under the pH1N1 scenario to a net gain of $1,112 per QALY gained for the moderate pandemic and a net gain of $1,431 per QALY gained for the severe pandemic. This shows that the cost

Scenario	Attack Rate	Hospitalizations	Mortalities	QALYs Lost
Widespread antiviral use and reported vaccine use	3% (-88%)	56,802 (-91%)	7,672 (-94%)	180,934 (-94%)
Limited antiviral treatment use and reported vaccine use	12% (-54%)	235,786 (-62%)	31,852 (-75%)	756,035 (-74%)
Reported vaccine use only	14% (-48%)	277,157 (-55%)	54,243 (-57%)	1,257,533 (-56%)
Widespread antiviral use only	18% (-33%)	379,559 (-39%)	52,896 (-58%)	1,223,682 (-58%)
No antiviral or vaccine use	27%	619,582	127,125	2,879,743

Table 10: Life impact of the *severe spring* pandemic. The quantities in brackets are the percentage changes from the no intervention scenario.

Scenario	Direct Healthcare Costs ($m)	Vaccine Used ($m)	Antivirals Used ($m)	Annualized Lost GDP ($m)	Annualized Lost GDP (%)
Widespread antiviral use and reported vaccine use	$309 (-93%)	$117	$59	$1,971 (-92%)	0.12% (-92%)
Limited antiviral treatment use and reported vaccine use	$1,281 (-71%)	$117	$18	$8,205 (-67%)	0.49% (-67%)
Reported vaccine use only	$1,987 (-55%)	$117	$0	$11,566 (-53%)	0.69% (-53%)
Widespread antiviral use only	$2,056 (-54%)	$0	$321	$11,117 (-55%)	0.66% (-55%)
No antiviral or vaccine use	$4,426	$0	$0	$24,560	1.46%

Table 11: Economic impact of the *severe spring* pandemic. The quantities in brackets are the percentage changes from the no intervention scenario. All costs are in 2009 dollars.

Scenario	QALYs Gained	Cost of Intervention used ($m)	Healthcare Costs Saved ($m)	Gross ICER ($/QALY)	Net ICER ($/QALY))
Widespread antiviral use and reported vaccine use	2,698,809	$176	$4,116	$65	-$1,460
Limited antiviral treatment use and reported vaccine use	2,123,708	$135	$3,144	$64	-$1,417
Reported vaccine use only	1,622,210	$117	$2,438	$72	-$1,431
Widespread antiviral use only	1,656,061	$321	$2,370	$194	-$1,237

Table 12: Cost effectiveness of interventions during the *severe spring* pandemic excluding the cost of vaccine not used. Negative ICER values indicate a net savings per QALY gained. All costs are in 2009 dollars.

effectiveness of vaccines do improve significantly as the severity of a pandemic increases subject to the timing of arrival of the vaccine.

3.2.2 Potential Life and Economic Impact of a pH1N1-Like Pandemic: Fall Scenarios

Examination of possible impacts if pH1N1 was a fall moderate/severe pandemic, under the assumption that the applied antiviral and vaccine usage proportions seen during pH1N1 did not change, yielded the following results:

- Fall moderate pandemic was estimated to have ten times the hospitalization impact and thirty two times the mortality impact of pH1N1. Vaccines were estimated to arrive 12 weeks after the potential pandemic peak;
- Fall severe pandemic was estimated to have seventy two times the hospitalization impact and over two hundred times the mortality impact of pH1N1. As in the moderate scenario, vaccines were estimated to arrive 14 weeks after the potential pandemic peak.

These scenario results revealed how much worse, in orders of magnitude of pH1N1, the experience of a pandemic could have been when the severity and timing of a pandemic was changed. For example, if antiviral and vaccine interventions remained the same, a fall moderate pandemic was expected to result in approximately 88,206 hospitalizations; 13,453 mortalities; 280,658 QALYs lost; direct healthcare costs of $529 million and GDP impact from absenteeism of $4.3 billion (0.21% of GDP). The detailed outcome of each fall moderate and severe pandemic scenario evaluated is contained in Tables 14 through 19.

The fact that the pH1N1 struck Canada in two waves with a relatively quiescent summer period provided a considerable length of time to prepare for the expected fall resurgence. In contrast, if the pandemic had struck in the early fall, it would largely have been over by the time vaccines were available. Figure 7, which plots the number of infectious individuals in Canada throughout the moderate and severe pandemics, highlights the timing issue. The role of antivirals was much more important in situations where the pandemic struck quickly and vaccines were not quickly available. Since vaccines arrived as the pandemic was almost over, with no antiviral use the reduction in hospitalizations and mortality was less than 0.4% in all scenarios. In contrast, the use of wide-spread antivirals reduced the attack rate by 33%, hospitalizations by 39%, and mortality by over 55%.The addition of vaccination to widespread antivirals further reduced hospitalizations and mortality by less than 1%.

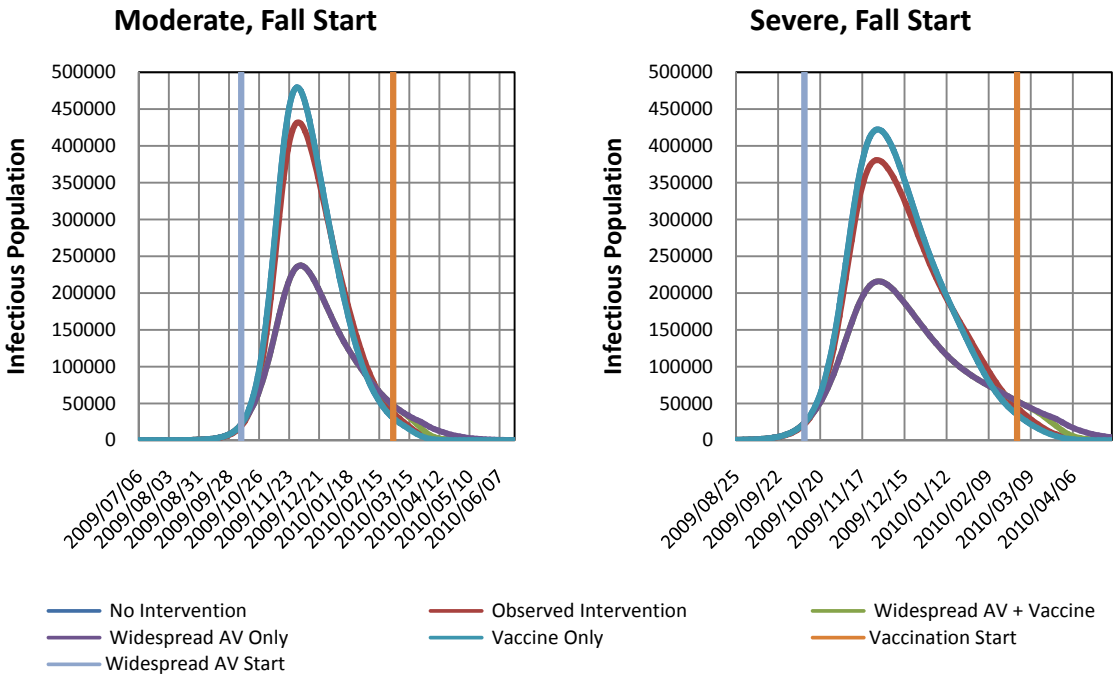

Figure 7: The infectious population in Canada under a moderate (left) and severe (right) pandemic which start in the fall.

Scenario	Attack Rate	Hospitalizations	Mortalities	QALYs Lost
Widespread antiviral use and reported vaccine use	20% (-34%)	56,126 (-40%)	8,442 (-57%)	176,527 (-57%)
Limited antiviral treatment use and reported vaccine use	29% (-3%)	88,206 (-6%)	13,453 (-32%)	280,658 (-31%)
Reported vaccine use only	30% (0%)	93,430 (0%)	19,597 (0%)	407,488 (0%)
Widespread antiviral use only	20% (-32%)	57,367 (-39%)	8,652 (-56%)	180,558 (-56%)
No antiviral or vaccine use	30%	93,677	19,656	408,549

Table 13: Life impact of the *moderate fall* pandemic. The quantities in brackets are the percentage changes from the no intervention scenario.

Scenario	Direct Healthcare Costs ($m)	Vaccine Used ($m)	Antivirals Used ($m)	Annualized Lost GDP ($m)	Annualized Lost GDP (%)
Widespread antiviral use and reported vaccine use	$339 (-53%)	$117	$306	$2,831 (-43%)	0.17% (-43%)
Limited antiviral treatment use and reported vaccine use	$529 (-27%)	$117	$29	$4,319 (-13%)	0.26% (-13%)
Reported vaccine use only	$722 (0%)	$117	$0	$4,960 (0%)	0.30% (0%)
Widespread antiviral use only	$346 (-52%)	$0	$315	$2,897 (-42%)	0.17% (-42%)
No antiviral or vaccine use	$724	$0	$0	$4,973	0.30%

Table 14: Economic impact of the *moderate fall* pandemic. The quantities in brackets are the percentage changes from the no intervention scenario. All costs are in 2009 dollars.

