# Contrast of Prophylactically Protecting Canadian Health Care Workers and Emergency Service Providers:

## A Moderate Canadian Pandemic Mathematical Assessment

**May 2009**


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RiskAnalytica is a mathematical modeling group that conducts population based assessments of health policy interventions designed to reduce the burden of disease events. This report and the analysis it contains was prepared independently by RiskAnalytica at the request of Hoffmann-La Roche Canada Limited (Roche). At no time during the course of this analysis had Roche sought to influence the results or the way in which the results were reported.

**Acknowledgements**

This report and the analysis it contains was prepared by RiskAnalytica using its Life at Risk® simulation platform. The authors wish to thank the members of RiskAnalytica's Infectious Disease Advisory Board for their advice, direction and review of the infectious disease model development process. Infectious Disease Advisory Board members include: Dr. Mark Loeb (Professor, Department of Pathology and Molecular Medicine, McMaster University); Dr. Alison McGeer (Director Infection Control, Department of Microbiology, Mount Sinai Hospital); Dr. Neil Simonsen (Canadian Science Centre for Human and Animal Health National Microbiology Laboratory).

The authors wish to also thank the members of the independent Pandemic Advisory Board for their advice and direction during the performance of this study. Pandemic Advisory Board members include: Dr. Daniel Kollek (Executive Director, Centre for Excellence in Emergency Preparedness); Dr. Andrew Travers (Provincial Medical Director, Nova Scotia); Pat McKernan (Director of Risk Management & Quality Improvement, St. Michael's Hospital); Kevin Hummel (Director, Ontario Provincial Police Association); Jim Lee (Assistant to the General President, Canadian Operations, International Association of Fire Fighters); and John Iverson (British Columbia Professional Fire Fighters Association).

**Citation**

Smetanin, Paul; Kobak, Paul; Stiff, David; Sherman, Glen; Briante, Carla (2009). Contrast of Prophylactically Protecting Canadian Health Care Workers and Emergency Service Providers: A Moderate Canadian Pandemic Mathematical Assessment. May 2009.

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# Abstract

**BACKGROUND:** The spread of the avian strain of H5N1 influenza and the current worldwide outbreak of influenza A (H1N1) highlights an urgent need for preparedness and coordinated health system strategies to effectively combat a potential influenza pandemic. Canada acknowledges the benefits of antivirals (both therapeutically and prophylactically) in reducing the impact of a pandemic. A Canadian Pandemic Influenza Plan (CPIP) exists and Canadian governments have stockpiled antivirals. The use of antivirals as treatment and prophylaxis within the CPIP Annex E are based on the recommendations put forth by the Task Group on Antiviral Prophylaxis (TGAP). The strategy does not recommend use of antiviral prophylaxis for emergency service providers and limited post exposure prophylaxis for health care workers.

**OBJECTIVE:** The purpose of this study was to contrast different antiviral policy scenarios under the conditions of a first wave of a moderate pandemic, with the assumption that an additional antiviral stockpile is used as prophylaxis for all Canadian health care workers (HCWs) and emergency service providers (ESPs).

**METHODS:** A deterministic mathematical model of the transmission dynamics of influenza was used to track the Canadian population during an assumed moderate pandemic. The Canadian population was stratified into thirty seven non-overlapping geographical regions, age and gender groups. The population was further subdivided into risk of infection, risk of mortality given infection, epidemiological states (e.g., susceptible, exposed, infectious, recovered) and economic states (e.g. employed, unemployed, non labour force participating, age dependent wage, absenteeism profiles). The model was parameterized using available Canadian data as well as key estimates from available literature on United States and Canadian data from the 1957/58 pandemic. The model was run under current Canadian policy based on two interpretations of the TGAP recommendations as well as a policy in which antiviral drugs were used for treatment only. Subsequently, a series of nine additional simulations were conducted under modified antiviral use policies in which HCWs and ESPs were to receive antiviral drugs as pre and post exposure prophylaxis. The nine policies were to be adopted under the inherent assumption that an additional stockpile was to be purchased in order to satisfy each simulation. The burden associated with an infectious disease pandemic as well as the benefits due to the implementation of various antiviral use scenarios were assessed with respect to eight contrast measures: (1) reduced population deaths; (2) reduced hospitalizations; (3) reduced general practitioner visits; (4) HCW reduced deaths; (5) ESP reduced deaths; (6) HCW reduced absences; (7) ESP reduced absences; (8) net present value added from the intervention.

**RESULTS:** While there are significant life and economic benefits associated with the use of the current Canadian stockpile, the current model indicated that it is insufficient to support the Canadian population under the current TGAP recommendations. Depending upon the TGAP interpretation in use, the model indicated that the current stockpile begins to run out prior to the passing of the first wave of the pandemic.

When compared against all combinations of the contrast measures, all additional stockpile scenarios outperformed the respective TGAP interpretations. Those that involved the purchase of additional stockpiles for either an 84 day pre-exposure prophylaxis for HCWs and ESPs or post-exposure prophylaxis for HCWs and ESPs ranked the highest. These scenarios would require the purchase of 51 to 83 million additional doses of antivirals. Measured against a current stockpile utilization of treatment only, for HCW and ESP populations, such an investment would incrementally reduce infections by 51-61%, reduce deaths by 40-48%, reduce expected peak absenteeism by 57,600 - 59,704; and provide an incremental net present value gain for society in the range of $421-$521 million.

**CONCLUSION:** Under the assumptions, the results of this study suggest that the purchase of an additional antiviral stockpile for the purposes of either an 84 day pre-exposure prophylaxis or post-exposure prophylaxis for all HCWs and ESPs is a worthwhile investment. Either investment represents a risk reduction strategy that would increase the protection of health care workers and emergency service providers with complementary benefits for the population as a whole (less infections, deaths, hospitalizations and general practitioner visits).

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# EXECUTIVE SUMMARY

## BACKGROUND

The spread of the avian strain of H5N1 influenza and the current worldwide outbreak of influenza A (H1N1) has heightened the urgency for development of coordinated health system strategies and preparedness to effectively combat a potential influenza pandemic in Canada. A pandemic is an unpredictable event both in terms of its virulence (severity) and timing. Pandemic influenza occurs when a new influenza A strain, for which humans have no immunity, spreads throughout a large population. A moderate pandemic in Canada, characteristic of the Asian influenza pandemic that occurred in 1957/58 has the potential to:

- Infect over 11 million Canadians with mortality of over 16,800;
- Increase hospitalizations by over 66,900;
- Increase general practitioner visits by over 5.39 million;
- Increase the absenteeism of health care workers and emergency service providers to 25% at the peak of the pandemic; and
- Impact societal economic wealth by over $11.9 billion[1].

As a result of a pandemic's capricious nature, and the short time period between the evolution of a pandemic virus and an outbreak, an effective vaccine for the particular pandemic influenza is generally expected not be available until the emergence of a second wave of the pandemic[2]. Technical constraints on vaccine production—foremost among these being the time required to initiate mass vaccine production during a pandemic—will limit the effectiveness of this measure in the first stages of the pandemic[3]. In this context, antiviral drugs are expected to play a major role both in prevention and in treatment[4]. Between the first and second waves of a pandemic, antiviral drugs are generally expected to provide an effective intervention for the reduction of the risk of transmission, the spread of the disease and diminished severity of secondary complications. Furthermore, antivirals are expected to be 68-91% effective as prophylaxis and shorten the duration of the infectious period by 1-1.5 days when used for treatment[5 6 7 8 9].

In the face of a Pandemic announcement, the global demand and consequent availability of antiviral drugs is expected to present a key challenge. When considering such a large scale, long term, continuous prophylactic treatment, insufficient supplies and limited manufacturing ability could introduce further supply difficulties[10]. Given the lengthy lead times required for antiviral processing and production, industry manufacturers are unable to guarantee antiviral supply required to meet the demand once a pandemic hits. As a result, industry as well as public health officials and the World Health Organization recommend that governments stockpile in advance, a sufficient amount of antiviral drugs to reduce the health and economic consequences of a pandemic.

Canada acknowledges the benefits of antivirals (both therapeutically and prophylactically) in reducing the impact of a pandemic. A Canadian Pandemic Influenza Preparedness Plan (CPIP) exists at the national level along with

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[1] Sum of impacts due to health care costs, wages and corporate profits.
[2] Canadian Pandemic Plan (2006)
[3] Laver, G., Garman, E. (2001)The origin and control of pandemic influenza. Science. 293: 1776-7
[4] Balicer, R., Huerta, M. & Grotto, I. (2004) Tackling the next influenza pandemic. British Medical Journal. 328, 1391-1392.
[5] Cooper, N., Sutton, A., Abrams, K., Wailoo, A., Tuner, D. & Nicholson, K. (2003) Effectiveness of Neuraminidase Inhibitors in Treatment and Prevention of Influenza A and B: Systematic Review and Metanalyses of Randomised controlled trials. British Medical Journal. 326, 1235-1241.
[6] Monto, A. (2003) The role of Antivirals in the control of influenza. Vaccine, 21, 1796-1800.
[7] Longini, I.M., Halloran, M., Nizam, A. & Yang, Y. (2004) Containing pandemic influenza with antiviral agents. American Journal of Epidemiology., 159, 623-633
[8] Hayden, F. (2001) Perspectives on antiviral use during pandemic influenza. Philos. Trans. R. Soc. Lond. B, 356, 1877-1884.
[9] World health Organization (2004) WHO guidelines on the use of Vaccines and Antivirals during influenza Pandemics. Available at: http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_RMD_2004_8/en. Accessed April 15, 2009.
[10] Balicer, R., Huerta, M. & Grotto, I. (2004) Tackling the next influenza pandemic. British Medical Journal. 328, 1391-1392.

stockpiles of antivirals at secondary/other levels of government. The current Canadian antiviral stockpile is composed of a National Antiviral Stockpile (NAS), a National Emergency Stockpile System (NESS) and an Ontario Stockpile. These stockpiles sum 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. The purpose of the NESS as an emergency backup stockpile is to ensure an increased response and surge capacity to manage an influenza pandemic. Ontario has an additional stockpile that is reported to be sufficient to provide antivirals for 25% of its population in conjunction with the distribution of its share of the NAS.

It is generally accepted that antivirals can be used in the following three ways:

**Pre-Exposure or Outbreak Prophylaxis:** Prophylaxis against the influenza virus prior to exposure in order to prevent the virus from being contracted. The relative efficacy of pre-exposure prophylaxis ranges from 74% to 91% [11]. It is important to note that there is no consensus within the literature on the appropriate timing and duration of pre-exposure prophylaxis. The length of pre-exposure prophylaxis deemed appropriate ranges from 42 days[12] to 84 days[13].

**Post-Exposure Prophylaxis:** Prophylaxis beginning immediately after exposure to the influenza virus in order to prevent or reduce symptoms, secondary complications and mortality. The relative efficacy of post-exposure prophylaxis ranges from 68% to 89%[14] [15].

