# Adequacy of current antiviral stockpiles under the Canadian pandemic Influenza plan

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**OBJECTIVE:** The purpose of the current study was to analyze the adequacy of the current Canadian antiviral stockpile during a moderate, drug sensitive influenza pandemic in Canada under three potential interpretations of the Canadian Pandemic Influenza Plan (CPIP).

**METHODS:** A deterministic mathematical model of the transmission dynamics of influenza was used to track the Canadian population during the assumed pandemic. The Canadian population was stratified into thirty seven geographical regions and was further grouped by age, gender, health state and occupation. The parameters of the model were obtained from available Canadian and US data, allowing calibration to a moderate 1957/58 type influenza pandemic. Each interpretation of CPIP was then simulated to analyze its impact upon the disease spread and the use of currently available antiviral stockpiles. In addition, it was assumed that the antiviral wastage would vary between 0%-30%.

**RESULTS:** The results indicate that the current Canadian stockpiles may not be sufficient if antivirals are used as post exposure prophylaxis (PEP) for outbreak control in closed facilities during a moderate pandemic with a 33.4% attack rate.

**DISCUSSION:** The inadequacy of the current assumed stockpile in supporting the CPIP PEP interpretations creates the risk that Canada will run out of antivirals during a moderate pandemic, resulting in denial of treatment to a significant number of people seeking antivirals. These results should encourage a policy review of the size of the current stockpile or more precise stockpile use policies that manage the risk of complete depletion of the current stockpile.

**Key Words:** *Antivirals; Influenza; Pandemic; Preparedness plan; Mathematical Modeling.*

Seasonal influenza is an annual health threat causing increased absenteeism at work, increased rates of respiratory infections requiring hospitalization, deaths from influenza related complications, and a significant strain on the health system's resources. A pandemic influenza may increase this threat several fold as the number of possible infections within the population may rise as high as 35%. Due to the capricious nature of a pandemic its precise impact upon a population remains largely a matter of speculation. Previously, a great deal of research was conducted in an effort to understand the possible effects of past pandemics on our society, had they occurred today. Numerous mathematical models considering the dynamics of a severe pandemic such as the H1N1 strain responsible for the 1918/19 pandemic as well as milder pandemics such as the 1957/58 were analyzed.

The severity of a pandemic strain of influenza is usually not known until the time at which the strain is identified and its spread observed within a population. Despite this, a number of household trials suggest that there will likely be significant benefits associated with the use of antiviral drugs during an influenza pandemic [1]. As such, the drugs are generally accepted to be useful in outbreak control among high risk population groups. In this capacity, the drugs are expected to provide important protection before any pandemic vaccines can be produced in population relevant quantities. Currently, there are two general classes of antiviral drugs which are approved for use in Canada: neuraminidase inhibitors (NIs) and M2 ion channel inhibitors. Neuraminidase inhibitors include oseltamivir (Tamiflu) as well as zanamivir (Relenza) and have both been shown to be effective against the H5N1 strain of avian influenza in laboratory trials [2, 3, 4]. Both drugs are approved for use in Canada, and constitute a significant proportion of all antiviral drugs in the current Canadian stockpiles.

**Canadian NI stockpile and TGAP recommendations**

The current Canadian antiviral stockpile is composed of a National Antiviral Stockpile (NAS), a National Emergency Stockpile System (NESS) and an independent Ontario Stockpile. The NAS is composed of 55.7 million doses [5] and has been distributed among the provinces and territories on a per capita basis. Ontario is reported to have an additional stockpile that, in conjunction with its NAS allotment, is sufficient to provide antivirals for 25% of its population [6]. This represents an additional 10.38 million doses available to Ontario only. Finally, the NESS is composed of 14.9 million doses [5] and has been created as an emergency backup stockpile in order to ensure an increased response and surge capacity to manage an influenza pandemic. The stockpiles add up to a total of 80.98 million doses. The NAS is expected to be distributed across each province and territory on a per capita basis for use as treatment and post-exposure prophylaxis only. In contrast, the NESS is distributed to those in need regardless of the population demographics. In the current study, we reorganized the stockpiles into three independent groups: the NESS group which includes the entire NESS stockpile, Group 1 which includes the portion of the NAS stockpile which is not distributed to Ontario, and Group 2 which includes the Ontario portion of the NAS stockpile as well as the Ontario supplement.

The Task Group on Antiviral for Prophylaxis (TGAP) was established in May 2006 in an effort to determine whether governments should stockpile antivirals for the purpose of prophylaxis during

a pandemic influenza outbreak. The task group reported to the Public Health Network Council (PHNC) and was placed in charge of developing the details of a plan in which prophylaxis could be used in Canada in the event of a pandemic. Three reports addressing the efficacy and safety of antivirals were commissioned by TGAP and concluded that despite limited data, there is significant evidence to support the use of neuraminidase (NI) drugs as treatment and post-exposure prophylaxis of specific population groups. As a result of their extensive work, TGAP recommended the use of antiviral drugs for outbreak control, including treatment of cases, and post-exposure prophylaxis of contacts, in closed health care facilities and other closed facilities where high-risk people reside, during Canadian pandemic phases 6.1 and 6.2 [1].

In the current study, the TGAP recommendations are assumed to provide the recommendation on the use of NIs for the purposes of prophylaxis in the Canadian Pandemic Influenza Plan (CPIP). In this capacity, three separate policy scenarios were considered under the constraints of the currently available NESS, NAS and Ontario stockpiles. The first policy (CPIP-1) was a treatment only scenario. There would be no prophylaxis use under this regulation. Under the second policy, the TGAP recommendations were adopted, where limited use of prophylaxis was allowed in addition to the treatment policy of CPIP-1. In order to explore a possible range of effects, two interpretations of the TGAP recommendations were considered. A scenario under which the staff within closed facilities is given the post-exposure prophylaxis was labeled the CPIP-2 policy. A scenario under which the staff and the people they care for within closed facilities are given the post-exposure prophylaxis was labeled the CPIP-3 policy. Since the TGAP recommendations did not explicitly specify the exact populations which fall under the definitions of closed facilities (health and other), the current study adopted the definitions contained in the latest version of the CPIP report for the Health Sector [5].

## METHODS

The impact of various antiviral strategies during a potential influenza pandemic was simulated using a deterministic infectious disease model. The assumptions supporting the model can be found in Appendix A. The equations for the model can be found in Appendix B.

The Canadian population was subdivided into groups based on age, gender, health state, and population type within 37 geographical regions. The initial population data was obtained from Statistics Canada and was differentiated by occupation type. In the current study, individuals were separated into health care workers and non health care workers. The former accounted for nearly 2% of the Canadian population. The health care worker population was then further sub-divided into those who can be defined as faculty in closed facilities under the Canadian Pandemic Influenza Plan for the Health Sector [5]. The model divided the population into 5 basic health states: susceptible, infected but not infectious, early stage of infectiousness (within 48 hours of the onset of symptoms), late stage of infectiousness (later than 48 hours of the onset of symptoms), and recovered. In order to model the impact of antiviral use, the susceptible and infected states were subdivided into 2 categories based on PEP status, while both infectious states were divided into 4 categories based both on PEP status, and treatment status. This yields a total of 13 health states.