Scenario	QALYs Gained	Cost of Intervention used ($m)	Healthcare Costs Saved ($m)	Gross ICER ($/QALY)	Net ICER ($/QALY)
Widespread antiviral use and reported vaccine use	232,022	$423	$386	$1,822	$160
Limited antiviral treatment use and reported vaccine use	127,891	$146	$195	$1,141	-$385
Reported vaccine use only	1,061	$117	$2	$110,057	$108,260
Widespread antiviral use only	227,991	$315	$378	$1,380	-$278

Table 15: Cost effectiveness of interventions during the *moderate fall* pandemic excluding the cost of vaccine not used. Negative ICER values indicate a net savings per QALY gained. All costs are in 2009 dollars.

Under a moderate fall pandemic, assuming antivirals and vaccines were used the same way, due to the late arrival of the vaccine, the percentage reduction of hospitalization, mortality and QALY benefits were significantly less than in the pH1N1 analysis and for the fall pandemic antivirals contributed to the bulk of the reductions. The net cost of $817 per QALY saved under pH1N1 becomes a net gain of $385/QALY under the moderate fall pandemic assuming the same level of intervention as observed in 2009. The improvement in cost-effectiveness is due to the effectiveness of the antivirals and vaccines to scale against increased risk while costs were held relatively constant.

The GDP impact estimate for a fall moderate pandemic was 0.26% with the reported antiviral and vaccine use interventions. This result did not vary significantly when the effect of those interventions were taken out, indicating a very small impact of limited antiviral use and late vaccine arrival. An effect was only seen when antivirals were used in a widespread fashion, reducing the GDP percentage impact to 0.18%.

Scenario	Attack Rate	Hospitalizations	Mortalities	QALYs Lost
Widespread antiviral use and reported vaccine use	19% (-34%)	392,909 (-40%)	54,851 (-59%)	1,262,769 (-59%)
Limited antiviral treatment use and reported vaccine use	28% (-4%)	622,559 (-5%)	88,796 (-34%)	2,042,553 (-33%)
Reported vaccine use only	29% (0%)	656,564 (0%)	134,816 (0%)	3,043,133 (0%)
Widespread antiviral use only	20% (-33%)	404,368 (-39%)	56,601 (-58%)	1,302,335 (-57%)
No antiviral or vaccine use	29%	658,584	135,278	3,052,949

Table 16: Life impact of the *severe fall* pandemic. The quantities in brackets are the percentage changes from the no intervention scenario

Scenario	Direct Healthcare Costs ($m)	Vaccine Used ($m)	Antivirals Used ($m)	Annualized Lost GDP ($m)	Annualized Lost GDP (%)
Widespread antiviral use and reported vaccine use	$2,129 (-55%)	$117	$300	$10,647 (-50%)	0.63% (-50%)
Limited antiviral treatment use and reported vaccine use	$3,364 (-28%)	$117	$48	$16,874 (-21%)	1.00% (-21%)
Reported vaccine use only	$4,690 (0%)	$117	$0	$21,424 (0%)	1.28% (0%)
Widespread antiviral use only	$2,191 (-53%)	$0	$310	$10,966 (-49%)	0.65% (-49%)
No antiviral or vaccine use	$4,705	$0	$0	$21,491	1.28%

Table 17: Economic impact of the *severe fall* pandemic. The quantities in brackets are the percentage changes from the no intervention scenario. All costs are in 2009 dollars.

Scenario	QALYs Gained	Cost of Intervention used ($m)	Healthcare Costs Saved ($m)	Gross ICER ($/QALY)	Net ICER ($/QALY)
Widespread antiviral use and reported vaccine use	1,790,180	$417	$2,576	$233	-$1,206
Limited antiviral treatment use and reported vaccine use	1,010,396	$165	$1,340	$163	-$1,164
Reported vaccine use only	9,816	$117	$14	$11,899	$10,439
Widespread antiviral use only	1,750,614	$310	$2,514	$177	-$1,259

Table 18: Cost effectiveness of interventions during the *severe fall* pandemic excluding the cost of vaccine not used. Negative ICER values indicate a net savings per QALY gained. All costs are in 2009 dollars.

Under a severe fall pandemic, again assuming antivirals and vaccines were used the same way as in 2009, the percentage reduction of hospitalization, mortality and QALY benefits were similar to the fall moderate pandemic results with the net cost of $160/QALY. The GDP percentage impact estimates of a fall severe pandemic were 1.28% with the reported antiviral and vaccine use interventions. The impact of widespread antiviral use was over twice as large as for limited antiviral use reducing the GDP impact by 50%. As with the spring moderate and severe pandemic analysis, the results of increasing the use of antivirals to a widespread antiviral scenario showed significant incremental benefits when faced with either a fall moderate or severe pandemic.

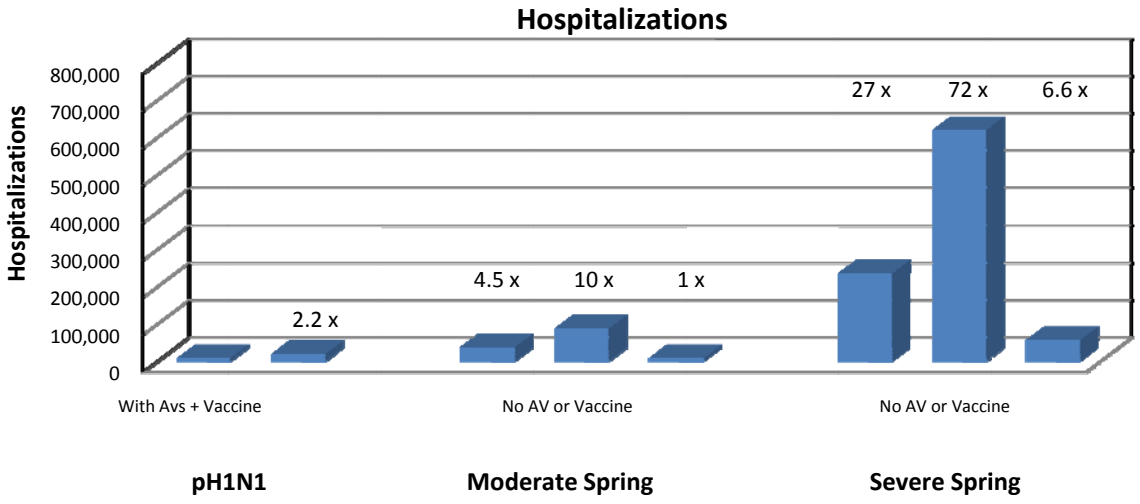

Figure 8: The total hospitalizations in a moderate and severe spring pandemic compared to what occurred with pH1N1.

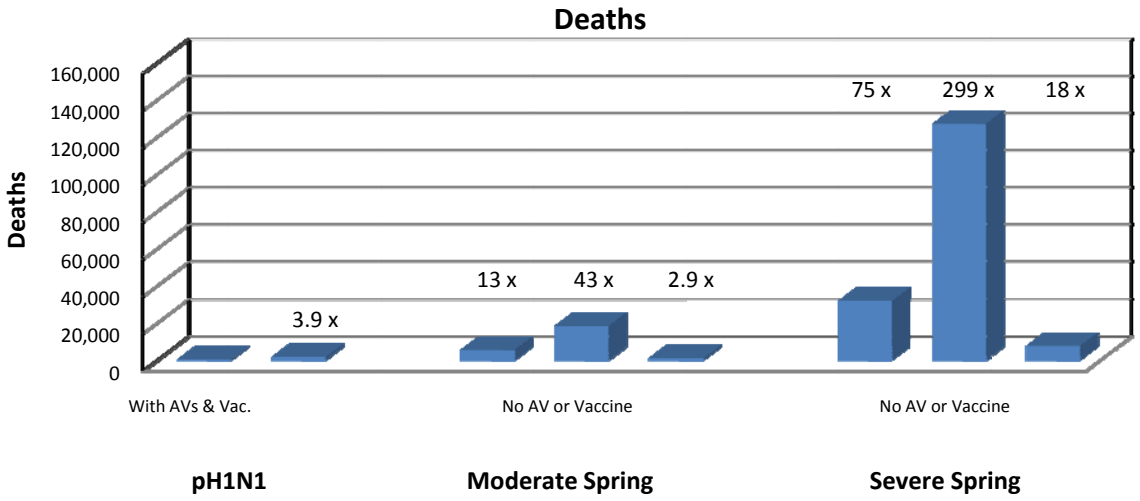

Figure 9: The total deaths in a moderate and severe spring pandemic compared to what occurred with pH1N1.

Under a fall moderate pandemic scenario, the widespread use of antivirals versus the limited pH1N1 use of antivirals was estimated to have incrementally increased the joint benefits of antivirals with vaccine with:

- A further reduction in attack rate by from 29% to 20%;
- Hospitalization reduction from 6% to 40% (an additional 32,080 saved);
- Mortality reduction from 32% to 57% (an additional 5,011 saved);
- QALY saved increased from 31% to 57% (an additional 104,131 saved);
- Healthcare cost savings improved by $190 million;
- GDP impact reduction from 13% to 43% (additional saving of $1.5 billion GDP) ;

While the gross cost per QALY saved increased $1,141 to $1,822, once health cost savings are included, the use of widespread antivirals is still very cost-effective with a net cost of $160/QALY gained. In this situation, the ICER does not provide a clear preference over limited or widespread antiviral use, but the significant reduction in hospitalizations and mortalities under the widespread scenario makes that the more favourable scenario.