**Treatment:** Treatment beginning within 48 hours of symptom onset to reduce the duration and severity of the symptoms and secondary complications. Antivirals have been shown to reduce hospitalizations by 59%[16] and patient recovery time by 25% to 30%[17]

The use of antivirals as treatment and prophylaxis within the Canadian pandemic strategy are based on the recommendations put forth by the Task Group on Antiviral Prophylaxis (TGAP) [18] that were recently incorporated as Annex E. The current Canadian policy and National Guidelines put forth by TGAP recommend that antivirals are used as follows:

- Antivirals for pre-exposure prophylaxis should not be stockpiled by governments during early pandemic alert and pandemic phases;
- During pandemic early alert phases, early treatment of cases and post-exposure prophylaxis of close contacts with a novel virus infection should be offered;
- During a pandemic:
    - Cases of pandemic influenza should have access to early treatment during a pandemic;
    - Critical infrastructure workers should have rapid access to antivirals for early treatment to minimize social disruption;
    - Antivirals should be available for the control of laboratory-confirmed influenza outbreaks in closed health care facilities and other closed facilities where high-risk populations reside.[19]

[11] Hayden F., Perspectives on AV use during pandemic influenza. Phil Trans R Soc London 2001; 356:1877-84
[12] Roche clinical safety data for Oseltamivir
[13] US Department of Health and Social Services
[14] PAN-Canadian Public Health Network Council Report and Policy Recommendations on the use of Antivirals for Prophylaxis during an Influenza pandemic, June 2007.
[15] Holloran E., Hayden F., Yang Y., Longini I., Monto A., Antiviral effects on influenza viral transmission and pathogenicity: Observations from Household-based trials, American Journal of Epidemiology, November 6, 2006: Vol. 165, No.2.
[16] Kaiser Laurent, Wat C., Mills T., Mahoney P., Ward P., Hayden F., Impact of Oseltamivir treatment on influenza-related lower respiratory track complications and hospitalizations, Intern. Med. (2003), vol. 163.
[17] Aoki F., Macleod M., Paggiaro P., Carewicz O., El SAwy A., Wat C., Griffiths M., Waalberg E., Ward P., Early administration of oral oseltamvir increases the benefits of influenza treatment, Journal of Antimicrobacterial Chemotherapy (2003) 51, 123-129.
[18] PAN-Canadian Public Health Network Council Report and Policy Recommendations on the use of Antivirals for Prophylaxis during an Influenza pandemic, June 2007.
[19] Annex E. Canadian Pandemic Influenza Plan for the Health Sector. The Use of Antiviral Drugs during a Pandemic. May 12, 2009.

## RESEARCH OBJECTIVES

The indispensable roles of health care workers and emergency service providers in administering care and essential services to the community are particularly vital during a pandemic. Currently, CPIP/TGAP does not recommend prophylaxis use of antivirals for emergency service providers and limited prophylaxis use is recommended for health care workers.

The purpose of this research study is to contrast the benefits associated with an additional antiviral stockpile that would allow for the prophylaxis of Canadian health care workers (HCWs) and emergency service providers (ESPs) under the conditions of a potential moderate influenza pandemic in Canada. As part of this research focus it is also necessary to compare the potential health and economic impacts of the way in which the current Canadian antiviral stockpile is used, as these use cases will impact the contrast results of an additional HCW and ESP antiviral stockpile.

## ANTIVIRAL UTILIZATION CASES

This study evaluates twelve different antiviral utilizations; three of which deal with possible utilization of the current Canadian antiviral stockpile, and nine others that deal with the utilization of an additional stockpile that is geared towards prophylactic protection of HCW and ESP populations. The twelve distinct antiviral utilizations are grouped as follows:

### Group 1: Current Stockpile: Treatment Only

**Tx**: Current Stockpile: Treatment Only: The current Canadian stockpile of 80.98 million doses is assumed to be used for all sick who seek treatment, on a first-come-first-served basis while available. There is no pre-exposure or post-exposure prophylaxis for anyone.

**Tx + Post**: Tx plus Additional Stockpile for Post-Exposure Prophylaxis for HCWs and ESPs: The current Canadian stockpile of 80.98 million doses is used as treatment only. An additional antiviral stockpile of 51.04 million doses[20] is purchased and used when required, as post-exposure prophylaxis for all HCWs and ESP for 10 days (one pill a day) after high risk contact. Neither stockpile is used for pre-exposure prophylaxis.

**Tx + Pre 56days**: Tx plus Additional Stockpile for 56 day Pre-Exposure Prophylaxis for HCWs and ESPs: The current Canadian stockpile of 80.98 million doses is used as treatment only. An additional antiviral stockpile of 53.78 million doses is purchased and used as pre-exposure prophylaxis for all HCWs and ESPs. Length of pre-exposure prophylactic treatment is assumed to be 56 days[21] with a dosing of one pill a day for the duration of the pre-exposure prophylaxis treatment.

**Tx + Pre 84days**: Tx plus Additional Stockpile for 84 day Pre-Exposure Prophylaxis for HCWs and ESPs: The current Canadian stockpile of 80.98 million doses is used as treatment only. An additional antiviral stockpile of 82.77 million doses is purchased and used as pre-exposure prophylaxis for all HCWs and ESPs. Length of pre-exposure prophylactic treatment is assumed to be 84 days with a dosing of one pill a day for the duration of the pre-exposure prophylaxis treatment.

[20] An average of 5 post-exposure courses per HCW and ESP
[21] Recommendation of Toronto Academic Health Sciences Network, Pandemic Influenza Planning Guidelines, May 31st, 2006. V1.

## Group 2: Current Stockpile: TGAP Interpretation 1

**Interp. 1**: Current Stockpile: TGAP Interpretation 1: The current Canadian stockpile of 80.98 million doses is assumed to be used as follows:

- Antiviral drugs are provided to the general population, healthcare workers and emergency service providers who contract influenza during the pandemic as treatment.
- Antivirals are provided for use as post-exposure prophylaxis and treatment of close contact HCWs employed in closed facilities during the pandemic.
- Antivirals are provided as treatment of patients residing in closed facilities during the pandemic.
- Antivirals are not provided for use as post-exposure prophylaxis of patients residing in closed facilities during the pandemic.

**Interp. 1 + Post**: TGAP Interpretation 1, plus Additional Stockpile for Post-Exposure Prophylaxis for HCWs and ESPs: The current Canadian stockpile of 80.98 million doses is used according to TGAP Interpretation 1. An additional antiviral stockpile of 28.07 million doses[22] is purchased and used when required as post-exposure prophylaxis that is provided to all HCWs and ESP for 10 days (one pill a day) after high risk contact. Neither stockpile is used for pre-exposure prophylaxis.

**Interp. 1 + Pre 56days**: TGAP Interpretation 1, plus Additional Stockpile for 56 day Pre-Exposure Prophylaxis for HCWs and ESPs: The current Canadian stockpile of 80.98 million doses is used according to TGAP Interpretation 1. An additional antiviral stockpile of 54.42 million doses is purchased and used as pre-exposure prophylaxis for all HCWs and ESPs. Length of pre-exposure prophylactic treatment assumed to be 56 days with a dosing of one pill a day for the duration of the pre-exposure prophylaxis treatment.

**Interp. 1 + Pre 84days**: TGAP Interpretation 1, plus Additional Stockpile for 84 day Pre-Exposure Prophylaxis for HCWs and ESPs: The current Canadian stockpile of 80.98 million doses is used according to TGAP Interpretation 1. An additional antiviral stockpile of 83.15 million doses is purchased and used as pre-exposure prophylaxis for all HCWs and ESP. Length of pre-exposure prophylactic treatment is assumed to be 84 days with a dosing of one pill a day for the duration of the pre-exposure prophylaxis treatment.

## Group 3: Current Stockpile: TGAP Interpretation 2

**Interp. 2**: Current Stockpile: TGAP Interpretation 2**:** The current Canadian stockpile of 80.98 million doses is assumed to be used as follows:

- Antiviral drugs are provided to the general population, healthcare workers and emergency service providers who contract influenza during the pandemic.
- Antivirals are provided for use as post-exposure prophylaxis and treatment of healthcare workers employed in closed facilities during the pandemic.
- Antivirals are provided for use as post-exposure prophylaxis and treatment of patients residing in closed facilities during the pandemic.

**Interp. 2 + Post**: TGAP Interpretation 2 plus Additional Stockpile for Post-Exposure Prophylaxis for HCWs and ESPs: The current Canadian stockpile of 80.98 million doses is used according to TGAP Interpretation 2. An additional antiviral stockpile of 37.23 million doses[23] is purchased and used when required as post-exposure prophylaxis that is provided to all HCWs and ESP for 10 days (one pill a day) after high risk contact. Neither stockpile is used for pre-exposure prophylaxis.

[22] An average of 3 post-exposure courses per HCW and ESP
[23] An average of 4 post-exposure courses per HCW and ESP

**Interp. 2 + Pre 56days**: TGAP Interpretation 2 plus Additional Stockpile for 56 day Pre-Exposure Prophylaxis for HCWs and ESPs: The current Canadian stockpile of 80.98 million doses is used according to TGAP Interpretation 2. An additional antiviral stockpile of 54.41 million doses is purchased and used as pre-exposure prophylaxis for all HCWs and ESPs. Length of pre-exposure prophylactic treatment assumed to be 56 days with a dosing of one pill a day for the duration of the pre-exposure prophylaxis treatment.

**Interp. 2 + Pre 84days**: TGAP Interpretation 2 plus Additional Stockpile for 84 day Pre-Exposure Prophylaxis for HCWs and ESPs: The current Canadian stockpile of 80.98 million doses is used according to TGAP Interpretation 2. An additional antiviral stockpile of 83.07 million doses is purchased and used as pre-exposure prophylaxis for all HCWs and ESPs. Length of pre-exposure prophylactic treatment is assumed to be 84 days with a dosing of one pill a day for the duration of the pre-exposure prophylaxis treatment.

## METHODS AND APPROACH

The three groups of antiviral utilizations are contrasted by comparing the results of each against the results of a moderate pandemic without any assumed interventions. A moderate pandemic without any assumed interventions is called the base case, and the different possible applications of the current and additional antiviral stockpiles are called the scenario cases. The value proposition to society of each antiviral use scenario in life and economic terms is then determined by subtracting the potential impacts of the base case from each of the scenario cases.