The progression of an individual from susceptible through to recovered is shown in Figure 1. The initial transition from susceptible to infected depends on the number of age-dependent contacts made by an individual per unit time, the probability that contact is with an infectious individual, and the probability of infection given contact. The number and type of contacts which were used in the current study were adopted directly from the recent European contact study by Mossong et al. (2008) [7]. The age-dependent probability of infection is from Haber et al. (2007) [8].

Once infected, individuals with the influenza virus first pass through a latent period. During this period the individuals are not infectious and do not exhibit any symptoms of the disease. In this study we adopt an average period of 1.9 days for the latency period. At the end of the period, all infected people will develop symptoms and will become infectious. The infectious period is divided into two mutually exclusive groups; those in an early stage of infectiousness, and those in a later stage of infectiousness. The late stage represents a period during which the use of antiviral drugs is not expected to have any effect on the recovery of the patient. Case fatality was assumed to vary with age but not with any other factors (such as weak immune system or the pre-existence of co-morbid conditions). A “U-shaped” age-dependant mortality rate, typical of the 1957/58 pandemic [8] was used. The simulated pandemic was assumed to be caused by the introduction of a completely new virus to which nobody in Canada had any previously acquired immunity. As a result, no immunity is assumed among the susceptible populations.

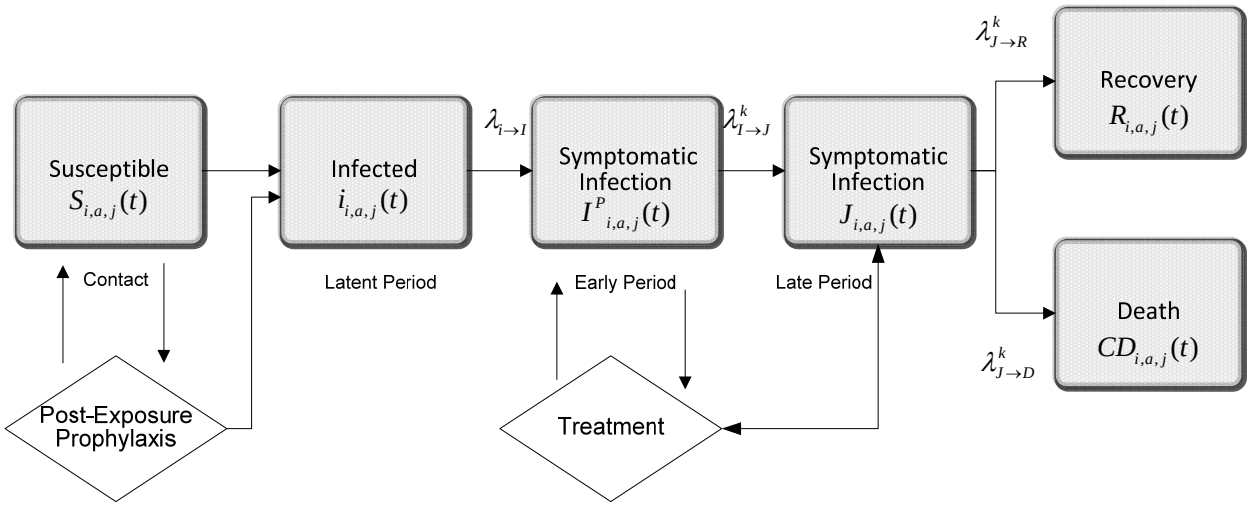


**Figure 1:** Flowchart diagram identifying the main processes and states within the current study. After a contact (with an infectious individual), the model recognizes two types of populations given by $S^P(t)$ and $S(t)$ and representing those with and without antiviral protection respectively. After symptomatic disease develops, the model differentiates between those individuals who had undergone timely (within 48 hours) antiviral (NI) treatment $I^P(t)$ as well as those who did not. The treatment is expected to reduce the mean recovery time (by moving individuals into $J(t)$ sooner). $CD_{i,a,j}(t)$ represents the cumulative number of deaths since the start of the pandemic. The parameter $\lambda^k_{A\to B}$ represents the rate of evolution of individuals from group A into those in group B with the protection of NIs (k=P) or without its protection (k=0).

There are currently two types of NIs in the Canadian stockpiles: oseltamivir and zanamivir. The current model assumes a reduction in the probability of infection of 75% when used as post-exposure prophylaxis, and a 25% reduction in recovery time when used as treatment [2, 9, 10, 11]. In order to be most effective, NIs should be administered within 48 hours of the onset of symptoms. Therefore, it is assumed that if antivirals are administered to those in the late stage of infectiousness, they are ineffective.

Three separate antiviral drug policies were tested in the current model. The first policy (CPIP-1) involved the use of NIs for treatment only and therefore no one was allowed post-exposure prophylaxis. All three of the currently available AV stockpiles supported the policy. The model also considered the use of two additional policies (CPIP-2 and CPIP-3) which are assumed to be consistent with the TGAP recommendations. Under these policies a subset of the population was allowed access to NIs as post-exposure prophylaxis. This population was associated with the staff and the people they care for in closed facilities [5]. The staff in the closed facilities (CPIP-2 policy) accounted for about 2% of the Canadian population in 2007, while the staff and the people they care for (CPIP-3 policy) accounted for almost 3.5% of the 2007 Canadian population [12].

In the model, the NIs administered on a “first come, first serve” basis, are assumed to be readily available at the beginning of the pandemic, and are to be administered by the members of the health care community. The administration rate of NIs is dependent upon the state of the health care system (please refer to the Appendix for details). The model assumed that as health care workers become ill, the rate at which antivirals can be administered to the sick population decreases. Therefore, ensuring the wellbeing of the health care population by targeting people in closed facilities for prophylaxis under the TGAP recommendations, not only helps those individuals directly, but the overall population through the prompt delivery of NI drugs.
The beginning of the pandemic is marked by an event which is assumed to be of sufficient importance to warrant the use of the antiviral stockpile during a moderate pandemic. In the present case this is assumed to be represented by 20 cumulative deaths (related to complications from the disease) within Canada.

The wastage of NIs due to their unintended use may account for a substantial mechanism in the depletion of the current stockpile. In general, the most obvious sources of this waste may result from misdiagnosis and can be driven by the co-existence of seasonal flu and various respiratory infections (whose effects may be difficult to distinguish from those of pandemic influenza). In the current study we consider various levels of such wastage as a proportion of the NIs which are actually administered to those with pandemic influenza. The specific nature of the wastage is not considered in the current study. Instead, it is simply assumed to uniformly increase the consumption of the NI drugs by a constant factor across all of the Canadian stockpiles. In the results section, simulated results are shown under wastage parameters of 0%, 5%, 10%, 20% and 30%.