Under a fall severe pandemic scenario, the widespread use of antivirals versus the limited pH1N1 use of antivirals was estimated to have incrementally increased the joint benefits of antivirals with vaccine with:

- A further reduction in attack rate from 28 to 19%%;
- Hospitalization reduction from 5% to 40% (an additional 229,650 saved);
- Mortality reduction from 34% to 59% (an additional 33,945 saved);
- QALY reduction from 33% to 59% (an additional 779,784 saved);
- Healthcare cost savings improve by $1.2 billion;
- GDP impact reduction from 21% to 50% (additional saving of $6.2 billion GDP);

The modelling of the fall scenarios highlights two important issues. First, the current production timeframe for vaccines of 6 months could be significantly too long if a pandemic has an intense first wave. This is not simply a theoretical situation. The results are quite similar to what was observed in Australia where the pandemic was largely over prior to vaccine availability (40; 41). Due to the timing issue, the ICER of vaccines for a moderate fall pandemic grows to a cost of $110,057 per QALY gained. The second important conclusion is the significance of antiviral use in reducing severe consequences prior to vaccine availability.

Finally, a direct comparison between what occurred in 2009 and the potential pandemic outcomes with higher severity and different intervention policies highlights the importance of ongoing pandemic planning. Figure 8 and Figure 9 show that with interventions, the severe spring pandemic could result in 72 times the number of hospitalizations and almost 300 times the number of deaths. Figure 10 and Figure 11 reveals that if the severe fall pandemic were to strike and interventions were not available, there could be 76 times the hospitalizations and almost 320 times as many mortalities. In each figure, the vertical axis is the total number of hospitalizations or deaths, while the number above each bar is how many times more people could be hospitalized or die in each of the scenarios.

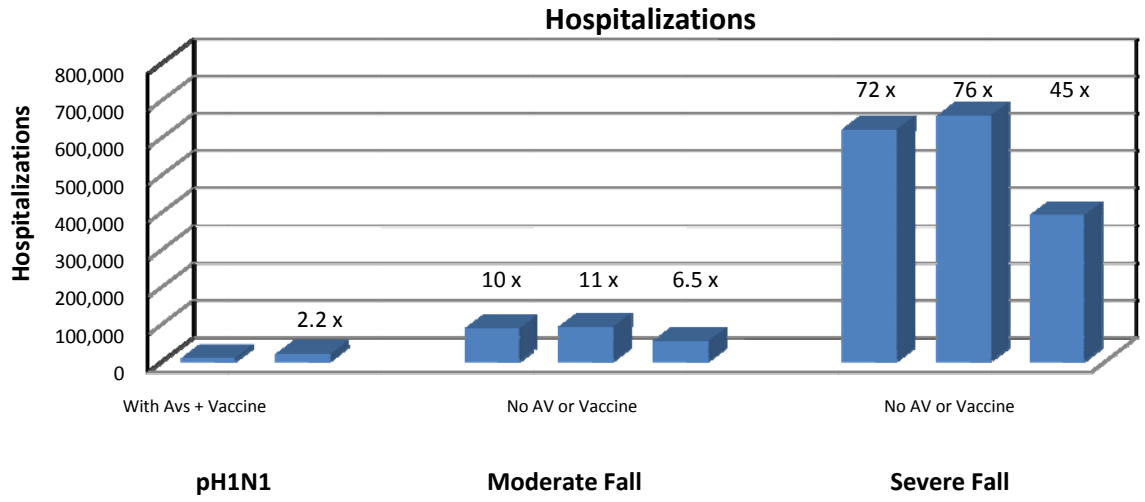

Figure 10: The total hospitalizations in a moderate and severe fall pandemic compared to what occurred with pH1N1.

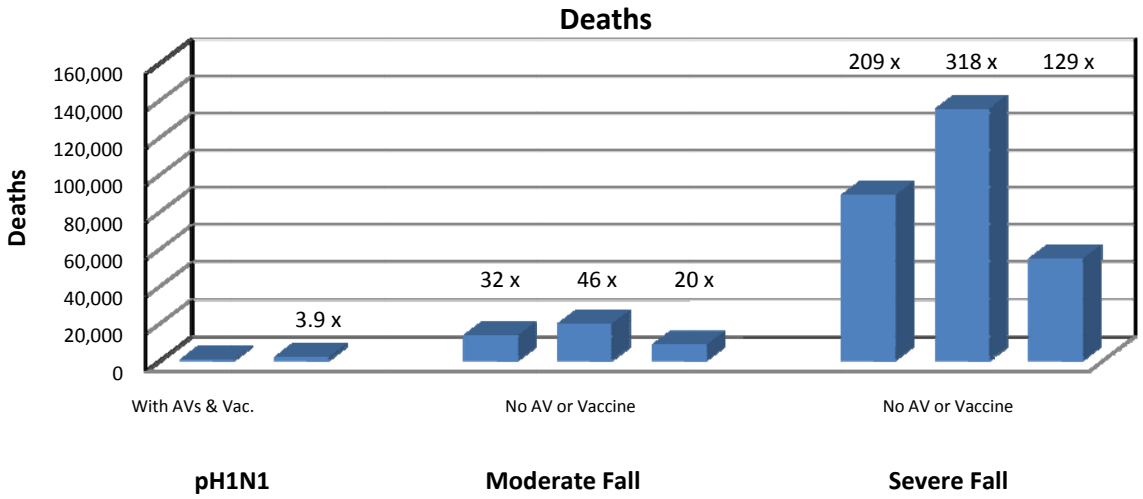

Figure 11: The total deaths in a moderate and severe fall pandemic compared to what occurred with pH1N1.

4 CONCLUSIONS

4.1 GENERAL CONCLUSIONS

The present research focused on understanding the general Canadian life and economic impacts of pH1N1 and sought to demonstrate how such impacts could have changed under different severity and pandemic timing scenarios.

The pH1N1 analysis suggests that the joint use of antiviral and vaccine intervention played a pivotal role in the reduction of the potential negative impacts of pH1N1. Without the reported use of antivirals and vaccines during 2009, the impact of pH1N1 could have been approximately twice as large in terms of hospitalizations and GDP, almost three times as great in terms of hospitalization costs and QALYs and almost four times as large in terms of deaths. The analysis also indicated that antivirals played a therapeutic role for the sick, while vaccine served as the primary means by which infection could be prevented. Both interventions are considered very cost effective in their own right and as a joint intervention effort.

The pandemic severity and timing analysis demonstrated how much worse a 2009/2010 pandemic experience could have been. The results of the current analysis indicated that a moderate to severe spring pandemic could have resulted in seven to 28 times the pH1N1 mortality. A moderate to severe fall pandemic could have resulted in 18 to 200 times the pH1N1 mortality. The relative mildness of the pH1N1 experience raises three key issues for consideration, further discussion and research.

Public health interventions are significantly dependent on the cooperation and perception of risk of healthcare workers, emergency service providers and the public. Arguably, the perception of risk waxed and waned throughout pH1N1, which may have resulted in sporadic capacity and expectation management issues, with an overall reduction in antiviral use and vaccine uptake. It is not known how the recent pandemic experience has affected the public's perception of the risk of future pandemics, a potentially important issue for policymakers and public health authorities to consider. It would be unfortunate if the relative success of healthcare measures in 2009, in the face of a relatively mild pandemic influenza, were to create a false sense of security that undermines future preparedness.

The pandemic timing analysis demonstrated the consequences of current vaccine manufacturing and approval processes. The analysis strongly suggested that, under current distribution timelines, vaccine is unlikely to arrive before the peak of a pandemic's first wave, with significant and serious consequences for the health and welfare of a population.

The pandemic severity and timing analysis demonstrated and emphasized the importance and role of a widespread antiviral strategy given its availability prior to and therapeutic properties during a mass vaccination effort. On their own, the widespread use of antivirals could significantly reduce hospitalizations and deaths. Antivirals are also cost effective to the point of generating positive value for the healthcare system, and they could reduce absenteeism substantially, thereby helping to protect the productive capacity of the economy in the face of a pandemic.

4.2 STRENGTHS AND LIMITATIONS

The research was focused on making broad conclusions about the effectiveness of antivirals and vaccine during pH1N1 and providing general scenario analysis to inform policy discussions in the aftermath of the pH1N1 pandemic. The research was oriented toward population health management and future risk-mitigation issues.

The main limitation in determining the impact of pH1N1 was the quality and quantity of data available at the time of analysis. As time passes, it is likely that pH1N1 hospitalization and mortality data will be updated. While updates may change the specifics of the results, given the very cost effective nature of antivirals, we do not expect that it would change the general conclusions made for population health management and future risk-mitigation purposes. The same conclusion applies to the moderate and severe pandemic analysis, where conservative hospitalization and mortality case ratios were used.

A primary limitation for the assessment of the cost effectiveness of vaccines was the issue around the timing of vaccine introduction and distribution. Any additional delay would result in a material change in the cost effectiveness results for antivirals and vaccine use during pH1N1. The cost effectiveness of vaccination declines if the vaccine is distributed only after the pandemic has peaked, although even under this scenario it is likely that vaccines would be judged cost effective. Antiviral use becomes still more cost effective in this scenario. Again, while the specific results change, the general conclusions for population health management and future risk mitigation purposes do not.

The remaining study limitations relate to the specification of the pandemic model in terms of the use of Ontario age-dependent data, contact rates adopted from a multi-country survey, expert-driven parameterization of average latency, asymptomatic cases, antiviral use, mean time to treatment, misdiagnosis wastage, vaccine-induced immunity and antiviral or vaccine adverse affects. The use of Ontario age-dependent data was due to its timely availability. This limitation was mitigated by fitting Ontario's age-dependent data to each province's pH1N1 time series hospitalization and mortality data. While some provinces may have substantially different age-dependent data, because of the province-by-province fitting, it is unlikely that the general conclusions would change.