### 1.1.1 THE MODEL

The quantification of the potential impacts of a moderate pandemic in Canada requires a mathematical model. A deterministic mathematical model of the transmission dynamics of influenza was used to track the Canadian population during an assumed moderate pandemic. The model was parameterized using available Canadian data as well as key estimates from a combination of available literature on United States and Canadian data from the 1957/58 pandemic[24]. This parameterization was consistent with that used by CPIP in all relevant respects with the exception of case fatality. Based on the literature[25], case fatality was set at 0.174% which is 62% less than what is used for the CPIP.[26]

The Canadian population was stratified into thirty seven non-overlapping geographical regions, and by age and gender groups. The population was then further subdivided into risk of infection, risk of mortality given infection, epidemiological states (e.g., susceptible, exposed, infectious, hospitalized recovered) and employment status (health care workers, emergency service providers and others in both the public as well as private sectors). Parameterization of the model followed peer reviewed literature and statistics provided by Statistics Canada. A list of model assumptions is provided at the end of this Executive Summary.

The travel of individuals between each of the thirty seven non-overlapping geographical regions was determined in a manner which was consistent with data from the 2004 Canadian Travel Survey (CANSIM)[27]. Two additional regions which encompassed the entire United States and Mexico was added to the model in order to incorporate a significant proportion of cross-border infections arising from international travel. The current model imposed static travel conditions and therefore assumed no changes in the travel patterns (both internationally as well as

[24] Although the model was calibrated using the 1957/58 United States influenza parameters, it was parameterized using Canadian-specific demographic data.
[25] Haber M. J., Shay D., K., et al. Effectiveness of interventions to reduce contact rates during a simulated influenza pandemic, EID Journal, Volume 13, Number 4, April 2007
[26] The decision to use 0.174% is in keeping with our focus on using literature defined parameters. The source of the CPIP mortality rate was unknown to the authors.
[27] Statistics Canada. 2004. Canadian Travel Survey, Domestic Travel, Statistics Canada Catalogue no. 87-212-XIE

domestically) during the pandemic. Although the assumption was primarily driven by the lack of data supporting any specific changes in travel (arising from potential border crossings and other restrictions), the model has been designed to be general enough to consider the sensitivity of such travel restrictions in future studies.

The model was used to generate the expected future dynamics of a pandemic by capturing the complex coupling of demographics, infectiousness, pathogenicity and virulence of a spreading pathogen (among interacting populations) as well as expected Canadian economic activity. In addition to the effects upon health state of the Canadian population, an infectious disease pandemic has been shown to inflict unexpected economic production loss. Such loss, as a result of pandemic related deaths and workplace absenteeism, was further linked to wage loss and corporate profit reduction within the model. In this context, the current model seeks to provide benefits to various antiviral drug policies not just in terms of the standard life measures such as the attack rate, hospitalizations or mortality but also in terms of economic measures such as the impact upon private and government incomes and expenses.

A hypothetical pathogen capable of causing a moderate pandemic in Canada that is sensitive to antivirals was assumed for the purposes of this study. The infectiousness, pathogenicity and virulence of the virus were assumed to be similar to the H2N2 virus responsible for the 1957/58 worldwide pandemic. United States data based on the spread of this pandemic within the United States was chosen to calibrate the current model to a 33.4% attack rate with a 0.174% case fatality rate[28],[29]. The virus was further assumed to be associated with a sufficiently unique strain, for the population immunity to be negligible. The model adopted contact mechanics from a multi-country European study by Massong et al.[30] and considered close contacts within households, work/schools and community. Each day, the transition to becoming infected was used among all susceptible individuals under the assumption that all infectious individuals may transfer the pathogen upon contact and the frequency with which this occurs was calibrated to the 1957 data[31]. In the model, individuals infected with influenza pass through a latent period during which they are not infectious and do not show any symptoms of the disease. The infection was assumed to be symptomatic in 100% of the infected cases and could lead to severe disease requiring hospitalization, leading to either death or recovery.

The current model uses the Canadian antiviral stockpiles which currently comprise of the National, Federal as well as the Ontario supplement. The National and Ontario stockpiles contain Oseltamivir and Zanamivir. The current model adopts relative efficacy for the use of both drugs as post-exposure and pre-exposure prophylaxis from the "household contacts" and "healthy individuals" trials respectively. The household trials indicated similar relative efficacy for both drugs when used as post-exposure prophylaxis (efficacy of 68%-89%[32] [33] for Oseltamivir and efficacy of 79% to 81% [34] [35] for Zanamivir). When used as pre-exposure prophylaxis, trial evidence suggests a relative efficacy of 74%[36] to 91%[37] for Oseltamivir and 67% to 84%[38] for Zanamivir. The current model did not

[28] Longini I., Holloran E., Nizam A., Yang Y., Containing Pandemic Influenza with antiviral agents, American Journal of Epidemiology April 1 2004, Volume 159, number 7.
[29] Longini I., Holloran E., Nizam A., Yang Y., Containing Pandemic Influenza with antiviral agents, American Journal of Epidemiology April 1 2004, Volume 159, number 7.
[30] Mossong J., Hens N., Beutels P., Auranen K., Mikolajczyk R., Massari M., Salmaso S., Tomba G., Wallinga J., Haijne J., Todys M., Rosinska M., Edmunds J., Social Contacts and mixing patterns relevant to the spread of infectious diseases, PLOS Medicine, March 2008, Volume 5, Issue 3, e74.
[31] Evveback L. R., Fox J. P., Ackerman E., et al. An influenza simulation model for immunization studies. Am. J. Epidemiol 1976; 103: 152-65.
[32] Hayden FG, Belshe R, Villanueva C, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. J Infect Dis 2004;189:440-449.
[33] Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. JAMA 2001;285:748-754.
[34] Hayden FG, Gubareva LV, Monto AS, et al. Inhaled zanamivir for the prevention of influenza in families. N Engl J Med 2000;343:1282-1289.
[35] Monto AS, Pichichero ME, Blanckenberg SJ, et al. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. J Infect Dis 2002;186:1582-1588.
[36] Hayden FG, Atmar RL, Schilling M, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. N Engl J Med 1999;341:1336-1343.

specifically differentiate between the two types of drugs and instead used the combined relative efficacies for the two types of drugs.

In the current study, the use of antiviral drugs as pre-exposure prophylaxis is assumed to be confined to a specific period (two periods: 56 days and 84 days were examined). The extended use of the drugs beyond the selected period is prohibited. The specific point in time during the pandemic at which pre-exposure prophylaxis should be administered to HCWs and ESPs was determined under the condition of minimizing absenteeism in the HCW and ESP labour force. This procedure provided start times of 64 and 48 days (after a pandemic is declared) under the 56 day and the 84 day pre-exposure prophylaxis scenarios respectively.

In addition, the current model assumed a 10 day use of antiviral drugs as post-exposure prophylaxis for all HCWs and ESP after high risk contact. In the case of continuous high risk contacts during a pandemic, there is the risk that a HCW or ESP could be continuously subjected to post-exposure prophylaxis well in excess of the deemed appropriate course period of 84 days. Given this, it was assumed that HCWs or ESPs would be rotated away from high risk contacts within the model if they were at risk of continuous high risk contacts for more than 84 days.

Modeling of the use of antiviral stockpiles for pandemic control is dependent upon the assumption of when antivirals are to be used. In Canada, a pandemic begins when Canadian activity levels reach pandemic Phase 6.1, a point at which efficient and sustained human-to-human transmission is observed. The current worldwide outbreak of influenza A (H1N1) has shown the difficulties associated with the declaration of a pandemic given greater emphasis upon the distributional spread of the disease and less emphasis upon its virulence[39]. To avoid model ambiguity, it was assumed that the use of antiviral stockpiles would begin across Canada when the number of confirmed deaths due to the pandemic strain numbered twenty in total for Canada[40] [41].

The state of the employed population's health at any particular time was assumed to be a key parameter of the Canadian production capacity and therefore the economic welfare of the entire country. In this respect a coupled economic model capable of estimating the costs of a pandemic in terms of lost productivity in the workplace was incorporated. This represents a macro-economic model in which a demand-for-labor component and other relevant economic variables are simulated directly from the underlying industry data. A change in the health status of an employed individual will have an impact upon production. Symptomatic infection was assumed to be associated with work absenteeism for the duration of the recovery period, resulting in an overall decrease in labor hours and therefore a decrease in production. This loss was directly linked to loss of income, consumption and investment. The economic model embedded in the current study is a version of a model known as Klein's Model 1 [42].

### 1.1.2 CONTRAST MEASURES AND THE RANKING OF ANTIVIRAL UTILIZATION CASES

The burden associated with an infectious disease pandemic as well as the benefits due to the implementation of various antiviral use scenarios were assessed with respect to eight contrast measures: (1) reduced population deaths; (2) reduced hospitalizations; (3) reduced general practitioner visits; (4) HCW reduced deaths; (5) ESP reduced deaths; (6) HCW reduced absences; (7) ESP reduced absences; (8) net present value added from the intervention.

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[37] Peters PH Jr, Gravenstein S, Norwood P, et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. J Am Geriatr Soc 2001;49:1025-1031.
[38] Monto AS, Robinson PD, Herlocher LM, et al Zanamivir in the Prevention of Influenza Among Healthy Adults. JAMA. 1999;282(1):31-35
[39] Refer to WHO Influenza Pandemic Task Force, Report of the first meeting, Geneva, Switzerland, 25 September 2006
[40] Supported by advice received from our Infectious Disease Advisory Board
[41] Note that according to the model results for the base case, this is 26 days after the first confirmed death due to the pandemic strain
[42] L. Klein (1950), Economic Fluctuations in the United States 1921-1941, Wiley, pp. 58-80.

Of these outcomes there are 255 different combinations ($2^{n-1}$) which performance could be assessed against. To test for the rank dominance of an antiviral use scenario, each scenario was assessed against each possible outcome combination assuming an equal weighting of outcomes. This allowed a ranking summary to be produced that indicated the frequency (percent) of how many times an antiviral use scenario ranked first, second, third and so on.

### 1.1.3 MODEL VALIDATION AND COLLABORATION WITH SUBJECT MATTER EXPERTS

The model is intended to provide a scenario planning tool that generates a reasonable representation of a moderate pandemic and the current public health measures for antiviral use as outlined in the TGAP recommendations[43]. It demonstrates how a typical pandemic may unfold in Canada and the potential benefits of changes to the current Canadian antiviral stockpile. A key challenge to modeling a pandemic is the uncertainty that surrounds the unknowns of this type of event. This includes when a pandemic will occur, where it will occur and the severity of the viral strain. As a result of these uncertainties, assumptions must be made.

Given the unknown variables of a pandemic, an independent group of recognized Canadian infectious disease experts forming the Infectious Disease Advisory Board (IDAB) were consulted throughout this study. The role of IDAB was to provide theoretical verification and face validity to the model and its outcomes. In this respect, the IDAB provided an understanding of the epidemiology of pandemic influenza, examined and reviewed the reasonableness of the calibration model and assumptions; and provided direction and advice on literature and data sources to inform the logistics, influenza life cycle and assumptions of the model.