## RESULTS

The results indicate that the use of current stockpiles of NIs will be beneficial as it is expected to significantly reduce the overall attack rate as well as the overall population mortality. Several wastage scenarios were imposed on each of the CPIP policies in order to analyze the impacts of high antiviral use on the spread of the pandemic influenza. Table 1, illustrates that a significant reduction in the Canadian attack rate from 32% to 25.75% can be expected under the CPIP-1 policy for all wastage scenarios. The results indicated that the currently available stockpiles are not expected to be depleted retaining as much as 47.9% of the original NESS stockpile. The wastage from testing of NI drugs is not expected to have any effect on the attack rate, number of hospitalizations or even the number of deaths, as the current stockpile is sufficient when used for treatment purposes only.

The use of NI drugs for prophylaxis was also explored. Under CPIP-2 and CPIP-3, while the attack rates were found to fall under 25%, the results (Table 2 and Table 3) indicated that most of the stockpiles were fully depleted before the end of the pandemic, even when no wastage was considered. This was particularly true under the CPIP-3 policy (Table 3).

| CPIP-1 Results | No Intervention Case | CPIP-1, W0 | CPIP-1, W05 | CPIP-1, W10 | CPIP-1, W20 | CPIP-1, W30 |
|---|---|---|---|---|---|---|
| **Population Generally** | | | | | | |
| Number Infected | 10,547,096 | 8,483,679 | 8,483,679 | 8,483,679 | 8,483,679 | 8,483,679 |
| Attack Rate | 32.01% | 25.75% | 25.75% | 25.75% | 25.75% | 25.75% |
| Deaths | 16,523 | 9,976 | 9,976 | 9,976 | 9,976 | 9,976 |
| **Health Care Workers** | | | | | | |
| Number Infected | 88,219 | 69,516 | 69,516 | 69,516 | 69,516 | 69,516 |
| Attack Rate | 17.04% | 13.43% | 13.43% | 13.43% | 13.43% | 13.43% |
| Deaths | 33 | 20 | 20 | 20 | 20 | 20 |
| | | | | | | |
| **Stockpile Residual at End of Pandemic** | | | | | | |
| NESS | 100.00% | 63.01% | 60.71% | 58.33% | 53.31% | 47.86% |
| Group 1 NI Stockpile | 100.00% | 38.08% | 35.14% | 32.23% | 26.51% | 20.95% |
| Group 2 NI Stockpile | 100.00% | 50.11% | 47.66% | 45.21% | 40.34% | 35.50% |

**Table 1:** The results of the simulation run under CPIP-1 policy. The results clearly indicate that the current stockpiles will not be depleted during a potential pandemic. None of the current stockpiles had been expected to fall under 20% of its initial value by the end of the pandemic period.

Despite the result that the stockpiles run out under CPIP-2 and CPIP-3 policies when wastage is not considered, the results indicated that policies which include the TGAP recommendations can reduce the attack rate beyond that which can be expected when the current stockpiles are used for treatment only (CPIP-1). However, as the results indicate in Tables 3 and 4, such policies can no longer be justified if wastage is taken into account. When the stockpile is limited, the prophylactic use of NI drugs among closed contacts in closed facilities may exhaust the stockpile to a point at which effective treatment may no longer be possible. Under such circumstances, the overall attack rate may actually increase with respect to CPIP-1. The main reason for this result is that the use of NIs as prophylaxis is considerably more expensive in terms of the average number of doses required per patient during a pandemic than their use as treatment only. Instead of a single course for treatment, prophylactic use will in general require multiple courses after each potential high risk contact.

Results for simulations under the CPIP-2 and CPIP-3 policies (Table 2 and Table 3) indicate that the full potential of the antiviral policy could not be reached as a result of the full depletion of the current NI stockpiles. When considering wastage, the attack rates under CPIP-2 can be expected to increase from 24.5% (without wastage) to 25.98% (under a wastage scenario of 30%). Under CPIP-3, the attack rates can be expected to increase from 24.4% to 26.46%, resulting in an attack rate which is higher than either CPIP-1 or CPIP-2. Among health care workers, this effect was expected to be even more severe as attack rates increased from 4.23% to 6.22% and from 5.56% to 8.08% under the CPIP-2 and CPIP-3 policies respectively.

The full depletion of the NESS and Group 1 stockpiles occur generally at the same time for wastage scenarios greater than 10%. Although the stockpiles fully deplete near the end of the pandemic, the number of yet-to-be infected individuals that will not have the opportunity to use NI drugs ranges from 35,063 to 845,400, across the wastage scenarios.

| CPIP-2 Results | CPIP-2, W0 | CPIP-2, W05 | CPIP-2, W10 | CPIP-2, W20 | CPIP-2, W30 |
|---|---|---|---|---|---|
| **Population Generally** | | | | | |
| Number Infected | 8,082,204 | 8,142,356 | 8,213,510 | 8,382,846 | 8,557,619 |
| Attack Rate | 24.53% | 24.72% | 24.93% | 25.45% | 25.98% |
| Deaths | 9,464 | 9,626 | 9,830 | 10,316 | 10,823 |
| **Health Care Workers** | | | | | |
| Number Infected | 21,869 | 23,228 | 24,763 | 28,416 | 32,188 |
| Attack Rate | 4.23% | 4.49% | 4.78% | 5.49% | 6.22% |
| Deaths | 7 | 7 | 8 | 9 | 11 |
| | | | | | |
| **Pandemic Stage at Full Depletion** | | | | | |
| NESS | 99.58% | 97.85% | 94.43% | 90.19% | 85.84% |
| Group 1 NI Stockpile | 99.29% | 96.86% | 94.43% | 90.19% | 85.84% |
| Group 2 NI Stockpile | N/A | N/A | N/A | N/A | 96.86% |
| | | | | | |
| **Pandemic Days at Full Depletion** | | | | | |
| NESS | 192 | 156 | 136 | 124 | 116 |
| Group 1 NI Stockpile | 180 | 148 | 136 | 124 | 116 |
| Group 2 NI Stockpile | N/A | N/A | N/A | N/A | 148 |
| | | | | | |
| **Yet to be infected at Full Depletion** | | | | | |
| Group 1 | 35,063 | 156,216 | 279,649 | 502,604 | 741,025 |
| Group 2 | N/A | N/A | N/A | N/A | 104,375 |
| Total Yet to be infected | 35,063 | 156,216 | 279,649 | 502,604 | 845,400 |

**Table 2**: The results of the simulation run under CPIP-2 policy. The results indicate that, with the exception of the Ontario stockpiles, all of the current stockpiles had been expected to be depleted during a potential pandemic. Under a 30% wastage scenario, the results further indicated that all stockpiles can be expected to be fully depleted.