Throughout the study, four workshops and numerous sensitivity analyses were performed with the participation of experts around their consensus-driven parameterization of the pandemic model. Given that the approach was to arrive at a pH1N1 base model that represented the best-fit match of the observed hospitalizations, mortalities and early confirmed cases, the procedure exerted constraints on the results that protected it from erroneous and/or unreasonable assumptions. Although attack rate proved sensitive to differences in assumptions, this sensitivity did not significantly affect the general conclusions. An increase in attack rates resulted in a decrease in hospitalization and mortality case rates to produce a model fit consistent with reported hospitalizations and mortalities. Given that the temporal evolution of absenteeism is proportional to observed rates, absenteeism also did not alter significantly from the sensitivity of attack rates to model parameters.

The pandemic model is a system of differential equations and hence is a continuous model. However, the pandemic process is more likely to be stochastic in reality. The divergence of results from a continuous model and a stochastic model are noticeable when dealing with small sample sizes; this was not a problem in the current study, which dealt with the Canadian population.

This study had several strengths. Subject matter experts and policymakers have expressed an interest in this type of model and its resultant life and economic analysis. The model is robust in its ability to fit numerous pandemic parameters to observed data and to apply different sensitivity analyses and diverse hypothetical scenarios. The model is also unique in the way that it couples demographic and pandemic simulation processes to a macroeconomic simulation process. Furthermore, as data are updated, the analyses can be repeated to examine the implications of improved measurement. Finally, since the model is a scenario analysis tool, experts and policymakers can use it to explore other scenarios of interest.

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APPENDIX B: PH1N1 OBSERVATIONS

The base pandemic model was calibrated to the reported observations in Canada. The age-dependent hospitalizations and mortalities for Ontario are shown in Table 19 and Table 20. A change in Ontario's reporting policy occurred at the end of October when the age-groups categories were changed.

	Hospitalizations					Mortalities				
Date	**0 - 5**	**5-20**	**20 - 50**	**50 - 65**	**65+**	**0 - 5**	**5-20**	**20 - 50**	**50 - 65**	**65+**
2009-09-04	68	107	106	50	35	0	3	4	9	7
2009-09-11	70	107	108	50	35	0	3	4	9	7
2009-09-18	70	108	107	51	34	0	3	4	9	7
2009-09-26	71	108	109	51	34	0	3	4	10	7
2009-10-03	71	109	112	53	34	0	3	4	10	7
2009-10-10	71	112	114	55	35	0	3	4	11	7
2009-10-17	76	120	118	57	36	0	3	4	11	7
2009-10-24	79	132	130	61	37	0	4	5	12	7
2009-10-31	97	159	161	80	46	0	6	4	13	7

Table 19: Cumulative hospitalizations and mortalities in Ontario by age in age-groups used up to October 31st, 2009 **(42)**

	Hospitalizations						Mortalities					
Date	**0 - 5**	**5-15**	**15 - 25**	**25 - 45**	**45 - 65**	**65+**	**0 - 5**	**5-15**	**15 - 25**	**25 - 45**	**45 - 65**	**65 +**
2009-11-20	263	275	156	228	289	114	1	5	7	10	34	22
2009-11-27	318	302	168	269	343	141	1	5	7	16	41	25
2009-12-04	333	324	178	289	380	151	1	5	8	17	45	28
2009-12-11	353	333	179	297	399	163	1	5	9	18	49	31
2009-12-19	362	336	185	299	411	170	2	5	10	18	52	31
2009-12-26	365	342	187	302	421	171	2	5	10	18	55	31
2010-01-02	368	343	187	304	423	172	2	5	10	18	55	31
2010-01-09	371	343	187	305	425	172	2	5	10	18	55	31
2010-01-16	372	348	189	307	425	173	2	5	10	18	57	31
2010-01-23	375	357	189	312	433	177	2	5	10	18	60	31
2010-01-29	370	355	189	309	430	173	2	5	10	18	61	31
2010-02-05	374	358	190	311	436	174	2	5	10	18	62	31
2010-02-12	373	358	190	312	436	173	2	5	10	18	62	31
2010-02-19	373	358	190	312	436	173	2	5	10	18	62	31

Table 20: Cumulative hospitalizations and mortalities in Ontario by age in age-groups used after October 31st, 2009 **(42)**

	AB	BC	MB	NB	NL	NS	NT	ON	PE	QC	SK	YK
%	35%	39%	38%	62%	70%	64%	62%	38%	58%	57%	49%	52%
Reference	(43)	(44)	(45)	(46)	(47)	(48)	(49)	(50)	(51)	(52)	(53)	(54)

Table 21: Percentage of population vaccinated in each province and territory

Month	AB	BC	MB	NB	NL	NS	NT	ON	PE	QC	SK	YK
January	130	356	11	19	1	18	0	2536	3	519	4	1
February	276	1214	14	33	44	27	0	4329	6	1683	27	1
March	348	1449	24	245	31	175	1	4781	1	1195	127	0
April	1027	1719	101	142	131	448	1	6315	16	2073	113	0
May	773	1555	110	106	103	292	0	5525	4	1401	116	1
June	908	989	650	17	49	43	9	7170	0	2618	246	1
July	1065	1514	329	90	64	217	7	3847	5	954	125	1
August	757	1393	193	58	88	135	7	2787	8	572	66	1
September	1350	5412	343	132	225	152	13	4414	17	963	150	0
October	12310	27394	1260	821	4190	1359	17	34718	259	5768	2064	38
November	18835	26905	5971	5033	9231	4380	8	43700	402	11508	9285	30
December	1780	2949	1678	312	285	331	1	9226	6	874	977	5

Table 22: Antiviral prescriptions by province and month for 2009 **(55)**

Date	Confirmed Cases	Date	Confirmed Cases
2009-05-02	0	**2009-07-11**	3650
2009-05-09	30	**2009-07-18**	3820
2009-05-16	100	**2009-07-25**	3890
2009-05-23	260	**2009-08-01**	3940
2009-05-30	430	**2009-08-08**	3980
2009-06-06	910	**2009-08-15**	4010
2009-06-13	1520	**2009-08-22**	4030
2009-06-20	2380	**2009-08-29**	4040
2009-06-27	3120	**2009-09-05**	4050
2009-07-04	3470		

Table 23: Cumulative confirmed cases in Ontario. Note that in Ontario, individual level reporting of cases ended on June 20th, 2009 and confirmed cases after that time is not used.

Date	AB	BC	MB	NB	NL	NS	NT	NU	ON	PE	QC	SK	YK
2009-06-05	8	5	12	0	0	1	0	8	38	0	73	4	0
2009-06-12	10	6	43	0	0	1	0	18	54	0	160	6	0
2009-06-19	23	5	75	0	0	1	0	20	82	0	247	7	0
2009-06-27	34	7	83	0	0	4	0	33	138	0	314	9	0
2009-07-04	61	7	94	1	0	6	0	38	234	0	426	11	0
2009-07-11	87	14	201	1	0	8	0	38	266	1	488	11	0
2009-07-18	101	20	201	1	1	9	0	40	278	1	526	17	0
2009-07-25	114	25	201	1	1	10	0	42	290	1	564	22	0
2009-08-01	116	27	201	1	2	10	0	42	314	1	579	22	0
2009-08-08	122	36	201	2	2	15	1	48	332	1	584	22	0
2009-08-14	123	39	217	2	3	17	4	56	346	1	590	24	0
2009-08-21	126	42	217	2	3	17	4	62	353	1	591	23	0
2009-08-28	127	42	221	2	3	17	4	62	361	1	591	23	0
2009-09-04	128	44	221	2	3	17	4	66	365	1	571	23	0
2009-09-11	129	48	220	2	3	17	6	66	370	1	574	23	0
2009-09-18	129	51	221	2	3	17	7	66	371	1	576	23	0
2009-09-26	129	52	221	2	3	17	10	66	374	1	580	24	0
2009-10-03	131	64	226	2	3	17	10	66	380	1	580	24	0
2009-10-10	133	78	226	2	3	17	18	66	387	1	586	24	0
2009-10-17	139	111	227	2	3	17	22	66	407	1	585	24	0
2009-10-24	183	199	227	3	3	17	30	66	439	1	587	24	0
2009-10-31	263	361	227	8	30	33	40	66	544	4	833	27	4
2009-11-06	480	601	238	48	119	83	46	66	758	22	1268	27	8
2009-11-13	893	755	250	84	142	83	48	67	1069	37	1963	36	11
2009-11-20	1103	858	259	131	238	222	50	75	1325	47	2628	42	14
2009-11-27	1196	957	259	162	248	268	51	74	1541	48	2927	50	14
2009-12-04	1236	1009	259	163	265	270	52	77	1656	50	2994	52	14
2009-12-11	1250	1032	259	165	265	282	52	77	1725	50	3033	57	14
2009-12-19	1259	1037	365	164	265	283	52	77	1763	50	3047	60	14
2009-12-26	1262	1042	369	164	270	281	52	77	1780	50	3051	61	15
2010-01-02	1264	1047	373	164	274	278	52	77	1796	50	3055	62	15
2010-01-09	1268	1049	373	163	277	289	52	77	1803	50	3055	66	15
2010-01-16	1273	1032	383	163	277	289	52	80	1814	50	3055	66	15
2010-01-23	1275	1032	377	164	277	289	52	80	1843	50	3061	67	15
2010-01-29	1276	1059	379	164	277	289	52	80	1826	50	3062	67	15
2010-02-05	1276	1058	379	163	277	293	52	80	1843	50	3062	67	15