To support the validation of the antiviral scenario development process, an independent group of frontline healthcare workers and emergency service providers were brought together to serve as a Pandemic Advisory Committee (PAC) which was consulted throughout this study. The role of PAC was to provide face validity to the scenarios, reasonableness assessment of HCW and ESP relevant assumptions and review of scenario outputs. In this respect, PAC assisted with the development of two potential intervention scenarios associated with stockpiling antivirals for use as pre-exposure prophylaxis and post-exposure prophylaxis for Canada's frontline healthcare workers and emergency service providers. The expertise from PAC provided an on-the-ground understanding of frontline health and emergency care providers under a pandemic to ensure that the scenarios would provide a reasonable representation of how a pandemic would unfold with the administration of antivirals.

## RESULTS

The results of the base case (a moderate Canadian pandemic with no interventions) were found to be in accordance with the number of cases and hospitalizations estimated in the Canadian plan. The mortality results were significantly less, as the current model used a lower case fatality rate as prescribed by the literature.

While there are significant life and economic benefits that can be associated with the use of the current Canadian stockpile, it was found to be insufficient to support the two TGAP interpretations tested[44]. Where the current stockpile is used therapeutically for the general population and prophylactically for HCWs, post exposure in closed facilities (TGAP Interpretation 1), the stockpile is estimated to begin running out 152 days after the initial use of antivirals. Where the current stockpile is used therapeutically for the general population and prophylactically for

[43] PAN-Canadian Public Health Network Council Report and Policy Recommendations on the use of Antivirals for Prophylaxis during an Influenza pandemic, June 2007.
[44] Further recognizing that antiviral wastage is assumed to be zero.

HCWs and their patients post-exposure, in closed facilities (TGAP Interpretation 2), the stockpile is estimated to begin running out 124 days after the initial use of antivirals [45].

Contrast of each antiviral utilization case involved comparison against 255 combinations of the contrast measures. All additional stockpile scenarios outperformed their respective TGAP interpretations. This is due in part to there being an insufficient current Canadian stockpile to support each TGAP interpretation and in part due to the effects of an additional stockpile protecting the capacity of HCWs to dispense antivirals and a significant reduction in ESP infection rates.

When compared against 255 combinations of the contrast measures, TGAP interpretation 1 coupled with an 84 day outbreak prophylaxis for HCWs and ESPs outperformed all other scenarios. A close second was the scenario that involved the use of the current stockpile as treatment only coupled with post-exposure prophylaxis for HCWs and ESPs. The 84 day outbreak prophylaxis would require an additional stockpile of 83.15 million doses at a cost of approximately $212.4 million. The post-exposure prophylaxis would require an additional stockpile of 51.04 million doses at a cost of approximately $130.4 million.

### 1.1.4 BASE CASE RESULTS OF A MODERATE PANDEMIC IN CANADA

The results of the base case were found to be consistent with the number of cases and hospitalizations reported by the CPIP with the exception of the number of deaths. The mortality results of the current model were 62% less, due to the CPIP using a case fatality rate of 0.40%, while the current model used a case fatality rate of 0.174%. Remembering that the base case represents the results of a moderate pandemic in Canada in 2010, without any intervention, the model results were:

**Exhibit 1 Burden of a moderate pandemic in Canada in 2010**

| Base Case Results for Total Population | Impact |
|---|---|
| Number Infected | 11,162,574 |
| Attack Rate | 32.9% |
| Deaths (using 1957/58 age dependent case fatality rates) | 16,800 |
| Hospitalizations | 66,961 |
| General Practitioner Visits | 5,393,801 |
| 2010 Societal Perspective of Cost of Pandemic | $11.9 billion |
| 2010 Government Perspective of Cost of Pandemic | $4.5 billion |
| **Base Case Results for HCW and ESP Populations** | |
| Number Infected | 238,875 |
| Attack Rate | 23.8% |
| Deaths (using 1957/58 age dependent case fatality rates) | 90 |
| HCW Peak Absenteeism | 24.3% |
| ESP Peak Absenteeism | 25.0% |

[45] Note that the CPIP recognizes that information of vaccine availability is unlikely to be available until the pandemic has begun. A vaccine would have to be made widely available by the run out dates indicated in order to mitigate the effects of the full depletion of the current stockpile.

Peak HCW absenteeism of 24.3% corresponds to the absence of 125,721 HCWs. Peak ESP absenteeism of 25.0% corresponds to the absence of 121,346 ESPs. PAC members had advised that ordinary service expectations could not be met during such peak absences, and that a pandemic would only exacerbate the challenges.

The distinction between antiviral utilization cases is drawn by comparing how different antiviral interventions reduce this burden. The societal perspective of the cost of a pandemic is the sum of the impact upon total hospitalization costs, indirect wage and corporate profits. The governmental perspective of the cost of a pandemic is the sum of the total hospitalization costs, indirect income tax revenues and consumption tax revenues for all Canadian Governments combined.

### 1.1.5 UTILIZATION CASE RESULTS OF THE CURRENT STOCKPILE

The antiviral utilization cases of the current Canadian stockpile were examined. The current stockpile has a sum total of 80.98 million doses and it was assumed that this stockpile could be used as:

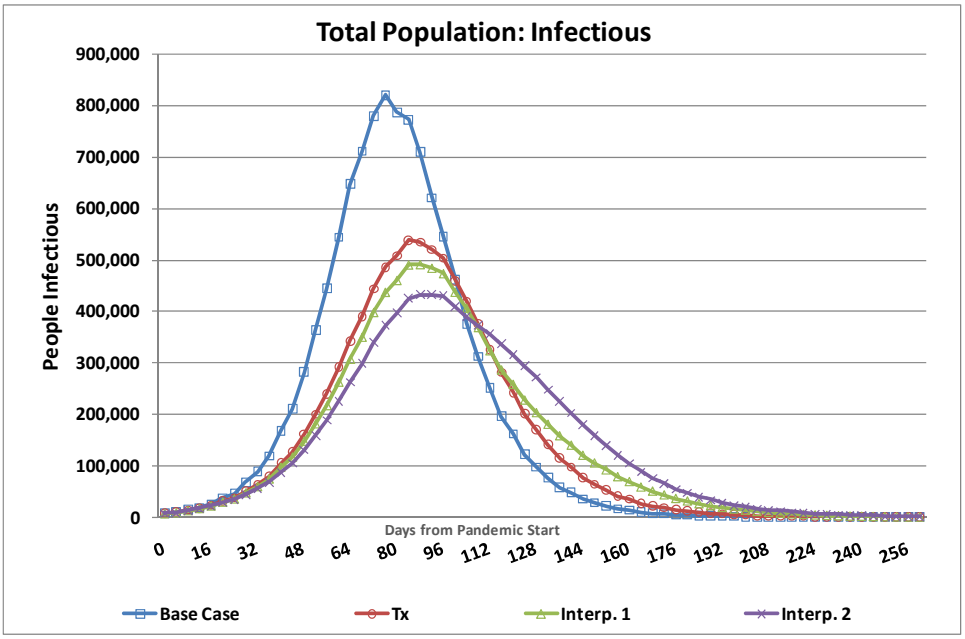
- **Treatment (Tx):** All sick who seek treatment from the current stockpile on a first-come-first-served basis while available;

- **TGAP Interpretation 1:** All sick who seek treatment from the current stockpile on a first-come-first-served basis while available. Post exposure prophylaxis for HCWs in closed facilities only (hospitals, LTC facilities, nursing homes, psychiatric institutions, correctional facilities) using the current stockpile on a first come first served basis while available; and

- **TGAP Interpretation 2:** All sick who seek treatment from the current stockpile on a first come first served basis while available. Post exposure prophylaxis for HCWs and their patients in closed facilities only using the current stockpile on a first-come-first-served basis while available.

The timing and number of infectious Canadians that result from a moderate pandemic for each of the current stockpile antiviral utilization cases is graphed below.

**Exhibit 2 Infectious population: Moderate pandemic**



The blue line represents the results of the base case (no antiviral intervention case). The red, green and purple lines represent the results of the various antiviral utilization cases for the current Canadian stockpile. From exhibit 2 it is evident that the use of antivirals has the ability to reduce the concentration of Canadians with the pandemic flu (at any one time) and to shift the timing of the peak of the pandemic to a later period. The base case number of infectious individuals peaks at 76 days. The utilization of the current stockpile as Tx reduces the number of cumulative infections by 37% (by day 76); TGAP Interpretation 1 reduces the number of cumulative infections by 42% (by day 76); and TGAP Interpretation 2 reduces the number of cumulative infections by 47% (by day 76).

The value propositions of each of the antiviral utilization cases of the current Canadian stockpile are significant. When compared against the burden of a moderate pandemic (base case), the reductions of the burden of each of the antiviral utilization cases of the current Canadian stockpile are as follows:

**Exhibit 3 Reduction of burden: Current Canadian stockpile antiviral utilization cases**

| | Treatment only | TGAP Interpretation 1 | TGAP Interpretation 2 |
|---|---|---|---|
| **Reduced Population Infected** | **-19.3%** (-2,156,763) | **-18.1%** (-2,021,422) | **-16.4%** (-1,826,454) |
| **Reduced Population Deaths** | **-39.6%** (-6,648) | **-36.7%** (-6,165) | **-30.7%** (-5,150) |
| **Reduced Hospitalizations** | **-23.1%** (-15,480) | **-21.2%** (-14,190) | **-18.7%** (-12,553) |
| **Reduced GP Visits** | **-19.3%** (-1,042,157) | **-18.1%** (-976,759) | **-16.4%** (-882,550) |
| **Reduction of Societal Economic Impact** | **-23.9%** (-2.85 billion) | **-22.6%** (-2.70 billion) | **-19.8%** (-2.36 billion) |
| **Reduced HCW Infections** | **-21.1%** (-19,095) | **-70.5%** (-63,887) | **-59.5%** (-53,974) |
| **Reduced HCW Deaths** | **-38.0%** (-13) | **-75.1%** (-25) | **-62.7%** (-21) |
| **Reduced HCW Peak Absenteeism** | **-20.2%** (-25,369) | **-41.8%** (-52,589) | **-43.3%** (-54,488) |
| **Reduced ESP Infections** | **-19.3%** (-28,667) | **-16.9%** (-25,071) | **-14.3%** (-21,166) |
| **Reduced ESP Deaths** | **-37.0%** (-21) | **-34.0%** (-19) | **-27.8%** (-16) |
| **Reduced ESP Peak Absenteeism** | **-20.7%** (-25,102) | **-23.7%** (-28,760) | **-27.5%** (-33,411) |

The reduction of the burden of a moderate pandemic that accrues from the antiviral utilization scenario is indicated in parenthesis.