Unlike CPIP-2, the NESS and Group 1 stockpiles all fully deplete at 16.84% of the pandemic remaining under CPIP-3, which rises to 24.30% at the 30% wastage assumption. Moreover, the Group 2 stockpile depletes at a significantly faster rate as wastage is increased, with full depletion occurring at 21.46% of the pandemic remaining, under the 30% wastage assumption. The number of yet to be infected individuals that will not have the opportunity to use NI drugs ranges across the wastage scenarios from 876,000 to 2 million.

| CPIP-3 Results | CPIP-3, W0 | CPIP-3, W05 | CPIP-3, W10 | CPIP-3, W20 | CPIP-3, W30 |
|---|---|---|---|---|---|
| **Population Generally** | | | | | |
| Number Infected | 8,046,090 | 8,178,485 | 8,302,815 | 8,525,784 | 8,716,650 |
| Attack Rate | 24.42% | 24.83% | 25.20% | 25.88% | 26.46% |
| Deaths | 9,929 | 10,273 | 10,599 | 11,190 | 11,700 |
| **Health Care Workers** | | | | | |
| Number Infected | 28,793 | 31,293 | 33,660 | 37,985 | 41,798 |
| Attack Rate | 5.56% | 6.05% | 6.50% | 7.34% | 8.08% |
| Deaths | 9 | 10 | 11 | 13 | 15 |
| | | | | | |
| **Pandemic Stage at Full Depletion** | | | | | |
| NESS | 83.16% | 78.54% | 78.54% | 72.46% | 68.79% |
| Group 1 NI Stockpile | 83.16% | 83.16% | 83.16% | 78.54% | 75.70% |
| Group 2 NI Stockpile | 98.48% | 93.62% | 90.73% | 83.16% | 78.54% |
| | | | | | |
| **Pandemic Days at Full Depletion** | | | | | |
| NESS | 124 | 116 | 116 | 108 | 104 |
| Group 1 NI Stockpile | 124 | 124 | 124 | 116 | 112 |
| Group 2 NI Stockpile | 200 | 156 | 144 | 124 | 116 |
| | | | | | |
| **Yet to be infected at Full Depletion** | | | | | |
| Group 1 | 828,359 | 841,989 | 854,789 | 1,118,441 | 1,295,004 |
| Group 2 | 47,643 | 202,944 | 299,235 | 558,002 | 726,936 |
| Total Yet to be infected | 876,002 | 1,044,933 | 1,154,024 | 1,676,443 | 2,021,940 |

**Table 3**: The results of the simulation run under CPIP-3 policy. The results indicate that all of the current stockpiles had been expected to be depleted during a potential pandemic.

In the current model, the pandemic declaration threshold was assumed to be at 20 cumulative Canadian deaths. This marked the time at which the use of antiviral drugs, and therefore the use of the current stockpile, would be initiated. Under this start time, stockpiles were exhausted under CPIP-2 and CPIP-3 even when wastage was not taken into account.

An optimization was carried out to determine the optimal threshold under which the minimum attack rate can be achieved with the current stockpile. In the optimization, the initial start time (point at which NI treatment and prophylaxis) is varied as a function of the number of mortal cases. Under the CPIP-3 policy with wastage of 30%, the optimization revealed that a 25.9% attack rate is possible given a threshold of 750 cumulative mortalities (at approximately 4.3% of the total pandemic attack rate). This represents a 0.56% reduction in total attack rate from the previously assumed value of 20 mortalities (Table 3). The exercise had shown that the CPIP-3 policy under a 30% wastage assumption will always be inferior to CPIP-1 under the currently available stockpile.

Table 4, shows the results of a scenario in which a sufficient stockpile existed to accommodate the total NI demand and therefore realize the full potential of CPIP-2 and CPIP-3 policies. The results indicated that under such conditions, the overall attack rate can be expected to drop by an additional 0.9% and 2.68% under the CPIP-2 and CPIP-3 policies respectively. This would also lead to as many as 1,149 fewer deaths but would require as much as 42.50 million additional doses of NIs. This is nearly a 50% increase from the currently available stockpiles.

| Sufficient Stockpile Results | Reduction from CPIP-1 | | Extra Stockpile Needed (million doses) | | | | |
|---|---|---|---|---|---|---|---|
| | Attack Rate | Deaths | w=0 | w=0.05 | w=0.1 | w=0.2 | w=0.3 |
| CPIP-2 | -0.90% | -529 | 0.07 | 0.57 | 4.45 | 12.22 | 19.99 |
| CPIP-3 | -2.68% | -1,149 | 14.97 | 18.76 | 23.50 | 33.00 | 42.50 |

**Table 4**: The amount of stockpile which would be needed if CPIP-2 and CPIP-3 were to achieve their full potential.

## DISCUSSION

Despite the incremental creation of antiviral stockpiles, by some accounts, the role of prophylaxis during a pandemic remains uncertain. The TGAP report indicated that limited use of prophylaxis during a pandemic may have significant benefits in reduction of the overall attack rate and the availability of health resources. This study indicated that under the current stockpile, the use of NIs based on TGAP recommendations is meaningful only when potential wastage of the drugs remains low. However, when higher wastage scenarios are considered, the results indicate a significant risk that the current Canadian stockpile would not be sufficient to support a pandemic policy with the use of post-exposure prophylaxis. In general, most policies which include the use of prophylaxis involve the administration of multiple courses of drugs to individuals and would inevitably exhaust the current stockpiles of antivirals in Canada. Furthermore, this cannot be solved by changing the timing of administration of the NIs. Indeed, even when the administration of the drug is postponed until 4.3% of the pandemic has passed; the current stockpile cannot support the use prophylaxis under CPIP-2 and CPIP-3 policies. As expected, the results also reveal the superiority, (in terms of attack rates and death) of CPIP-2 and particularly CPIP-3 over CPIP-1 when sufficient stockpiles are made available within Canada. This would involve an approximately 50% increase to the current stockpile under the extreme case of CPIP-3 with wastage at 30%, which could reduce the attack rate by as much as 2.68%.

The inadequacy of the current assumed stockpile to support the TGAP recommendations results in the risk of running out of antiviral treatments and PEP during a moderate pandemic in Canada. Under CPIP-2 (30% wastage), this risk could be realized by up to 448,000 people being turned away when seeking NI drug treatment. Under CPIP-3 (30% wastage), this risk could be realized by up to 1.07 million people being turned away when seeking NI drug treatment. The identification of these risks should encourage a policy review of either the size of the current stockpile or more precise current stockpile use policies that mitigate against the expected full depletion of the current stockpile, or both.