Table 24: Confirmed cumulative hospitalizations for each province and territory in Canada **(5)**

Date	AB	BC	MB	NB	NL	NS	NT	NU	ON	PE	QC	SK	YK
2009-06-05	1	0	0	0	0	0	0	0	2	0	1	0	0
2009-06-12	1	0	2	0	0	0	0	0	2	0	7	0	0
2009-06-19	1	0	2	0	0	0	0	0	7	0	11	0	0
2009-06-27	1	0	2	0	0	0	0	0	10	0	12	2	0
2009-07-04	2	0	5	0	0	0	0	0	13	0	14	3	0
2009-07-11	3	1	6	0	0	0	0	0	15	0	17	3	0
2009-07-18	3	1	6	0	0	0	0	1	16	0	18	4	0
2009-07-25	4	2	7	0	0	1	0	1	18	0	20	4	0
2009-08-01	5	2	7	0	0	1	0	1	19	0	21	4	0
2009-08-08	7	4	7	0	0	1	0	1	21	0	21	4	0
2009-08-14	7	4	7	0	0	1	0	1	21	0	25	4	0
2009-08-21	7	4	7	0	0	1	0	1	22	0	25	4	0
2009-08-28	7	4	7	0	0	1	0	1	23	0	25	4	0
2009-09-04	8	4	7	0	0	1	0	1	23	0	26	4	0
2009-09-11	8	5	7	0	0	1	0	1	23	0	27	4	0
2009-09-18	8	6	7	0	0	1	0	1	24	0	27	4	0
2009-09-26	8	6	7	0	0	1	0	1	24	0	27	4	0
2009-10-03	8	6	7	0	0	1	0	1	24	0	27	4	0
2009-10-10	8	7	7	0	0	1	0	1	25	0	27	4	0
2009-10-17	8	9	7	0	0	1	0	1	25	0	27	5	0
2009-10-24	12	12	7	0	0	1	0	1	27	0	27	5	0
2009-10-31	14	14	7	0	1	1	0	1	30	0	27	5	0
2009-11-06	20	23	8	0	2	2	0	1	37	0	35	6	1
2009-11-13	42	29	8	2	7	2	0	1	61	0	58	8	1
2009-11-20	50	34	9	6	7	4	1	1	79	0	76	11	2
2009-11-27	57	42	9	7	15	6	1	1	95	0	89	12	2
2009-12-04	62	47	9	7	16	7	1	1	104	0	99	13	3
2009-12-11	64	51	10	7	16	7	1	1	113	0	103	14	3
2009-12-19	65	52	10	7	16	7	1	1	118	0	106	15	3
2009-12-26	67	53	10	7	17	7	1	1	119	0	107	15	3
2010-01-02	69	54	11	8	18	7	1	1	121	0	108	15	3
2010-01-09	70	55	11	8	18	7	1	1	121	0	108	15	3
2010-01-16	71	56	11	8	18	7	1	1	123	0	108	15	3
2010-01-23	71	56	11	8	18	7	1	1	126	0	108	15	3
2010-01-29	71	56	11	8	18	7	1	1	127	0	108	15	3
2010-02-05	71	55	11	8	18	7	1	1	128	0	108	15	3

Table 25: Confirmed cumulative mortalities in Canada for each province and territory **(5)**

APPENDIX C: DETAILED METHODOLOGY

The basic model is a Susceptible-Exposed-Infectious-Recovered (SEIR) model with additional compartments so that antivirals and vaccination can be included in the model. Table 26 and Table 27 describe the detailed population compartments used in the model.

The equations for the model are decomposed into the base model, which includes infection, recovery and mortality, and correction terms which deal with specific processes such as vaccination. The full model is then described by the sum of the base model plus all correction terms. Any terms not explicitly given are zero. Lower case superscripts indicate any value in that axis while upper case superscripts indicate the specific state defined in Table 27. For example, $\dot{X}^{ab} = -\lambda_X X^{ab}$ means the equation is valid for any combination of *a* and *b*. In contrast, for the quantity Y^{ab}, the statement $\dot{Y}^{aN} = -\lambda_Y Y^{aN}$ means the equation is only valid when parameter *b* has value *N*. For any other values of b, the derivative of *Y* is zero.

THE BASE MODEL

The equations for the base model are:

$$\dot{S}^{agtrv}\Big|_{\text{Base}} = -S^{agtrv}\sum_{b}\rho^{abtv}C^{ab}\sum_{gkrh}\frac{\epsilon_k I^{bgkrvh}}{P^b}$$

$$\dot{i}^{agtrv}\Big|_{\text{Base}} = S^{agtrv}\sum_{b}\rho^{abtv}C^{ab}\sum_{gkrh}\frac{\epsilon_k I^{bgkrvh}}{P^b} - \lambda_L^N i^{agtrv}$$

$$\dot{I}^{agtrvh}\Big|_{\text{Base}} = \lambda_L^h i^{agtrv} - \lambda_{R,I}^{th} I^{agtrvh} - \lambda_{M,I}^{agtrh} I^{agtrvh} - \lambda_J I^{agtrvh}$$

$$\dot{J}^{agtrvh}\Big|_{\text{Base}} = \lambda_J I^{agtrvh} - \lambda_{R,J}^{th} J^{agtrvh} - \lambda_{M,J}^{agtrh} J^{agtrvh}$$

$$\dot{R}^{agrvh}\Big|_{\text{Base}} = \sum_{t}\lambda_{R,I}^{th} I^{agtrvh} + \sum_{t}\lambda_{R,J}^{th} J^{agtrvh}$$

$$\dot{M}^{agtrvh}\Big|_{\text{Base}} = \lambda_{M,I}^{agtrh} I^{agtrvh} + \lambda_{M,J}^{agtrh} J^{agtrvh}$$

Table 26 defines each of the parameters. The first equation is the change in susceptible individuals due to contact with an infectious person. The second describes the newly infected cases that are not yet infectious (first term) and the transition from not infectious to infectious (second term). The third and fourth equations describe the recovery and mortalities of the infectious population. Finally, the last two equations track the cumulative recoveries and cumulative mortalities respectively.

HOSPITALIZATIONS

Once people are infectious, they are eligible for hospitalization. The hospitalization rate, λ_H^{agr}, depends on age, gender and risk factors.

Symbol	Quantity	Dimensions
S^{agtrv}	Susceptible	Age-group, gender, antiviral status, risk factor, vaccination status
i^{agtrv}	Infected	Age-group, gender, antiviral status, risk factor, vaccination status
I^{agtrvh}	Infectious Early	Age-group, gender, antiviral status, risk factor, vaccination status, hospitalization status
J^{agtrvh}	Infectious Late	Age-group, gender, antiviral status, risk factor, vaccination status, hospitalization status
R^{agtrvh}	Recovered	Age-group, gender, risk, vaccinated, hospitalized
M^{agtrvh}	Mortalities	Age-group, gender, antiviral, risk, vaccinated, hospitalized
P^{b}	Population	Age-group

Table 26: Population compartments used in the model

Dimension	Symbol	States
Age-Group	*a*	Ages 0-5, 5-10, ...
Gender	*g*	Male, Female
Antiviral Status	*t*	No antivirals but will seek treatment (N), On early treatment (T), On late treatment (L), Post-exposure (P), Forbidden (F), Won't seek treatment (X)
Risk Factors	*r*	High, Low
Vaccination Status	*v*	Vaccinated (V), Not vaccinated but will seek to be (N), Not vaccinated and will not seek vaccination (X)
Hospitalization Status	*h*	Hospitalized (H), Not hospitalized (N)

Table 27: Elements of each population dimension.

Symbol	Description
ρ^{abtv}	Probability of infection given contact between a person in age-group *a* who has antiviral status *t*, and vaccination status *v*, and a person in age group *b*
C^{ab}	Contact rate between people in age-group *a* meeting a person in age-group *b*. This can be a function of time to account for seasonal changes such as school summer holidays.
ϵ_k	Relative infectiousness of a person with antiviral status *k*.
$1/\lambda_L^N$	Mean non-infectious time, where N indicates not hospitalized; λ_L^H is defined to be 0
$1/\lambda_J$	Mean time after which antiviral effectiveness for treatment is reduced
$\lambda_{R,\{I,J\}}^{th}$	Recovery rate for each antiviral status and hospitalization status
$\lambda_{M,\{I,J\}}^{agtrh}$	Mortality rate for each age-group, gender, antiviral status, risk factor and hospitalization status

Table 28: Definition of model parameters

$$\dot{I}^{agtrvN}\Big|_{\text{Hosp}} = -\lambda_H^{agr} I^{agtrvN}$$
$$\dot{I}^{agtrvH}\Big|_{\text{Hosp}} = \lambda_H^{agr} I^{agtrvN}$$
$$\dot{J}^{agtrvN}\Big|_{\text{Hosp}} = -\lambda_H^{agr} J^{agtrvN}$$
$$\dot{J}^{agtrvH}\Big|_{\text{Hosp}} = \lambda_H^{agr} J^{agtrvN}$$

$$\dot{J}^{agtrN}\Big|_{\text{Hosp}} = -\lambda_H^{agr} J^{agtrN}$$
$$\dot{J}^{agtrH}\Big|_{\text{Hosp}} = \lambda_H^{agr} J^{agtrN}$$