Given that the CPIP uses an age independent case fatality rate of 0.40%, for comparative reasons, the number of HCWs and ESPs lives saved under the CPIP case fatality rate assumptions are also reported as follows:

**Exhibit 4** **HCW/ESP death reduction under CPIP assumptions: Current Canadian stockpile antiviral utilization cases**

| | Treatment only | TGAP Interpretation 1 | TGAP Interpretation 2 |
|---|---|---|---|
| **HCW Reduced Deaths** | **-175** (48.3%) | **-292** (80.7%) | **-266** (73.5%) |
| **ESP Reduced Deaths** | **-279** (47.1%) | **-270** (45.5%) | **-260** (43.8%) |
| **Total of HCW and ESP Reduced Deaths** | **-454** (47.6%) | **-562** (58.9%) | **-526** (55.1%) |

The reduction of the burden of a moderate pandemic that accrues from the antiviral utilization scenario is indicated in parenthesis.

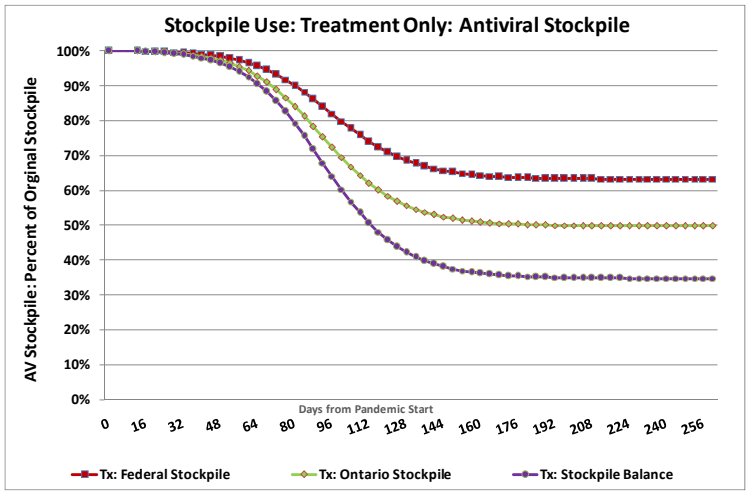
It is estimated that the current Canadian antiviral stockpile of 80.98 million doses will have cost $221.4 million by the end of 2010. It is evident from the results that there exists significant life and economic benefits with the 'Treatment only' scenario appearing to be superior in total population terms and the two TGAP interpretation scenarios appear superior in HCW and ESP population terms. The reason for the apparent superiority of the 'Treatment only' scenario in total population terms is a result of the unexpected finding that the current Canadian antiviral stockpile was insufficient to support the two TGAP interpretations tested.

In the scenario in which the current stockpile is used therapeutically for the general population and as post exposure prophylaxis for HCWs in closed facilities (TGAP Interpretation 1), the stockpile is estimated to begin running out 152 days after the initial use of antivirals (at which stage the pandemic has reached 92.9% of its infection potential). In the scenario in which the current stockpile is used therapeutically for the general population and as post exposure prophylaxis for HCWs and patients in closed facilities (TGAP Interpretation 2), the stockpile is estimated to begin running out 124 days after the initial use of antivirals (at which stage the pandemic has reached 72.8% of its infection potential).

The reason behind the deficiency of the current Canadian stockpile to support either TGAP interpretations is due to the utilization of the stockpile to support post exposure prophylaxis for HCWs in closed facilities (TGAP Interpretation 1) and for HCWs and their patients in closed facilities (TGAP Interpretation 2). Whereas an antiviral treatment consumes 10 doses, post exposure prophylaxis can consume multiple courses of 10 doses depending upon how many times a closed facility HCW or a patient reports a high risk contact. The effect is a faster consumption of the current Canadian stockpile under either TGAP interpretations, with fewer stockpiles being used for the treatment of the general population when required.

To understand the effect of the deficiency of the current Canadian stockpile to support either TGAP interpretation, consider the following graph that depicts the consumption of the current Canadian stockpile under the treatment only scenario.

**Exhibit 5 Treatment only scenario: Consumption of current Canadian stockpile**

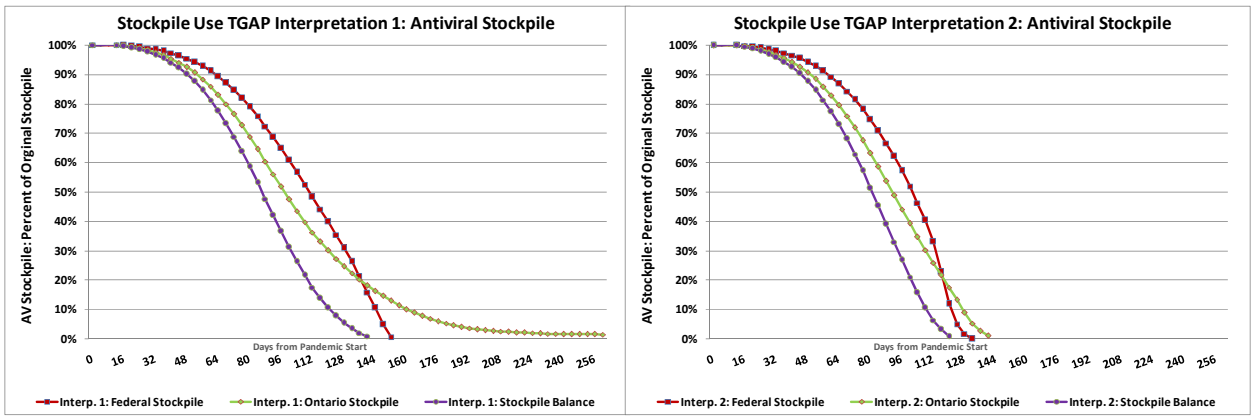



Here the stockpile has been broken down into three parts. The Federal stockpile, the Ontario stockpile and the stockpile used to support the balance of Canada. A separate Ontario stockpile is broken out from the rest of Canada as Ontario has an extra stockpile reportedly sufficient to meet the needs of 25% of its residents when used in combination with the national stockpile.

As can be seen from Exhibit 5, there is a sufficient stockpile to support a treatment only scenario, with 63.2% of the Federal stockpile, 49.8% of the Ontario stockpile and 34.7% of the balance of Canada stockpile left after the passing of the pandemic. It is worthwhile to note however, that stockpile wastage and treatment use for influenza like illnesses during a pandemic (i.e. not the pandemic strain) have been assumed to be zero.[46] An assumption above zero would yield lower stockpile reserves than indicated.

Under TGAP Interpretation 1, we found that the Federal stockpile runs out between 152 and 156 days, and the balance of Canada stockpile runs out between 140 and 144 days after the declaration of a pandemic. The Ontario stockpile does not run out with 1.4% left after the passing of the first wave of the pandemic.

**Exhibit 6 TGAP interpretations: Consumption of current Canadian stockpile**




[46] This assumption was due to the desire to be consistent with the stockpile assumptions of the Canadian Pandemic Influenza Plan.

Under TGAP Interpretation 2, we found that the Federal stockpile runs out between 128 and 132 days, the balance of Canada stockpile runs out between 120 and 124 days, and the Ontario stockpile runs out between 140 and 144 days after the declaration of a pandemic.

The effects of the deficiency of the current Canadian stockpile to support either TGAP interpretations can be seen in Exhibit 2 as the infectious results for TGAP Interpretation 1 and TGAP Interpretation 2 begin to exceed that of the treatment only scenario at the 120 day mark.

While not within the scope of this study, it is important to note that the deficiency of the current Canadian stockpile to support either TGAP interpretation may pose an ethical issue for community leaders as the benefits of protecting HCWs in this way are outweighed by the population health impacts. For example, under both TGAP interpretations, the number of deaths, hospitalizations and general practitioner visits are all estimated to be higher than the treatment only scenario that does not distinguish between members of the general population and HCWs. While the required Canadian stockpile to support either TGAP interpretations has not been estimated as part of this study, it is expected that if such a shortfall were to be remedied, both TGAP interpretations would prove superior to that of the treatment only scenario.

The deficiency of the current Canadian stockpile to support either TGAP interpretation also confounds the contrast of further additional stockpiles that are specifically related to HCWs and ESPs. When additional stockpiles are added for HCW use, their demand for post exposure prophylaxis in both the TGAP interpretations is reduced, hence more of the current Canadian stockpile can be used for the treatment of the general population.

### 1.1.6 UTILIZATION RESULTS OF ADDITIONAL HCW AND ESP PROPHYLACTIC STOCKPILES

When compared against 255 combinations of the contrast measures, all additional stockpile scenarios were superior to the respective TGAP interpretations. This is due in part to the insufficient current Canadian stockpile to support each TGAP interpretation and in part due to the effects of an additional stockpile protecting the capacity of HCWs to provide essential care services as well as a significant reduction in the infection rates of ESPs.

When compared against 255 combinations of the contrast measures, the four top ranked antiviral utilization scenarios in order of their performance were:

- **TGAP Interpretation 1 plus Pre 84days:** Current 80.98 million stockpile used according to TGAP interpretation 1 coupled with an additional stockpile of 83.15 million doses to support an 84 day pre-exposure prophylaxis duration for HCWs and ESPs;