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# APPENDIX A

List of key assumptions used to parameterize the mathematical model:

| Item | Assumptions |
|---|---|
| **Contact Types** | Close-contact interactions between individuals are considered. Individuals interact in mixing patterns of household, school, work and community based contacts. Contacts based on population based Multi-country (eight European countries) surveys across 15 age groups [7] had been adopted in the current model. |
| **Population Types** | Total 2010 population of 33,961,659. Model tracks general public, patients in closed facilities, HCW (Health Care Workers) and ESP (Emergency Service Providers) are considered. The proportions and age structure had been adopted from CIHI's 2006/07 surveys [12]. |
| **Probability of Virus Transmission** | The transmission probability is conditional upon contact with an infectious individual. The relative age group structure had been adopted based on 4 age groups (0-4, 5-18, 19-64, >65) [8]. The absolute transition probability had been obtained from the current calibration model under the constraint of a 33.4% attack rate. |
| **Attack Rate** | An overall 33.4% attack rate [11] was adopted based on the US data from the 1957/1958 Asian flu pandemic. The attack rate is consistent with the values adopted by most other studies (most prominently, the CPIP). |
| **Mortality Rate** | An age-dependant (U shaped) population morality is assumed based on the US data from the 1957/1958 Asian flu pandemic [8]. This corresponds to an approximate case specific mortality of around 0.17%. |
| **Average Latency** | 1.9 days. Incubation period is assumed to be equal to the Latent period. |
| **Average Infectious Period** | 3.1 days. Symptomatic cases are always assumed to be Infectious. |
| **Immunity (%)** | No prior population immunity to the virus is assumed within the current model. |
| **Travel and Migration** | The migration patterns are adopted from CANSIM 2006 survey [13] and are assumed to maintain Status Quo. No pandemic-based impacts upon the migration are assumed within the current model. Travel patterns are adopted from the 2004 Canadian Travel Survey and are likewise assumed to be maintained throughout the pandemic period. |
| **Antiviral use start date** | Antivirals used when cumulative confirmed deaths due to novel influenza A reaches 20 for Canada in total. |
| **Antiviral Resistance** | A 0.4% resistance to antiviral drug use (among adults) is assumed [1] |
| **Antiviral Administration** | Treatment administration rate is a function of the number of healthy HCW. If all HCW are healthy, mean time to administration is 1 day, if all HCW are sick; mean time to administration is 3.1 days (Average recovery time). |
| **Antiviral Efficacy** | Treatment is ineffective if administered more than 2 days after infectious stage begins, but given nonetheless. |
| **Antiviral Treatment** | 53% of people who are infectious will seek treatment [14] |
| **NESS Stockpile** | Distributed across regions according to number of people requiring treatment and administered at half the rate of local stockpile (to account for delays in NESS stockpile redistribution). |
| **HCW Contact and** | Health care workers have 1.92 more contacts than public (this corresponds to |

| | |
|---|---|
| **Infection Factor** | contact rate which are similar to those in retail industry). They are no more likely to get sick than the general public, so probability of infection is reduced by the same factor |
| **Post Exposure Prophylaxis Compliance** | Assumed 100% compliance. |
| **Relative Efficacy (Post-Exposure)** | The relative efficacy varies in studies between 68% [15] and 89% [3]. In the current model a average of 78.5% is assumed (midpoint between the results of the two studies). |
| **Efficacy for reducing pathogenicity** | The efficacy for reducing pathogenicity was assumed to be 56% (95% CI: 10,730) [4] |
| **Reduction in the duration of illness** | Anti-viral treatment was assumed to have a 25% reduction on the duration of illness (with oseltamivir 75 mg) [16] |

## APPENDIX B

The total Canadian population is divided into a number of mutually exclusives groups of individuals as:

$$P(t) = \sum_k \left\{ \sum_{r,a,g,j} \left\{ S_{rj}^{ag,k} + i_{rj}^{ag,k} + I_{rj}^{ag,k} + J_{rj}^{ag,k} + R_{rj}^{ag,k} \right\} \right\}$$

where the groups: $S_{rj}^{ag,k}$, $i_{rj}^{ag,k}$, $I_{rj}^{ag,k}$, $J_{rj}^{ag,k}$ and $R_{rj}^{ag,k}$ represent the susceptible, infected, early infectious, late infectious and recovered respectively. The indices $\{r,a,g,j\}$ represent the region, age, gender and occupation dimensions of the population respectively. The index $k \in \{U,E,F,L,FE,LE\}$ represents the possible types of treatment regimes such as untreated (U), given post-exposure (E), as well as fast treatment given with 48 hours of the onset of symptoms (F) and late treatment (L) administered after 48 hours. For the variables $S_{rj}^{ag,k}$ and $i_{rj}^{ag,k}$, the index $k$ ranges over only the types $\{U,E\}$. The late infectious category, $J$, was assumed to contain those individuals who had exhibited symptoms of the disease for at least 48 hours while the early infectious, $I$, are those who have had symptoms for less time.

The equations describing the evolution of the susceptible and the infected individuals are:

$$\frac{dS_{rj}^{ag,U}}{dt} = \underbrace{-f_r\beta_{rj}S_{rj}^{ag,U}\sum_{b,t}C_j^{ab}\rho_j^{ab,E}\eta^t F_r^{abg,t}}_{\text{became infected, given post-exposure}} \underbrace{-(1-f_r\beta_{rj})S_{rj}^{ag,U}\sum_{b,t}C_j^{ab}\rho_j^{ab,U}\eta^t F_r^{abg,t}}_{\text{became infected, not given earlier post-exposure}}$$
$$\underbrace{-f_r\beta_{rj}S_{rj}^{ag,U}\sum_{b,t}C_j^{ab}F_r^{abg,t}(1-\eta^t\rho_j^{ab,E})}_{\text{not infected, given post-exposure}} + \underbrace{\lambda_{E\to U}S_{rj}^{ag,E}}_{\text{Expiration of post-exposure}}$$

$$\frac{dS_{rj}^{ag,E}}{dt} = \underbrace{-S_{rj}^{ag,E}\sum_{b,t}C_j^{ab}\rho_j^{ab,E}\eta^t F_r^{abg,t}}_{\text{became infected, given post-exposure}} + \underbrace{f_r\beta_{rj}S_{rj}^{ag,U}\sum_{b,t}C_j^{ab}F_r^{abg,t}(1-\rho_j^{ab,E}\eta^t)}_{\text{not infected, given post-exposure}}$$
$$-\underbrace{\lambda_{E\to U}S_{rj}^{ag,E}}_{\text{Expiration of post-exposure}}$$

$$\left.\frac{di_{rj}^{ag,U}}{dt}\right|_{\text{infection}} = \underbrace{(1-f_r\beta_{rj})S_{rj}^{ag,U}\sum_{b,t}C_j^{ab}\rho_j^{ab,U}\eta^t F_r^{abg,t}}_{\text{became infected, not given post-exposure}}$$

$$\left.\frac{di_{rj}^{ag,E}}{dt}\right|_{\text{infection}} = \underbrace{f_r\beta_{rj}S_{rj}^{ag,U}\sum_{b,t}C_j^{ab}\rho_j^{ab,E}\eta^t F_r^{abg,t}}_{\text{became infected, given post-exposure}} + \underbrace{S_{rj}^{ag,E}\sum_{b,t}C_j^{ab}\rho_j^{ab,E}\eta^t F_r^{abg,t}}_{\text{became infected, given earlier post-exposure}}$$

where $t$ ranges over the states $\{1,2\}\times\{U,E,F,L,LE,FE\}$ where 1 corresponds to early infectious and 2 corresponds to late infectious.