VACCINATION

Those in the population who are susceptible and will seek vaccination are vaccinated at a time-dependent rate λ_V^{agr}. The vaccination rate can depend upon the risk factors, age-group, and gender.

$$\dot{S}^{agtrV}\Big|_{\text{Vac}} = \lambda_V^{agr} S^{agtrN}$$
$$\dot{S}^{agtrN}\Big|_{\text{Vac}} = -\lambda_V^{agr} S^{agtrN}$$
$$\dot{I}^{agtrV}\Big|_{\text{Vac}} = \lambda_V^{agr} I^{agtrN}$$
$$\dot{I}^{agtrN}\Big|_{\text{Vac}} = -\lambda_V^{agr} I^{agtrN}$$
$$\dot{I}^{agtrVh}\Big|_{\text{Vac}} = \lambda_V^{agr} I^{agtrNh}$$
$$\dot{I}^{agtrNh}\Big|_{\text{Vac}} = -\lambda_V^{agr} I^{agtrNh}$$
$$\dot{J}^{agtrVh}\Big|_{\text{Vac}} = \lambda_V^{agr} J^{agtrNh}$$
$$\dot{J}^{agtrNh}\Big|_{\text{Vac}} = -\lambda_V^{agr} J^{agtrNh}$$
$$\dot{R}^{agrVh}\Big|_{\text{Vac}} = \lambda_V^{agr} R^{agrNh}$$
$$\dot{R}^{agrNh}\Big|_{\text{Vac}} = -\lambda_V^{agr} R^{agrNh}$$

Note that since vaccines are not immediately effective, the time dependence of vaccination rate corresponds to the time the vaccine becomes effective, not when administered.

ANTIVIRAL TREATMENT

There are three aspects to antiviral treatment. The first is antiviral treatment upon hospitalization. It is assumed that when antivirals are available for treatment, all patients who are hospitalized and not currently on antivirals receive antiviral treatment immediately.

$$\dot{I}^{agTrvH}\Big|_{\text{Tx,Hosp}} = \dot{I}^{agNrvN}\Big|_{\text{Hosp}} + \dot{I}^{agXrvN}\Big|_{\text{Hosp}}$$
$$\dot{I}^{agNrvN}\Big|_{\text{Tx,Hosp}} = -\dot{I}^{agNrvN}\Big|_{\text{Hosp}}$$
$$\dot{I}^{agXrvN}\Big|_{\text{Tx,Hosp}} = -\dot{I}^{agXrvN}\Big|_{\text{Hosp}}$$
$$\dot{J}^{agLrvH}\Big|_{\text{Tx,Hosp}} = \dot{J}^{agNrvN}\Big|_{\text{Hosp}} + \dot{J}^{agXrvN}\Big|_{\text{Hosp}}$$
$$\dot{J}^{agNrvN}\Big|_{\text{Tx,Hosp}} = -\dot{J}^{agNrvN}\Big|_{\text{Hosp}}$$
$$\dot{J}^{agXrvN}\Big|_{\text{Tx,Hosp}} = -\dot{J}^{agXrvN}\Big|_{\text{Hosp}}$$

The second component is antiviral treatment among the public outside hospitalized. If $1/\lambda_T$ is the mean time for an infectious individual to receive treatment, then:

$$\dot{I}^{agTrvN}\Big|_{\text{Tx}} = \lambda_T I^{agNrvN}$$
$$\dot{I}^{agNrvN}\Big|_{\text{Tx}} = -\lambda_T I^{agNrvN}$$
$$\dot{J}^{agLrvN}\Big|_{\text{Tx}} = \lambda_T J^{agNrvN}$$
$$\dot{J}^{agNrvN}\Big|_{\text{Tx}} = -\lambda_T J^{agNrvN}$$

Finally, if $1/\lambda_E$ is the mean time that patients stay on antivirals, antiviral treatment expiry is modelled using:

$$\dot{I}^{agFrvh}\Big|_{\text{Tx,Expiry}} = \lambda_E I^{agTrvh}$$
$$\dot{I}^{agTrvh}\Big|_{\text{Tx,Expiry}} = -\lambda_E I^{agTrvh}$$
$$\dot{J}^{agFrvh}\Big|_{\text{Tx,Expiry}} = \lambda_E \left(J^{agTrvh} + J^{agLrvh} \right)$$
$$\dot{J}^{agTrvh}\Big|_{\text{Tx,Expiry}} = -\lambda_E J^{agTrvh}$$
$$\dot{J}^{agLrvh}\Big|_{\text{Tx,Expiry}} = -\lambda_E J^{agLrvh}$$

Note that after treatment, patients are no longer allowed to seek further antivirals.

POST-EXPOSURE PROPHYLAXIS

Post-exposure prophylaxis (PEP) is given to susceptible individuals who have contacted an infectious person regardless of whether the virus was transmitted or not. If the virus was transmitted, then α is the effectiveness of antivirals in preventing infection if given promptly. In practice, it is not possible to identify all contacts that occur. Therefore, the model incorporates an contact identification fraction, μ, to account for the fact that only a portion of all contacts are detected. In general, only a fraction of the susceptible population is eligible for PEP. Let β^{ag} be the fraction eligible:

$$\beta^{ag} = \frac{\sum_{rv} S^{agNrv}_{\text{Eligible}}}{\sum_{rv} S^{agNrv}}$$

To simplify the correction terms, define the quantities:

$$\chi^{agNrv} = \mu\beta^{ag}\sum_{b} C^{ab}\sum_{gkrh}\frac{I^{bgkrvh}}{P^{b}}$$

$$\zeta^{agNrv}_{\text{NotPrevented}} = (1-\alpha)\mu\beta^{ag}\sum_{b} C^{ab}\rho^{abNv}\sum_{gkrh}\frac{\epsilon_k I^{bgkrvh}}{P^{b}}$$

$$\zeta^{agNrv}_{\text{Prevented}} = \alpha\mu\beta^{ag}\sum_{b} C^{ab}\rho^{abNv}\sum_{gkrh}\frac{\epsilon_k I^{bgkrvh}}{P^{b}}$$

The correction terms for post-exposure prophylaxis are then:

$$\dot{S}^{agNrv}\Big|_{\text{Post}} = -\left(\chi^{agNrv} - \zeta^{agNrv}_{\text{NotPrevented}} - \zeta^{agNrv}_{\text{Prevented}}\right)S^{agNrv}$$

$$\dot{S}^{agPrv}\Big|_{\text{Post}} = \left(\chi^{agNrv} - \zeta^{agNrv}_{\text{NotPrevented}}\right)S^{agNrv}$$

$$\dot{i}^{agNrv}\Big|_{\text{Post}} = -\left(\zeta^{agNrv}_{\text{NotPrevented}} + \zeta^{agNrv}_{\text{Prevented}}\right)S^{agNrv}$$

$$\dot{i}^{agPrv}\Big|_{\text{Post}} = \zeta^{agNrv}_{\text{NotPrevented}}S^{agNrv}$$

As susceptible people become ill, or start prophylaxis, the eligible fraction will change and must be tracked as well:

$$\dot{\beta}^{ag} = \frac{1}{\sum_{rv} S^{agNrv}}\left(\sum_{rv}\dot{S}^{agNrv}_{\text{Eligible}} - \beta^{ag}\sum_{rv}\dot{S}^{agNrv}\right)$$

$$\dot{S}^{agNrv}_{\text{Eligible}} = \beta^{ag}\,\dot{S}^{agNrv}\Big|_{\text{Base}} + \dot{S}^{agNrv}\Big|_{\text{Post}} + \lambda_P S^{agPrv}$$

The expiry of PEP is modelled in the same manner as for treatment, except people are eligible for antivirals after receiving PEP if they are still susceptible.

$$\dot{S}^{agPrv}\Big|_{\text{Post,Expiry}} = -\lambda_P S^{agPrv}$$

$$\dot{S}^{agNrv}\Big|_{\text{Post,Expiry}} = \lambda_P S^{agPrv}$$

$$\dot{i}^{agPrv}\Big|_{\text{Post,Expiry}} = -\lambda_P i^{agPrv}$$

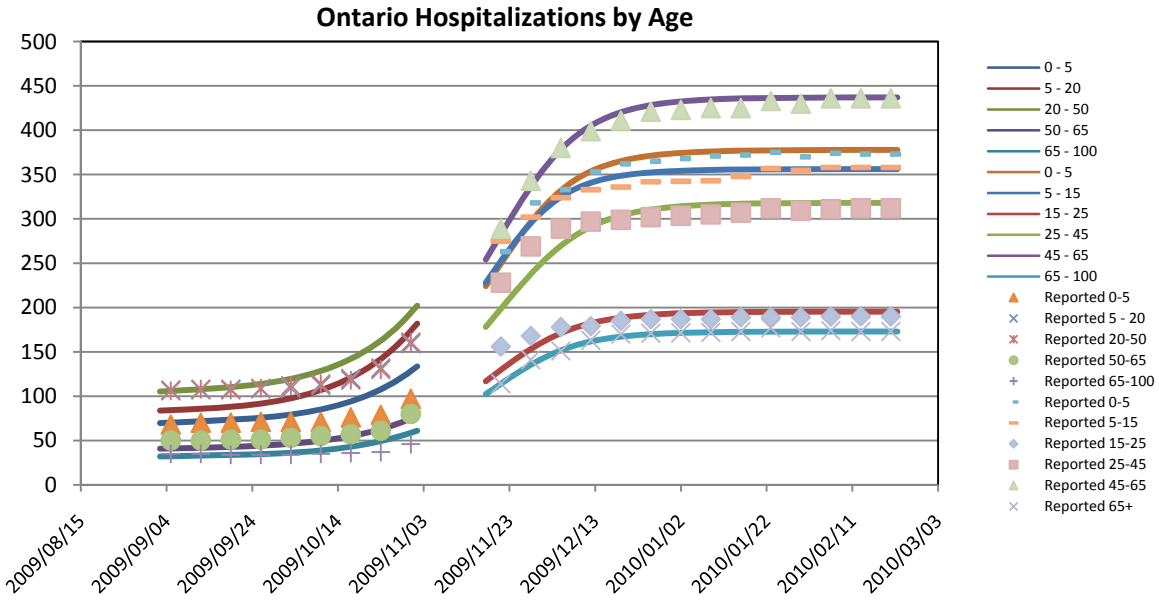
$$\dot{i}^{agNrv}\Big|_{\text{Post,Expiry}} = \lambda_P i^{agPrv}$$