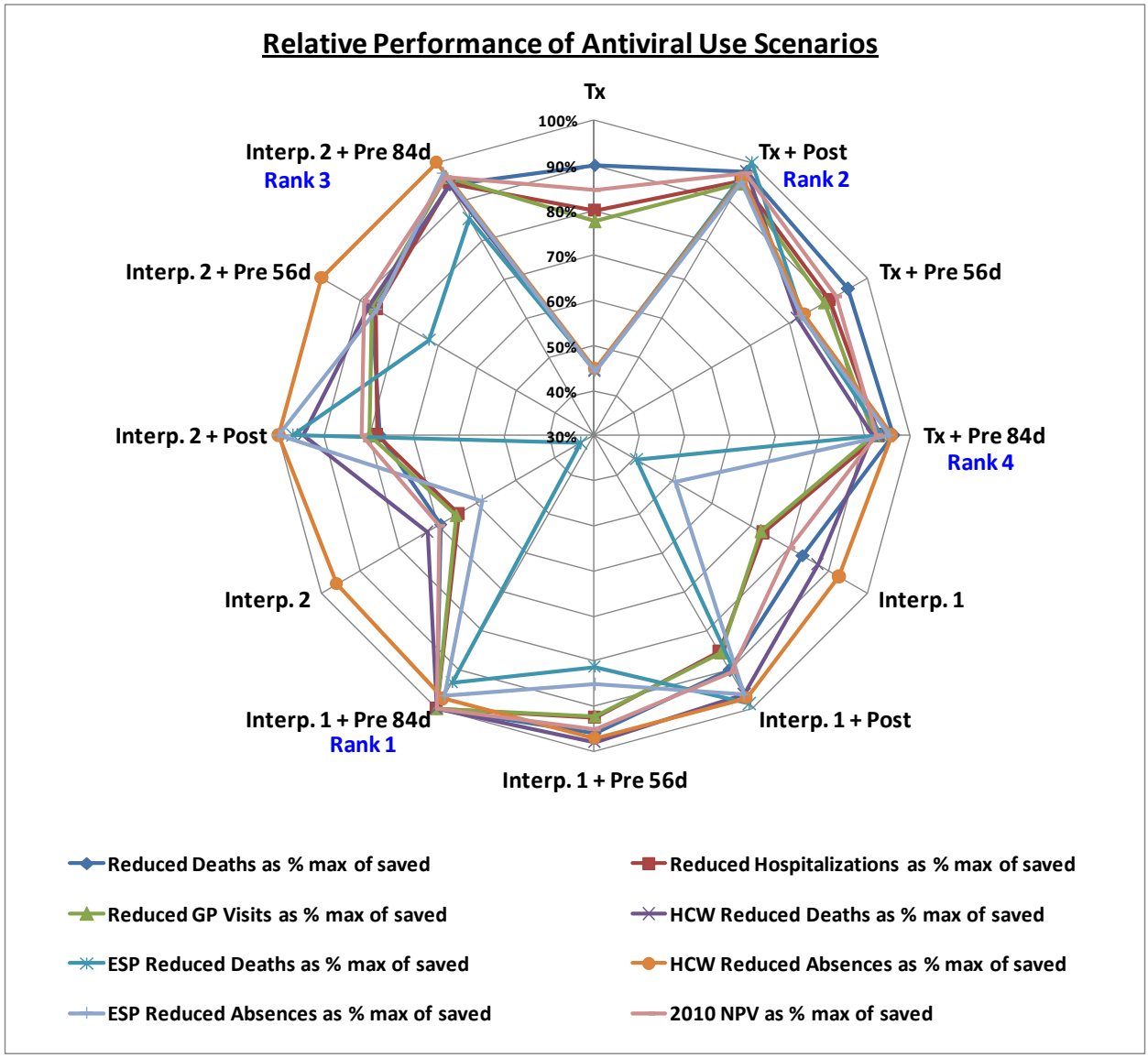
- **Treatment only plus Post:** Current 80.98 million stockpile used for treatment only coupled with an additional stockpile of 51.04 million doses to support as post-exposure prophylaxis for HCWs and ESPs (an average of 5 post-exposure courses per HCW and ESP);

- **TGAP Interpretation 2 plus Pre 84 days:** Current 80.98 million stockpile used according to TGAP interpretation 2 coupled with an additional stockpile of 83.07 million doses to support an 84 day pre-exposure prophylaxis duration for HCWs and ESPs.

- **Treatment only plus Pre 84 days:** Current 80.98 million stockpile used for treatment only coupled with an additional stockpile of 82.77 million doses to support an 84 day pre-exposure prophylaxis duration for HCWs and ESPs.

A radar chart of the results using the eight contrast measures shows the dominance of the four top ranked results. The radar chart standardizes each antiviral utilization scenario outcome against the maximum reduction of burden within each contrast class. Hence, the closer a result is to the boundary of the radar chart, the better its performance.

**Exhibit 7** **All results: Relative performance of antiviral use scenarios**




For each of the four top ranked antiviral utilization scenarios, it is evident that the contrast results are in close proximity to the boundary of the radar chart, indicating their superior relative performance to those scenarios not near the boundary.

A ranking of the results across all the scenarios is provided as Exhibit 8. It is evident that the treatment only scenario and each of the TGAP interpretation scenarios underperform relative to the other scenarios that are dependent upon additional purchases of antiviral stockpiles.

**Exhibit 8 Ranking of results**

| | Rank 1st | Rank 2nd | Rank 3rd | Rank 4th | Rank 5th | Rank 6th | Rank 7th | Rank 8th | Rank 9th | Rank 10th | Rank 11th | Rank 12th | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Interp. 1 + Pre 84d** | **89%** | 7% | 1% | 3% | 1% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 100% |
| **Tx + Post** | 8% | **64%** | 25% | 1% | 0% | 1% | 0% | 0% | 0% | 0% | 0% | 0% | 100% |
| **Interp. 2 + Pre 84d** | 0% | 24% | **35%** | 22% | 15% | 5% | 0% | 0% | 0% | 0% | 0% | 0% | 100% |
| **Tx + Pre 84d** | 0% | 0% | 20% | **45%** | 31% | 3% | 1% | 0% | 0% | 0% | 0% | 0% | 100% |
| **Interp. 1 + Post** | 0% | 3% | 12% | 13% | **27%** | 35% | 9% | 2% | 0% | 0% | 0% | 0% | 100% |
| **Interp. 1 + Pre 56d** | 0% | 2% | 5% | 16% | 24% | **31%** | 20% | 1% | 0% | 0% | 0% | 0% | 100% |
| **Interp. 2 + Post** | 3% | 0% | 2% | 0% | 1% | 16% | **27%** | 23% | 23% | 4% | 1% | 0% | 100% |
| **Interp. 2 + Pre 56d** | 0% | 0% | 0% | 0% | 0% | 3% | 19% | **39%** | 38% | 0% | 0% | 0% | 100% |
| **Tx + Pre 56d** | 0% | 0% | 0% | 0% | 0% | 6% | 24% | 35% | **32%** | 2% | 1% | 0% | 100% |
| **Interp. 1** | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 2% | **74%** | 24% | 0% | 100% |
| **Interp. 2** | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 4% | **60%** | 35% | 100% |
| **Tx** | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 5% | 16% | 13% | **65%** | 100% |
| **Total** | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | |

The shaded diagonal represents the number of times a scenario is ranked in priority to all other scenarios. For example, Interp. 1 + Pre 84d ranked first 89% of the time, while treatment only (Tx) ranked twelfth 65% of the time. It is evident from the ranking table (Exhibit 8) that the dominance of scenario groupings is as follows:

Group Rank 1. Those scenarios that involve 84 day pre-exposure prophylaxis for all HCWs and ESPs;
Group Rank 2. Those scenarios that involve post-exposure prophylaxis for all HCWs and ESP
Group Rank 3. Those scenarios that involve 56 day pre-exposure prophylaxis for all HCWs and ESP

Specifically, those scenarios that involve 84 day pre-exposure prophylaxis duration for HCWs and ESP typically perform better that those that involve a post-exposure prophylaxis for HCWs and ESP, which in turn typically perform better than those that involve 56 day pre-exposure prophylaxis duration for HCWs and ESP.

### 1.1.7 RESULTS OF THE FOUR TOP RANKED HCW AND ESP PROPHYLACTIC STOCKPILES

The dominant scenario group (84 day pre-exposure prophylaxis for all HCWs and ESPs) and the treatment only plus post-exposure prophylaxis scenario yields the four top ranked antiviral utilization scenarios. When compared against the burden of a moderate pandemic (base case), the reduction of the burden of each of the four top ranked antiviral utilization scenarios are as follows:

**Exhibit 9 Reduction of burden for society: Four top ranked antiviral utilization scenarios**

| | TGAP Interpretation 1 plus Pre 84days | Treatment only plus Post | TGAP Interpretation 2 plus Pre 84 days | Treatment only plus Pre 84 days |
|---|---|---|---|---|
| **Population Infected** | **-25.0%** (-2,785,571) | **-23.6%** (-2,628,928) | **-24.0%** (-2,675,463) | **-23.0%** (-2,563,278) |
| **Reduced Population Deaths** | **-44.0%** (-7,398) | **-42.9%** (-7,206) | **-41.5%** (-6,969) | **-42.4%** (-7,127) |
| **Reduced Hospitalizations** | **-28.9%** (-19,370) | **-27.5%** (-18,435) | **-27.4%** (-18,317) | **-26.9%** (-18,019) |
| **Reduced GP Visits** | **-25.0%** (-1,345,996) | **-23.6%** (-1,270,309) | **-24.0%** (-1,292,788) | **-23.0%** (-1,238,586) |
| **Reduction of Societal Economic Impact** | **-28.3%** (-$3.38 billion) | **-27.4%** (-$3.28 billion) | **-27.2%** (-$3.25 billion) | **-26.2%** (-$3.12 billion) |

The reduction of the burden of a moderate pandemic that accrues from the antiviral utilization scenario is indicated in parenthesis.

**Exhibit 10 Reduction of burden for HCWs and ESPs: Four top ranked antiviral utilization scenarios**

| | TGAP Interpretation 1 plus Pre 84days | Treatment only plus Post | TGAP Interpretation 2 plus Pre 84 days | Treatment only plus Pre 84 days |
|---|---|---|---|---|
| **Reduced HCW Infections** | **-82.1%** (-74,395) | **-79.3%** (-71,863) | **-77.4%** (-70,135) | **-72.8%** (-65,944) |
| **Reduced HCW Deaths** | **-86.1%** (-29) | **-84.0%** (-28) | **-81.0%** (-27) | **-78.9%** (-26) |
| **Reduced HCW Peak Absenteeism** | **-44.0%** (-55,296) | **-43.2%** (-54,295) | **-45.1%** (-56,718) | **-43.3%** (-54,381) |
| **Reduced ESP Infections** | **-70.5%** (-104,437) | **-77.6%** (-115,055) | **-63.9%** (-94,740) | **-70.7%** (-104,857) |
| **Reduced ESP Deaths** | **-77.5%** (-44) | **-83.1%** (-47) | **-71.1%** (-40) | **-77.8%** (-44) |
| **Reduced ESP Peak Absenteeism** | **-45.2%** (-54,893) | **-44.3%** (-53,802) | **-45.4%** (-55,063) | **-44.5%** (-53,996) |

The reduction of the burden of a moderate pandemic that accrues from the antiviral utilization scenario is indicated in parenthesis.

The results indicate a considerable reduction of the burden of a moderate pandemic largely stemming from the reduction in the number of people infected (23-25%) and substantially reduced HCW and ESP rates of absence[47]. Furthermore, with the exception of the TGAP Interpretation 2 plus Pre 84 days scenario, under these additional stockpile scenarios, the current stockpile of 80.98 million doses does not run-out during the course of the pandemic[48].

Given that the CPIP uses an age independent case fatality rate of 0.40%, for comparative reasons, the number of HCWs and ESPs lives saved under the CPIP case fatality rate assumptions are also reported as follows:

**Exhibit 11 HCW/ESP death reduction under CPIP assumptions: Four top ranked antiviral utilization scenarios**

| | TGAP Interpretation 1 plus Pre 84days | Treatment only plus Post | TGAP Interpretation 2 plus Pre 84 days | Treatment only plus Pre 84 days |
|---|---|---|---|---|
| **HCW Reduced Deaths** | **-320** (88%) | **-313** (86%) | **-309** (85%) | **-298** (82%) |
| **ESP Reduced Deaths** | **-478** (81%) | **-506** (85%) | **-453** (76%) | **-479** (81%) |
| **Total of HCW and ESP Reduced** | **-798** (84%) | **-819** (86%) | **-761** (80%) | **-777** (81%) |

The percentage reduction of the burden of a moderate pandemic that accrues from the antiviral utilization scenario is indicated in parenthesis.