In the above equations, the treatment rate factor $f_r$ moderates the rate at which prophylaxis can be obtained by those who require it. The infectious fraction $F_r^{abg,t}$ is proportional to the effective population of infectious people with antiviral state $t$ and age $b$ who might be contacted by a susceptible person with age $a$ and gender $g$ from region $r$. The fraction represents the effective number of infectious individuals who can be found in region $r$ once travel is taken into account (see later discussion on travel matrix). The parameter $\beta$ represents the fraction of susceptible individuals who are eligible for antivirals while the parameter $\eta$ indicates the relative infectiousness of individuals under any of the treatments. The contact matrix and the probability of infection given contact are represented by $C_j^{ab}$ and $\rho_j^{ab}$ respectively. The probability of infection given contact is reduced for a susceptible person on post-exposure prophylaxis.

The differential equations are built from the basic quantity

$$S_{rj}^{ag,U}\sum_{b,t}C_j^{ab}F_r^{abg,t}$$

which is the rate at which susceptible persons contact the infectious. The rate at which *protected* susceptible persons contact the infectious is

$$f_r\beta_{rj}S_{rj}^{ag,U}\sum_{b,t}C_j^{ab}F_r^{abg,t}$$

This flow is split according to whether infection occurs or not. The rate at which *unprotected* susceptible persons contact the infectious is the balance

$$\left(1-f_r\beta_{rj}\right)S_{rj}^{ag,U}\sum_{b,t}C_j^{ab}F_r^{abg,t}$$

a fraction of which proceed to infected.

In what follows, the quantity

$$\beta_{rj}S_{rj}^{ag,U}\sum_{b,t}C_j^{ab}F_r^{abg,t}$$

is interpreted as the rate at which eligible susceptible persons contact the infectious, and hence seek prophylaxis. This rate is split by the factor $f_r$ into those who actually obtain prophylaxis and those who do not.

The fraction of susceptible individuals who are eligible for NI drugs is defined by

$$\beta_{rj} = \frac{S_{rj}^{U}\,|_{eligible}}{S_{rj}^{U}}$$

where

$$S_{rj}^{U} = \sum_{ag} S_{rj}^{ag,U}$$

Differentiating yields

$$\frac{d\beta_{rj}}{dt} = \frac{1}{S_{rj}^{U}}\left(\frac{dS_{rj}^{U}\,|_{eligible}}{dt} - \beta_{rj}\frac{dS_{rj}^{U}}{dt}\right)$$

However,

$$\frac{dS_{rj}^{ag,U}\,|_{eligible}}{dt} = \underbrace{-f_r\beta_{rj}S_{rj}^{ag,U}\sum_{b,t}C_j^{ab}\rho_j^{ab,E}\eta^t F_r^{abg,t}}_{\text{became infected, given post-exposure}} \underbrace{-f_r\beta_{rj}S_{rj}^{ag,U}\sum_{b,t}C_j^{ab}F_r^{abg,t}(1-\rho_j^{ab,E}\eta^t)}_{\text{not infected, given earlier post-exposure}}$$
$$\underbrace{-(1-f_r)\beta_{rj}S_{rj}^{ag,U}\sum_{b,t}C_j^{ab}F_r^{abg,t}\eta^t\rho_j^{ab,U}}_{\text{became infected, not given post-exposure}} + \underbrace{\lambda_{E\to U}S_{rj}^{ag,E}}_{\text{Expiration of post-exposure}}$$

The differential equation for maintaining b is now complete. Its initial value depends upon the scenario under consideration.

The post-exposure treatment rate *f* must be a function of the available stockpile. Let $T_r$ be the available number of doses available in region *r*, and let $t_r$ be the mean waiting time for post-exposure intervention.

The post-exposure consumption rate is given by:

$$f_r = \min\left(\frac{T_r/\tau_r}{\sum_{j,a,g}\beta_{rj}\left(S_{rj}^{ag,U}\sum_{b,t}C_j^{ab}F_r^{abg,t}\right)},1\right)$$

The denominator is the total rate at which eligible susceptible persons contact the infectious, and hence seek prophylaxis. The numerator is the rate at which prophylaxis can be administered. With abundant stockpiles *f* is 1 while *f*=0 when the stockpile is empty.

The remainder of the differential equations govern the evolution of the infectious and recovered state (in addition to death) under the various combinations of NI drug applications. The equations are:

$$\frac{di_{rj}^{ag,X}}{dt} = \left.\frac{di_{rj}^{ag,X}}{dt}\right|_{\text{infection}} - \lambda_{i\to I} i_{rj}^{ag,X}$$

$$\frac{dI_{rj}^{ag,Y}}{dt} = 0$$

$$\frac{dI_{rj}^{ag,X}}{dt} = \lambda_{i\to I} i_{rj}^{ag,X} - \underbrace{\lambda_{I\to J} I_{rj}^{ag,X}}_{\text{Aging of Untreated}} - \underbrace{\lambda_{I\to R}^{X} I_{rj}^{ag,X}}_{\text{Recovery}} - \underbrace{\lambda_{I\to D}^{X} I_{rj}^{ag,X}}_{\text{Death}} - \underbrace{\gamma_r^{U\to F}\xi_r^{X} I_{rj}^{ag,X}}_{\text{Fast Treatment}}$$

$$\frac{dI_{rj}^{ag,Z}}{dt} = -\underbrace{\lambda_{I\to J} I_{rj}^{ag,Z}}_{\text{Aging of Treated}} - \underbrace{\lambda_{I\to R}^{Z} I_{rj}^{ag,Z}}_{\text{Recovery}} - \underbrace{\lambda_{I\to D}^{Z} I_{rj}^{ag,Z}}_{\text{Death}} + \underbrace{\gamma_r^{U\to F}\xi_r^{X(Z)} I_{rj}^{ag,X(Z)}}_{\text{Fast Treatment}}$$

$$\frac{dJ_{rj}^{ag,X}}{dt} = \underbrace{\lambda_{I\to J} I_{rj}^{ag,X}}_{\text{Aging of Untreated}} - \underbrace{\lambda_{J\to R}^{X} J_{rj}^{ag,X}}_{\text{Recovery}} - \underbrace{\lambda_{J\to D}^{X} J_{rj}^{ag,X}}_{\text{Death}} - \underbrace{\gamma_r^{U\to L}\xi_r^{X} J_{rj}^{ag,X}}_{\text{Late Treatment}}$$

$$\frac{dJ_{rj}^{ag,Y}}{dt} = -\underbrace{\lambda_{J\to R}^{Y} J_{rj}^{ag,Y}}_{\text{Recovery}} - \underbrace{\lambda_{J\to D}^{Y} J_{rj}^{ag,Y}}_{\text{Death}} + \underbrace{\gamma_r^{U\to L}\xi_r^{X(Y)} J_{rj}^{ag,X(Y)}}_{\text{Late Treatment}}$$

$$\frac{dJ_{rj}^{ag,Z}}{dt} = \underbrace{\lambda_{I\to J} I_{rj}^{ag,Z}}_{\text{Aging of Treated}} - \underbrace{\lambda_{J\to R}^{Z} J_{rj}^{ag,Z}}_{\text{Recovery}} - \underbrace{\lambda_{J\to D}^{Z} J_{rj}^{ag,Z}}_{\text{Death}}$$

Where $X \in \{U, E\}$, $Y \in \{L, LE\}$ and $Z \in \{F, FE\}$.