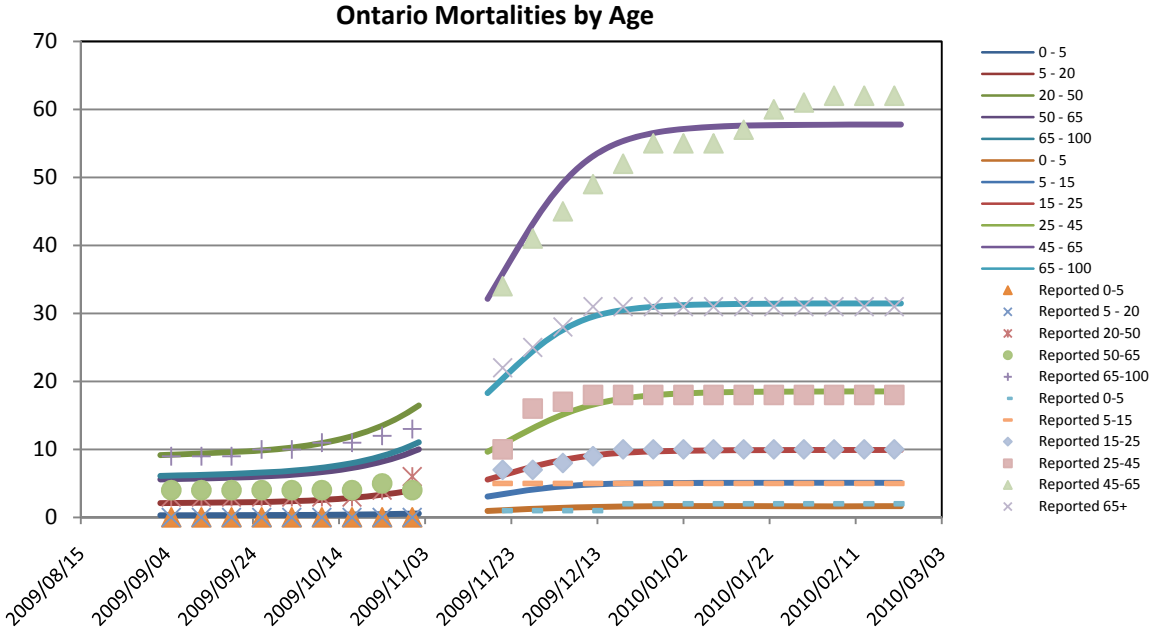
APPENDIX D: ECONOMIC FRAMEWORK

Please refer to the Supplementary Mathematical Appendix titled *Life at Risk® Economic Framework*

APPENDIX E: PH1N1 FIT RESULTS

ONTARIO AGE-DEPENDENT FITS





PROVINCIAL AGGREGATE FITS

Using the age-dependent hospitalization and morality rates determined from Ontario, the model was calibrated to each province's and each territory's reported values. The initial number of cases, overall hospitalization rate, mortality rate, and contact rates were allowed to vary in each of the provincial fits to account for differences in geography, reporting policies, and demographics. All other parameters, such as the recovery rate, were kept constant. Figure compares the observed hospitalizations and mortalities for each province and territory to the modelled values.

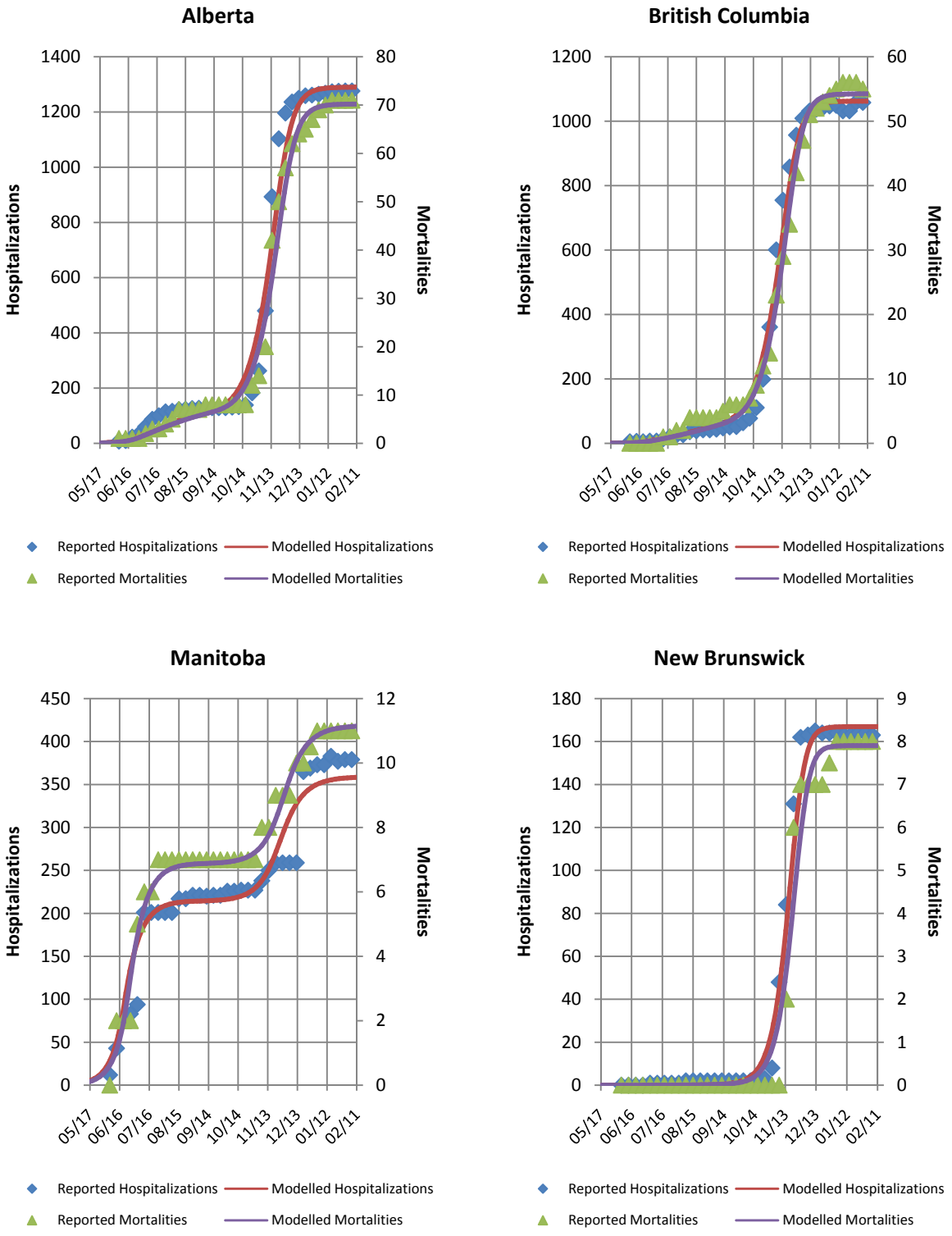


Figure 5 (a): Comparison of provincial reported hospitalizations (left-hand axis) and mortalities (right-hand axis).