Notwithstanding the increase in mortality rate assumed under the CPIP, the percentage of lives saved for each scenario had remained stable.

[47] The absence rates for HCWs and ESP are approximately 2.6% above those of usual seasonal flue rates.
[48] Hence mitigating any potential ethical issue for community leaders as the benefits of protecting HCWs and ESPs are not outweighed by the population health impacts.

### 1.1.8 TOP RANKED SCENARIO INCREMENTAL RESULTS

As a measure of incremental performance, each of the four top ranked antiviral utilization scenarios can be viewed as an additional strategy to their respective current Canadian stockpile scenarios. A challenge to this approach is that each current Canadian stockpile scenario has different characteristics (e.g. depletion rates of stockpile, HCW versus general population).

For the purposes of gauging incremental performance against a common current stockpile use scenario, each of the four top ranked antiviral utilization scenarios are measured against the treatment only use of the current stockpile (as the current stockpile is not fully depleted under this scenario). The results are an approximate measure of the further incremental reduction of a pandemic burden given an investment in an additional antiviral stockpile:

**Exhibit 12 Incremental reduction of a pandemic burden for society: Four top ranked antiviral utilization scenarios**

| | TGAP Interpretation 1 plus Pre 84days % Change to Treatment only | Treatment only plus Post % Change to Treatment only | TGAP Interpretation 2 plus Pre 84 days % Change to Treatment only | Treatment only plus Pre 84 days % Change to Treatment only |
|---|---|---|---|---|
| **Further Reduced Population Infected** | **-5.6%** (-628,808) | **-4.2%** (-472,165) | **-4.6%** (-518,699) | **-3.6%** (-406,515) |
| **Further Reduced Population Deaths** | **-4.5%** (-750) | **-3.3%** (-558) | **-1.9%** (-321) | **-2.8%** (-479) |
| **Further Reduced Hospitalizations** | **-5.8%** (-3,890) | **-4.4%** (-2,955) | **-4.2%** (-2,836) | **-3.8%** (-2,539) |
| **Further Reduced GP Visits** | **-5.6%** (-303,839) | **-4.2%** (-228,152) | **-4.6%** (-250,631) | **-3.6%** (-196,430) |
| **Further Reduction of Societal Economic Impact** | **-4.4%** (-521m) | **-3.5%** (-$421m) | **-3.3%** (-394m) | **-2.3%** (-270m) |

The incremental reduction of the burden of a moderate pandemic that accrues from the antiviral utilization scenario is indicated in parenthesis.

**Exhibit 13 Incremental reduction of a pandemic burden for HCWs and ESPs: Four top ranked antiviral utilization scenarios**

| | TGAP Interpretation 1 plus Pre 84days % Change to Treatment only | Treatment only plus Post % Change to Treatment only | TGAP Interpretation 2 plus Pre 84 days % Change to Treatment only | Treatment only plus Pre 84 days % Change to Treatment only |
|---|---|---|---|---|
| **Further Reduced HCW Infections** | **-61.0%** (-55,299) | **-58.2%** (-52,768) | **-56.3%** (-51,039) | **-51.7%** (-46,848) |
| **Further Reduced HCW Deaths** | **-48.1%** (-16) | **-46.0%** (-15) | **-43.0%** (-14) | **-40.9%** (-14) |
| **Further Reduced HCW Peak Absenteeism** | **-23.8%** (-29,927) | **-23.0%** (-28,926) | **-24.9%** (-31,349) | **-23.1%** (-29,012) |
| **Further Reduced ESP Infections** | **-51.1%** (-75,770) | **-58.3%** (-86,388) | **-44.6%** (-66,073) | **-51.4%** (-76,190) |
| **Further Reduced ESP Deaths** | **-40.5%** (-23) | **-46.1%** (-26) | **-34.0%** (-19) | **-40.8%** (-23) |
| **Further Reduced ESP Peak Absenteeism** | **-24.5%** (-29,791) | **-23.7%** (-28,699) | **-24.7%** (-29,961) | **-23.8%** (-28,893) |

The incremental reduction of the burden of a moderate pandemic that accrues from the antiviral utilization scenario is indicated in parenthesis.

The results indicate a considerable reduction in the burden of a moderate pandemic for HCWs and ESPs with additional benefits for society as a whole.

The incremental burden reductions of the four top ranked antiviral utilization scenarios using the CPIP case fatality rate assumptions for number of HCWs and ESPs lives saved are also reported as follows:

**Exhibit 14 HCW and ESP Incremental death reduction: Four top ranked antiviral utilizations, CPIP case fatality rate assumptions**

| | TGAP Interpretation 1 plus Pre 84days % Change to Treatment only | Treatment only plus Post % Change to Treatment only | TGAP Interpretation 2 plus Pre 84 days % Change to Treatment only | Treatment only plus Pre 84 days % Change to Treatment only |
|---|---|---|---|---|
| **HCW Reduced Deaths (using CPIP age independent case fatality rate of 0.40%)** | **-40.0%** (-145) | **-38.2%** (-138) | **-36.9%** (-134) | **-33.9%** (-123) |
| **ESP Reduced Deaths (using CPIP age independent case fatality rate of 0.40%)** | **-33.5%** (-199) | **-38.2%** (-227) | **-29.2%** (-173) | **-33.7%** (-200) |
| **Total of HCW and ESP Reduced Deaths (using CPIP age independent case fatality rate of 0.40%)** | **-36.0%** (-344) | **-38.2%** (-365) | **-32.1%** (-307) | **-33.8%** (-323) |

The percentage reduction of the burden of a moderate pandemic that accrues from the antiviral utilization scenario is indicated in parenthesis.

The incremental cost of each of the four top ranked antiviral utilization scenarios is measured by the cost of the additional antiviral stockpile (above and beyond the current Canadian stockpile) required to support the scenario. The incremental cost of each of the four top ranked antiviral utilization scenarios are:

- **TGAP Interpretation 1 plus Pre 84days:** Additional stockpile of 83.15 million at a 2010 cost of $212.4 million;
- **Treatment only plus Post:** Additional stockpile of 51.04 million at a 2010 cost of $130.4 million;
- **TGAP Interpretation 2 plus Pre 84 days:** Additional stockpile of 83.07 million at a 2010 cost of $212.2 million;
- **Treatment only plus Pre 84 days:** Additional stockpile of 82.77 million at a 2010 cost of $211.4 million.

These costs can then be compared against the economic benefits of the intervention. A net present value payback measure is used to measure the economic benefits as a ratio of the cost of the intervention. A payback of zero indicates the intervention's ability to "pay for itself". A payback of greater than zero indicates the intervention's ability to generate excess returns. A payback of less than zero indicates a net cost of the investment.

The societal net payback of an antiviral investment is the sum of the net benefits of the particular scenario, for society, divided by the accrued costs of the antiviral stockpile on hand. The net benefits for society include the

reduced impacts upon total hospitalization costs, indirect wages and corporate profits less the accrued costs of the antiviral stockpile on hand.

**Exhibit 15 Societal payback: Four top ranked antiviral utilization scenarios**

| Societal Payback on Additional Stockpile Cost | TGAP Interpretation 1 plus Pre 84days | Treatment only plus Post | TGAP Interpretation 2 plus Pre 84 days | Treatment only plus Pre 84 days |
|---|---|---|---|---|
| **Societal Payback if Pandemic in 2010** | **3.20 times** (+$679m) | **3.23 times** (+$421m) | **4.19 times** (+$889m) | **1.28 times** (+$270m) |
| **Societal Payback if Pandemic in 2015** | **4.89 times** (+$1,039m) | **3.57 times** (+$465m) | **4.60 times** (+$976m) | **1.45 times** (+$307m) |
| **Societal Payback if Pandemic in 2020** | **2.07 times** (+$658m) | **2.10 times** (+$409m) | **2.80 times** (+$888m) | **0.67 times** (+$210m) |

The net present value to society of the investment (present value of gains less present value of costs) that accrues from the antiviral utilization scenario is indicated in parenthesis.

It is evident from these results that each of the four top ranked antiviral utilization scenarios exhibits an ability to generate an incremental improvement upon their respective current Canadian stockpile scenarios.

The government net payback of an antiviral investment is the sum of the net benefits of the particular scenario, for government, divided by the accrued costs of the antiviral stockpile on hand. The net benefits for government include the reduced impacts upon total hospitalization costs, indirect income tax revenues and consumption tax revenues for all Canadian Governments combined less the accrued costs of the antiviral stockpile on hand.

**Exhibit 16 Government payback: Four top ranked antiviral utilization scenarios**

| Government Payback on Additional Stockpile Cost | TGAP Interpretation 1 plus Pre 84days | Treatment only plus Post | TGAP Interpretation 2 plus Pre 84 days | Treatment only plus Pre 84 days |
|---|---|---|---|---|
| **Government Payback if Pandemic in 2010** | **0.57 times** (+$121m) | **0.58 times** (+$75m) | **0.91 times** (+$193m) | **-0.15 times** (-$33m) |
| **Government Payback if Pandemic in 2015** | **1.16 times** (+$247m) | **0.70 times** (+$92m) | **1.06 times** (+$226m) | **-0.09 times** (-$18m) |
| **Government Payback if Pandemic in 2020** | **0.15 times** (+$46m) | **0.15 times** (+$29m) | **0.39 times** (+$125m) | **-0.38 times** (-$121m) |

The net present value to government of the investment (present value of gains less present value of costs) that accrues from the antiviral utilization scenario is indicated in parenthesis.

Of the top four ranked scenarios, the three top ranked antiviral utilization scenario payback measures show the ability for each scenario to not only recoup their costs but to also return incremental net present value gains. The Treatment only plus Pre 84 days scenario (ranked forth) exhibits an incremental net present value gain for society and an incremental net present value loss for governments (given the net payback measure is less than zero).