And where $X(W) = \begin{cases} U, & W \in \{F, L\} \\ E, & W \in \{FE, FL\} \end{cases}$

For each treatment state *t*, we get:

For each $k \in \{U, E, F, L, LE, FE\}$

$$\frac{dR_{rj}^{ag,k}}{dt} = \underbrace{\lambda_{I\to R}^{k} I_{rj}^{ag,k} + \lambda_{J\to R}^{k} J_{rj}^{ag,k}}_{\text{Recovery}}$$

$$\frac{dD_{rj}^{ag,k}}{dt} = \underbrace{\lambda_{I\to D}^{k} I_{rj}^{ag,k} + \lambda_{J\to D}^{k} J_{rj}^{ag,k}}_{\text{Death}}$$

If one is not interested in how a person reaches the recovered state, the health state index can be summed over to give

$$\frac{dR_{rj}^{ag}}{dt} = \sum_{k} \underbrace{\lambda_{I\to R}^{k} I_{rj}^{ag,k} + \lambda_{J\to R}^{k} J_{rj}^{ag,k}}_{\text{Recovery}}$$

Define

$$I_r^X = \sum_{agj} I_{rj}^{ag,X}$$

$$J_r^X = \sum_{agj} J_{rj}^{ag,X}$$

$$i_r^X = \sum_{agj} i_{rj}^{ag,X}$$

Let $\xi_r^X$ represent the fraction of individuals in region r with therapy state *X* (where *X* is *U* or *E* as above) who are willing to receive treatment:

$$\xi_r^X = \frac{I_r^{X,treatable} + J_r^{X,treatable}}{I_r^X + J_r^X}$$

Therefore,

$$\frac{d\xi_r^X}{dt} = \frac{1}{I_r^X + J_r^X}\left(\frac{d\left(I_r^{X,treatable} + J_r^{X,treatable}\right)}{dt} - \xi_r^X \frac{d\left(I_r^X + J_r^X\right)}{dt}\right)$$

If one assumes

$$\lambda_{I\to R}^X = \lambda_{J\to R}^X$$

$$\lambda_{I\to D}^X = \lambda_{J\to D}^X$$

$$\gamma_r^{U\to F} = \gamma_r^{U\to L} = \gamma_r$$

and by summing the differential equations for *I* and *J*, one gets:

$$\frac{d\left(I_r^X + J_r^X\right)}{dt} = \lambda_{i\to I} i_r^X - \underbrace{\lambda_{I\to R}^X\left(I_r^X + J_r^X\right)}_{\text{Recovery}} - \underbrace{\lambda_{I\to D}^X\left(I_r^X + J_r^X\right)}_{\text{Death}} - \underbrace{\xi_r^X \gamma_r\left(I_r^X + J_r^X\right)}_{\text{Treatment}}$$

$$\frac{d\xi_r^X}{dt} = \frac{\left(\xi_r^X(t_0) - \xi_r^X\right)\lambda_{i\to I} i_r^X}{I_r^X + J_r^X} - \xi_r^X(1-\xi_r^X)\gamma_r$$

To derive the second of these equations from the first, decompose the first into two equations:

$$\frac{d\left(\xi_r^X\left(I_r^X+J_r^X\right)\right)}{dt}=\xi_r^X(t_0)\lambda_{i\to I}i_r^X-\underbrace{\lambda_{I\to R}^X\xi_r^X\left(I_r^X+J_r^X\right)}_{\text{Recovery}}-\underbrace{\lambda_{I\to D}^X\xi_r^X\left(I_r^X+J_r^X\right)}_{\text{Death}}-\underbrace{\xi_r^X\gamma_r\left(I_r^X+J_r^X\right)}_{\text{Treatment}}$$

$$\frac{d\left((1-\xi_r^X)\left(I_r^X+J_r^X\right)\right)}{dt}=\left(1-\xi_r^X(t_0)\right)\lambda_{i\to I}i_r^X-\underbrace{\lambda_{I\to R}^X\left(1-\xi_r^X\right)\left(I_r^X+J_r^X\right)}_{\text{Recovery}}-\underbrace{\lambda_{I\to D}^X\left(1-\xi_r^X\right)\left(I_r^X+J_r^X\right)}_{\text{Death}}-\underbrace{0}_{\text{Treatment}}$$

where $\xi_r^X(t_0)$ is defined as the fraction of the newly infectious that are treatable, the recovery and death rates are the same in both equations, and the change due to treatment is concentrated in the first. Then calculate

$$\frac{d\xi_r^X}{dt}=\frac{1}{I_r^X+J_r^X}\left(\frac{d\left(\xi_r^X\left(I_r^X+J_r^X\right)\right)}{dt}-\xi_r^X\frac{d\left(I_r^X+J_r^X\right)}{dt}\right)$$

**Treatment Rates**

The rate at which people can receive treatment will depend upon the amount of antivirals available and the overall health of the health care system. If a significant portion of the health care workers are ill and unable to perform their duties, the rate at which people can be diagnosed and treated will be reduced. Let $P_r^{\text{CCW}}$ be the population of health care workers and let $H_r$ be the healthy health care workers.

$$P_r^{\text{CCW}}=\left[\sum_{ag}\left(\sum_{k\in\{U,E\}}\left(S_{rj}^{agk}+i_{rj}^{agk}\right)+\sum_{k\in\{U,E,F,L,FE,LE\}}\left(I_{rj}^{agk}+J_{rj}^{agk}+R_{rj}^{agk}\right)\right)\right]_{j=\text{CCW}}$$

$$H_r=\left[\sum_{ag}\left(\sum_{k\in\{U,E\}}\left(S_{rj}^{agk}+i_{rj}^{agk}\right)+\sum_{k\in\{U,E,F,L,FE,LE\}}R_{rj}^{agk}\right)\right]_{j=\text{CCW}}$$

The mean time to wait for treatment depends upon the maximum and minimum wait times, and the fraction of healthy close contact workers.

$$\tau_r^{\text{treatment}}=\frac{H_r}{P_r^{CCW}}\tau^{\min}+\left(1-\frac{H_r}{P_r^{CCW}}\right)\tau^{\max}$$

The total number of people to treat is:

$$W_r=\sum_{agj}\sum_{k\in\{U,E\}}\xi_r^k\left(I_{rj}^{ag,k}+J_{rj}^{ag,k}\right)$$