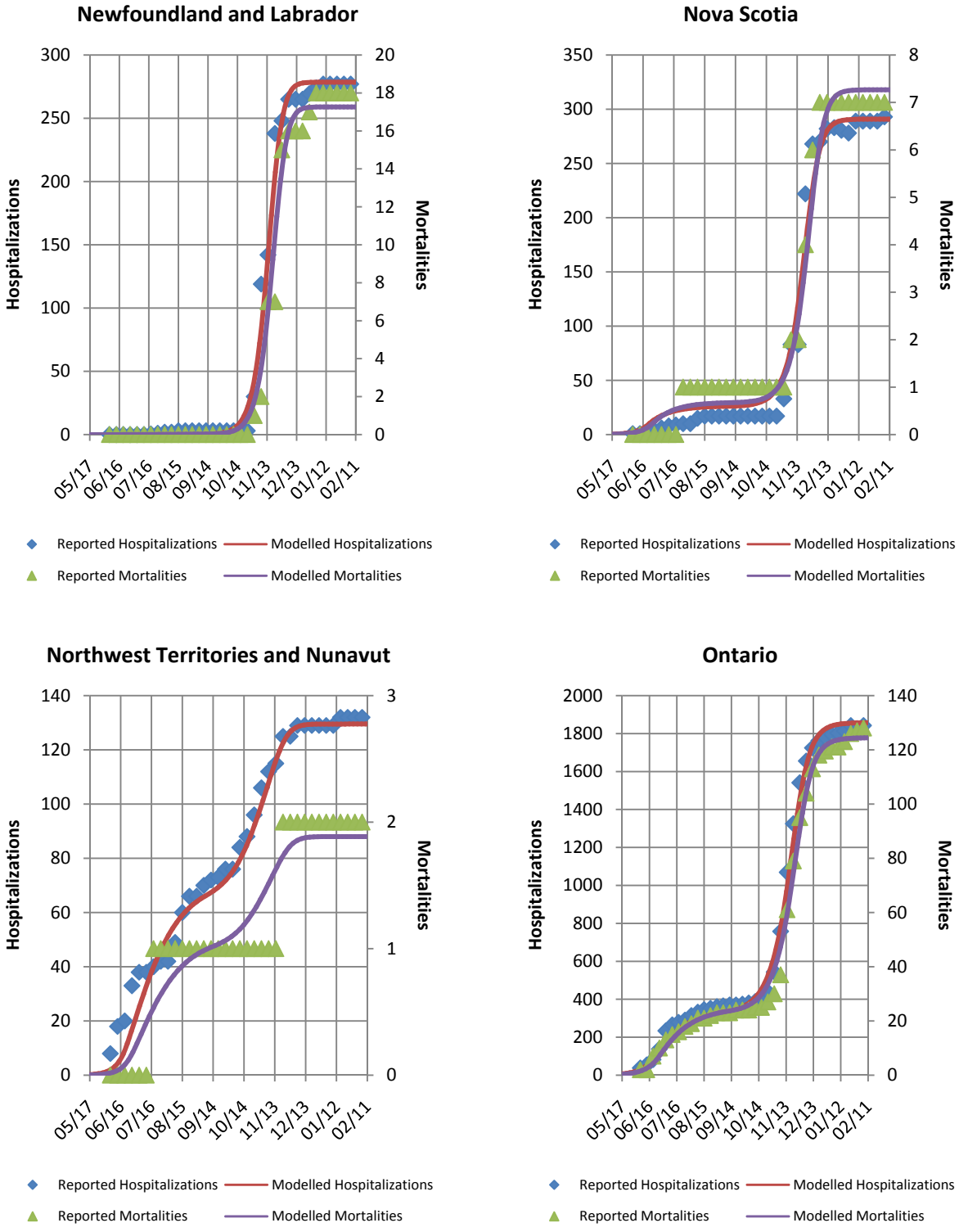


Figure (b): Comparison of provincial reported hospitalizations (left-hand axis) and mortalities (right-hand axis).

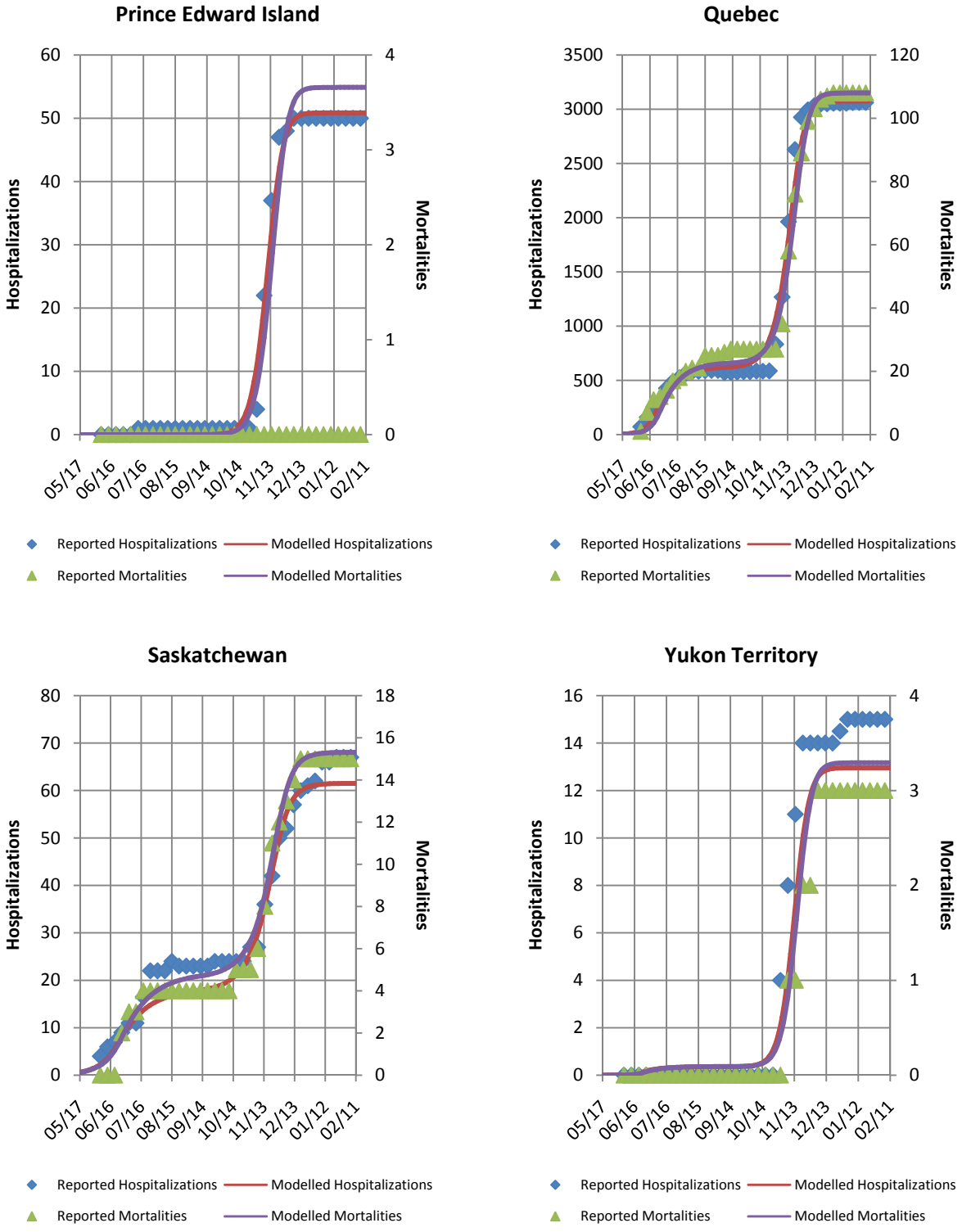


Figure (c): Comparison of provincial reported hospitalizations (left-hand axis) and mortalities (right-hand axis).

APPENDIX F: ASSUMPTIONS AND EXTERNAL DATA

Quantity	Description	Reference
Contact Types	Contacts based on multi-country survey across 15 age groups	(19)
Probability of Virus Transmission	The relative transmission probability between age groups in 4 age groups (0-4, 5-18, 19-64, >65).	(56)
Average Latency	1.5 days	PRAC recommendation
Asymptomatic Cases	Assumed no asymptomatic cases	PRAC recommendation
Antiviral use	Antiviral treatment is given immediately upon hospitalization. Widespread antiviral use begins when the pandemic is officially declared.	
Antiviral Efficacy	Treatment is 30% less effective if administered more than 2 days after infectious stage begins, but given nonetheless.	PRAC recommendation
Mean Time to Treatment	36 hours after symptoms begin.	PRAC recommendation
Contact Identification	25% of contacts that are eligible for post-exposure prophylaxis are identified.	Assumption
Relative Efficacy (Post-Exposure)	The relative efficacy varies in studies range between 68% and 89%. A conservative value of 68% is assumed.	(57), (58)
Effect of Antiviral Treatment	Antiviral treatment was assumed to have a 25% reduction on the duration of illness and a 65% reduction in mortalities.	(59)
Misdiagnosis Wastage	Assumed no wastage due to misdiagnosis.	PRAC recommendation
Cost of antivirals	Cost of oseltamivir 75 mg blister pack of 10 (a prescription) at pharmacy rate of $39.	Roche Canada
Morbidity QALYs	The QALY gained per morbid case prevented by age. Discount of 3% used.	(16)
Mortality QALYs	The QALY gained per death prevented by age. Discount of 3% used.	(16)
Absenteeism Factor	In addition to direct illness driving absenteeism, an additional factor proportional to hospitalizations for absenteeism due to all other causes is modelled.	(60)

Vaccination Start and Rollout	Vaccination starts at the end of October and is administered over 2 months with the majority occurring in November. Age and sex distribution of those who received vaccinations was similar to the seasonal vaccination distributions.	PRAC recommendation
Vaccine induced immunity	2 weeks after application.	PRAC recommendation
Antiviral or vaccine adverse affects	None.	PRAC recommendation
Healthcare costs	Physician office visits, emergency department visits, or hospitalization costs.	(16)
GDP absenteeism impacts	Impact of absenteeism on output: aggregate production function with an output-hours elasticity of 0.6 used for absenteeism.	(31)
Moderate Pandemic Rates	Average 1957/58 pandemic case ratios (hospitalization and mortality). CFR of 0.16%	(56)
Severe Pandemic Rates	Average lower estimates of 1918 pandemic case ratios (hospitalization and mortality). CFR of 1.4%	(18)