## LIMITATIONS AND FUTURE RESEARCH

During the course of the current study several key limitations were identified, that need further research. Once addressed, they could strengthen the conclusions of the current study. The limitations include:

- **The unique nature of a future pandemic:** Since a future pandemic will likely be driven by the emergence of a distinctive pathogen, the dynamics of such pandemic are unknown. In particular the infectiousness, pathogenicity and virulence of this strain cannot be exactly known and are generally (within literature) assumed from past observations (past pandemics). The current study assumed the emergence of a pathogen capable of producing a moderate pandemic in Canada. The parameters of such a pandemic were stylized on the 1957/58 Asian flu pandemic. Additional research concerning the effects of various levels of virulence and pathogenicity of the pandemic strain can be of value.
- **Possibility of a multi-strain pandemic:** The current study was limited to a single viral strain for which vaccines could be developed for the second wave. It was therefore assumed that vaccines may play a key role in any subsequent emergence of the virus (later waves). The existence of multiple wave pandemic (with mutating strain) may alter the use of antiviral drugs in the subsequent waves. Fixed travel and general contacts: Due to the lack of supporting evidence, the current study assumed static travel and general contact restrictions (travel and contacts between people do not change during a pandemic). Dynamic travel restriction and person to person contact should be investigated.
- **External impacts on Canada:** The effects of pandemic spread in the United States (or other nations) will have an effect on the dynamics of a pandemic in Canada. The absence of control measures (such as antiviral interventions) in the United States can have a significant impact upon the dynamics of a pandemic in Canada. As a result, it was assumed in the current study, that the United States followed the same control measures as pursued by Canadian authorities. Further research into this area would be of value to understanding the value proposition of a collective international antiviral intervention approach.
- **Impact of the timing at which antiviral stockpiles are used:** The dynamics of a pandemic are highly sensitive to the assumption of the start date of antiviral use. In the case of treatment and post-exposure prophylaxis use, the sooner antivirals are used, the greater their impact. This study is limited by the practical issue of not knowing when authorities are to declare a pandemic and when antiviral use would be approved for widespread use. The conclusions of this study could be further enhanced by sensitivity testing the point at which antivirals would be approved for widespread use, rather than relying upon a single assumption.
- **Organized pandemic public health and health care response:** The study assumes that public health and health care systems can efficiently and effectively distribute antivirals throughout the duration of a pandemic. More so, in order to deliver antivirals, the system needs to be able to assess patients and triage them to appropriate streams of therapy. These assumptions are untested and may not hold well. As such, it is important to consider the general preparedness of the health care system as an underpinning to any plan for antiviral delivery.
- **Consequences of stockpile wastage for anticipated stockpile adequacy:** The current study assumed no antiviral wastage due to unintended use. The inclusion of antiviral wastage analysis would increase the cost of an antiviral intervention, and would more importantly show faster stockpile depletion rates than have been reported in this study.
- **Size of current antiviral stockpiles in Canada:** The results of this study are limited by the finding that the presently assumed antiviral stockpile of 80.98 million doses is insufficient to support the two TGAP interpretations examined. Further, there may be other private stockpiles (e.g. hospital and corporate organizations that may have purchased antivirals as part of their emergency preparedness plans) in existence. The conclusions of this study could be further enhanced by testing value propositions under the assumptions of increasing the current antiviral stockpile to cover the TGAP interpretations and incorporating the effect of private stockpiles.
- **Antiviral intervention only:** The results of the study are limited by considering only antiviral intervention. Examination of antiviral interventions combined with the implementation of other public health

interventions designed to limit exposure would provide a test of the resilience of the value propositions reported in this study.

- **Absenteeism due to seasonal flu:** The absenteeism and economic impact results are dependent upon assumptions that have been taken from the CPIP. Empirical evidence of changes to HCW, ESP and other industry absenteeism in response to a pandemic is scarce and there is a need for future research in this area. Further, absenteeism is also confounded by the assumption of an 11.1% seasonal flu rate. Research is required on the effect of antivirals upon a coincident seasonal flu and subsequent absenteeism impacts.
- **The effects of ESP essential services on the dynamics of the pandemic:** Pandemic impacts upon the ability of ESPs to support and provide essential services to the community have not been accounted for. For this reason, the results of this study are likely to have been underestimated and further research is required.
- **The presence of vulnerable populations:** The study is limited to the extent that pandemic impacts on vulnerable populations such as those residing in isolated regions, aboriginal communities or the homeless population have not been taken into account. The value proposition of the role of antivirals for the protection of vulnerable populations is a worthy area of investigation.
- **The use of hospital resources:** The study is limited to the extent that changes to hospital resource configurations during a pandemic have not been assessed (e.g. the impact upon elective vs. emergency surgeries). This further impedes the assessment of impact for the chronically ill within the hospital system. For this reason, the results of this study are likely to have been underestimated and further research is required.

## CONCLUSION

In the current study a mathematical model was developed in an effort to draw a distinction between the effects of various antiviral policies on the dynamics of a potential influenza pandemic in Canada. In particular, the study investigated interpretations of the current TGAP recommendations and "treatment only" policies to include a 100% prophylaxis for health care workers and emergency service providers. The model simulations indicated that when dispensed in such a manner, the pre-exposure and post-exposure prophylaxis scenarios presented health and economic benefits despite the need for additional stockpile acquisition. The study indicated that in general, policies which are based on protecting health care workers and emergency service providers through the use of prophylaxis outperform those which do not provide such protection under every measure considered (life and economic).

Evaluated against antiviral use cases of the current Canadian stockpile, the dominant group of scenarios was those that involved an 84 day pre-exposure prophylaxis for all HCWs and ESPs. A stockpile of this magnitude would require the purchase of 83.15 million additional doses of antivirals. Measured against the current stockpile utilization of treatment only, an investment in the top ranked scenario would incrementally reduce infections by another 61.0% for HCWs and 51.1% for ESPs. It would reduce deaths by another 48.1% for HCWs and 40.5% for ESPs, in addition to reducing the expected peak absenteeism of HCWs and ESPs by 29,927 and 29,791 respectively. This would yield a net present value gain to society, of $521 million.

Post-exposure prophylaxis for all HCWs and ESPs coupled with a current stockpile utilization of treatment only also performed well (ranking second amongst individual scenario rankings). This scenario would require an additional post-exposure prophylaxis stockpile of 51.04 million doses of antivirals. Measured against a current stockpile utilization of treatment only, such an investment would incrementally reduce infections by a further 58.2% for HCWs and 58.3% for ESP. It would reduce deaths by a further 46.0% for HCWs and 46.1% for ESP, in addition to reducing the expected peak absenteeism of HCWs and ESP by 28,926 and 28,699 respectively. This would yield a net present value gain to society, of $421 million.

Such investments in additional antiviral stockpiles represent a risk reduction strategy that would increase the protection of health care workers and emergency service providers with complementary benefits for the population as a whole (less infections, deaths, hospitalizations and general practitioner visits). A number of limitations and possible future research questions were identified during the analysis of the current study. In particular, throughout the duration of the study, the nature of changes to the health system's infrastructure and resource allocations within hospitals during a potential pandemic remained difficult to ascertain. Research into this area would strengthen the conclusions of the current study.

## TABLE OF MODEL PARAMETERS AND ASSUMPTIONS

List of key assumptions used to parameterize the model:

| Item | Assumptions |
|---|---|
| **Number, Date and Location of the Initial Infection** | Pandemic begins in the United States on 1st January 2010. Infectious individuals begin to enter Canada from the United States and Mexico according to travel matrix. |
| **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 (Mossong 2008)[i] had been adopted in the current model. |
| **Population Types** | 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[ii]. |
| **Probability of Virus Transmission** | The transmission probability is conditional upon contact with an infectious individual. The relative age group structure had been adopted from Haber *et al*. (2007)[iii] based on 4 age groups (0-4, 5-18, 19-64, >65). 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 had been adopted from Longini et al (2004)[iv] 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 (Haber et al. 2007). This corresponds to an approximate case specific mortality of around 0.17%. |
| **Average Latency** | 1.9 days (Expert advice from the Infectious Disease Advisory Board). Incubation period is assumed to be equal to the Latent period. |
| **Average Recovery** | 4.1 days (Expert advice from the Infectious Disease Advisory Board). Symptomatic cases are always assumed to be Infectious. |
| **Immunity (%)** | No prior population immunity to the virus is assumed within the current model (Expert advice from the Infectious Disease Advisory Board) |
| **Asymptomatic Cases** | Assumed no asymptomatic cases (Expert advice from the Infectious Disease Advisory Board). |
| **Travel and Migration** | The migration patterns are adopted from CANSIM 2006 survey[v] 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. |
| **Hospitalization Rate** | Age dependent hospitalization rate (Source: Haber *et al*. (2007)). |
| **Absenteeism** | Three sources of absenteeism are computed within the current model[vi]:<br>Due to influenza symptoms (computed within the model)<br>Due to care giving (computed within the model based on CPIP recommendations)<br>Due to prudence (based on CPIP recommendations)[vii] |
| **GDP absenteeism impacts** | Impact of absenteeism on output: aggregate production function with an output-hours elasticity of 0.6 used for absenteeism due to mortality, illness followed by recovery, caregiving and workplace avoidance[viii]. |

| Item | Assumptions |
|---|---|
| **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 (Source: TGAP report)[ix] |
| **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 4.1 days (Average recovery time). |
| **Antiviral Efficacy** | Treatment is ineffective if administered more than 2 days after infectious stage begins, but given nonetheless (IDAB recommendation). |
| **Pre-Exposure Start and Duration** | 56 days and 84 days. The optimization model solved for the start dates (days after cumulative deaths reaches 20 for Canada) that produces the minimum absenteeism for HCWs and ESPs. |
| **Treatment Compliance** | 53% of people who are infectious will seek treatment[x] |
| **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 Infection Factor** | Health care workers have 1.92 more contacts than public (this corresponds to 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. (Source: PAC recommendation). |
| **POST and PRE Compliance for HCW & EMS** | Assumed 100% compliance. |
| **Misdiagnosis Wastage** | Assumed no wastage due to misdiagnosis. |
| **Relative costs of POST and PRE Administration** | No economic difference between distributing POST or PRE-Exposure prophylaxis. |
| **Life and economic Impact of ESP Absenteeism** | Assumed no impact as data was not available to support otherwise. |
| **TGAP Proportions** | 92.5% of HCW are in “closed facilities” for Interpretation 2 and 3<br>0% of ESP are in “closed facilities” for Interpretation 2 and 3<br>0.7% of Public are in “closed facilities” for Interpretation 2,<br>2.1% of Public are in “closed facilities” for Interpretation 3[xi] |
| **HCW and ESP Numbers** | Number of HCW accounts for 1.44% of population<br>Number of ESP accounts for 1.35% of population |
| **GP Visits** | 48.3% of sick visit a GP (OHPIP, 2008) |
| **Hospitalization Rate** | Age dependent hospitalization rate (Source: Haber *et al*. (2007)) |
| **Post-exposure Prophylaxis Limits** | 84 day limit on repetition of post-exposure prophylaxis cycle. |
| **Relative Efficacy (Pre-Exposure)** | The relative efficacy varies in studies between 74% (Hayden 2001)[xii] and 91% (Peters 2001). In the current model an average of 83% was assumed (average of values from various studies published in the TGAP report). |
| **Relative Efficacy (Post-Exposure)** | The relative efficacy varies in studies between 68% (Hayden 2004) and 89% (Welliver 2001)[xiii]. In the current model a average of 78.5% is assumed (midpoint between the results of the two studies). |

| Item | Assumptions |
|---|---|
| **Efficacy for reducing pathogenicity** | The efficacy for reducing pathogenicity was assumed to be 56% (95% CI: 10,73 Holloran 2006)[xiv] |
| **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, Nicholson 2000)[xv] |

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