Let $T_r$ be the available stockpile. One bound on the treatment rate $\gamma_r$ is given by

$$-\left.\frac{dW_r}{dt}\right|_{\text{treatment}} = \gamma_r W_r \le \frac{1}{\tau_r^{\text{treatment}}} \min\left(W_r, T_r\right)$$

Therefore $\gamma_r \le \frac{f_r^{\text{treatment}}}{\tau_r^{\text{treatment}}}$ where $f_r^{\text{treatment}} = \frac{\min(W_r, T_r)}{W_r}$

For another upper bound, let $s^{\max}$ be the maximum number of treatments per day a close contact worker can administrate. Then the maximum administration rate is $a_r^{\max} = s^{\max} P_r^{CCW}$ so

$$-\left.\frac{dW_r}{dt}\right|_{\text{treatment}} = \gamma_r W_r \le a_r^{\max}$$

and $\gamma_r \le \frac{a_r^{\max}}{W_r}$. The treatment rate is then:

$$\gamma_r^{U\to F} = \gamma_r^{U\to L} = \gamma_r = \min\left(\frac{f_r^{\text{treatment}}}{\tau_r^{\text{treatment}}}, \frac{a_r^{\max}}{W_r}\right)$$

**Transition rates**

The base rates for untreated individuals are taken from various studies (Appendix A) assumed to be $\lambda_{i\to I}^{-1} = 1.9\,\text{days}$, $\lambda_{I\to R}^{U\ -1} = 3.1\,\text{days}$. We assumed that:

- The parameters $\lambda_{I\to\theta}^{U} = \lambda_{J\to\theta}^{U}$ (with $\theta = \{R, D\}$ as required for consistency of the equations.
- Post-exposure prophylaxis use does not affect the recovery times for those who are infected. As a result, for any health state $x$ and $y$ we imposed the conditions that: $\lambda_{x\to y}^{FE} = \lambda_{x\to y}^{F}$ and $\lambda_{x\to y}^{LE} = \lambda_{x\to y}^{L}$
- The treatment is ineffective for late-treatment and therefore: $\lambda_{J\to R}^{L} = \lambda_{I\to R}^{U}$
- Under the assumption that "fast" treatment reduced recovery time by $\beta_R$ and that the fraction of individuals for whom the treatment does not work is $r$, we obtain:

$$\lambda_{I\to R}^{F} = \lambda_{I\to R}^{U} \frac{1 - r\beta_R}{1 - \beta_R}$$

**Inter-region Travel**

The effective infectious population in region *r* can be defined as:

$$I_i^{Eff} = \sum_i \xi_{ij} I_j$$

where the normalized travel matrix $\xi_{ij}$ is defined to be the fraction of the population of region $i$ expected to be visiting region $j$ at any time. The diagonal term $\xi_{ii}$ represents the fraction of the population in region $i$ expected to be found at home and so the travel matrix is chosen such that $\sum_{j=1}^{37} \xi_{ij} = 1$ for all choices of region $i$. Each component of the 37x37 travel matrix is calculated from the number and average duration of person-visits from region i to region j based on data from the 2004 Canadian Travel Survey. The rates of change of the various subsets of the susceptible population $S_i$ at home or visiting all contribute to the rate of change of the $S_i$ as a whole. Susceptible individuals who are visiting region $j$ find the probability that a given contact is with an infectious person to be based on the populations there.

In general the travel patterns depend upon age and gender, so there is actually a travel matrix for each age-group, *a*, and gender, *g*.

$$\sum_{j=1}^{37} \xi_{ij}^{ag} = 1$$

The infectious fraction $F_r^{abg,t}$ is computed from the normalized travel matrix as follows. Let $I_i^{bhk}$ and $J_i^{bhk}$ be the infectious populations with age $b$, gender $h$ and therapy $k$ that ordinarily reside in region $i$ obtained by summing over occupation.

$$I_i^{bhk} = \sum_j I_{ij}^{bhk}$$
$$J_i^{bhk} = \sum_j J_{ij}^{bhk}$$

Let $P_i^{bh}$ be the whole population with age $b$ and gender $h$ that ordinarily resides in region $i$.

$$P_i^{bh} = \sum_j \left( \sum_{k \in \{U,E\}} \left( S_{ij}^{bhk} + i_{ij}^{bhk} \right) + \sum_{k \in \{U,E,F,L,FE,LE\}} \left( I_{ij}^{bhk} + J_{ij}^{bhk} + R_{ij}^{bhk} \right) \right)$$

Let $I_{bdk}^{\mathrm{Eff}}$, $J_{bdk}^{\mathrm{Eff}}$ and $P_{bd}^{\mathrm{Eff}}$ be the populations with age $b$ that are actually present in region $d$. These are obtained by summing over the visiting populations from regions $i \neq d$ together with the population in region $i = d$ not travelling, and then summing over gender.

$$I_{bdk}^{\text{Eff}} = \sum_h \sum_i \xi_{id}^{bh} I_i^{bhk}$$
$$J_{bdk}^{\text{Eff}} = \sum_h \sum_i \xi_{id}^{bh} J_i^{bhk}$$
$$P_{bd}^{\text{Eff}} = \sum_h \sum_i \xi_{id}^{bh} P_i^{bh}$$

Let $\varphi_d^{bt}$ be the fraction of the population age $b$ actually present in region $d$ that has state $t \in \{1,2\} \times \{U, E, F, L, LE, FE\}$.

$$\varphi_d^{bt} = \varphi_d^{b(m,k)} = \begin{cases} I_{bdk}^{\text{Eff}} \Big/ P_{bd}^{\text{Eff}} & , m = 1 \\ J_{bdk}^{\text{Eff}} \Big/ P_{bd}^{\text{Eff}} & , m = 2 \end{cases}$$

Let Pat be a person with age $a$ and gender $g$ who ordinarily lives in region $r$. The infectious fraction $F_r^{abg,t}$ is the fraction of the population age $b$ contactable by Pat that is expected to be in state $t$. It is obtained by taking a weighted average over the places where Pat might actually be, including the possibility that Pat is at home.

$$F_r^{abg,t} = \sum_d \xi_{rd}^{ag} \varphi_d^{bt}$$

**Stockpile Consumption and Wastage**

Consumption of the stockpile is given by

$$\frac{dT_r}{dt} = -\Phi \left\{ f_r \sum_{agj} \beta_{rj} S_{rj}^{ag,U} \sum_{b,t} C_j^{ab} F_r^{abg,t} + \gamma_r \sum_{agj} \sum_{k \in \{U,E\}} \xi_r^k \left( I_{rj}^{ag,k} + J_{rj}^{ag,k} \right) \right\}$$

where the first term is consumption due to prophylaxis, the second term is consumption due to treatment, and the factor $\Phi \in \{1.00, 1.05, 1.10, 1.20, 1.30\}$ depending on the wastage scenario. The cause of the wastage is not considered in this study.