# The effect of timing of oseltamivir chemoprophylaxis in controlling influenza A H3N2 and influenza B outbreaks in long term care facilities in Manitoba, Canada, 2014-2015: A retrospective cohort study

by

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# Abstract

This study examines the effect of the timing of administration of oseltamivir chemoprophylaxis for the control of influenza A H3N2 and influenza B outbreaks among residents in long term care (LTC) facilities in Manitoba, Canada during the 2014-2015 influenza season. A retrospective cohort study was conducted of all LTC facility influenza A H3N2 outbreaks (n=94) and influenza B outbreaks (n=11) using a hierarchical logistic regression analysis. Delay of oseltamivir chemoprophylaxis was associated with increased odds of infection in both univariate (*t = 5.41, df = 51, p < 0.0001*), and multivariate analyses (*t = 6.04, df = 49, p < 0.0001*) with an adjusted odds ratio of 1.3 (*95% CI: 1.2-1.5*) per day for influenza A H3N2. No meaningful statistical analyses regarding influenza B could be conducted. From this study, we can conclude that the sooner chemoprophylaxis is initiated, the lower the odds of secondary infection with influenza in LTC facilities during outbreaks caused by influenza A H3N2 in Manitoba.

# Acknowledgements

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# Dedication

This work is dedicated to my wife, Dr. Ceri Richards, the smartest and most wonderful person I know. She is a constant source of love and encouragement.

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# Acronyms

CPL - Cadham Provincial Laboratory

IDSA - Infectious Diseases Society of America

IP&C - Infection Prevention and Control

LTC - Long Term Care

RHA - Regional Health Authority

# Definitions

Attack rate - the number of new cases of a specific disease reported during a time interval divided by the total population at risk of the disease at the start of the time interval.

Long term care facility - generally defined as institutions that take care of residents who are unable to take care of themselves; residents are also typically over the age of 65.

Outbreaks - an increased incidence of a disease, or number of new infections, compared to the background rate of that disease.

Regional Health Authority - an arms-length organization responsible for the delivery of publicly administered health care in a defined geographic area. Manitoba is divided into five RHAs: the Winnipeg Regional Health Authority (WRHA), Interlake-Eastern Regional Health Authority (IERHA), Northern Regional Health Authority (NRHA), Prairie Mountain Health (PMH), and Southern Health – Santé Sud (SH).

Rural - 10,000 people or less based on the Canadian Census conducted closest to the study period.

Secondary attack rate - a measure of the frequency of new cases of a disease among contacts of cases.

# Introduction

Influenza is a major cause of morbidity and mortality in Canada, accounting for an estimated 12,000 hospitalizations and 3,500 deaths every year [1]. It also disproportionately affects certain sub-groups of the population, with the elderly being affected most severely [1]. A proportion of elderly adults reside in long term care (LTC) facilities which, due to their population and configuration, are particularly prone to outbreaks of influenza.

LTC facilities are generally defined as institutions that take care of residents who are unable to take care of themselves; residents are also typically over the age of 65 [2]. Outbreaks are defined as an increased incidence, or number of new infections, of a disease compared to the background rate of the disease [3]. For some diseases, this can be just one case of infection, and for others there may need to be hundreds of new infections before it could be determined to be an outbreak. Outbreaks contribute to the significant morbidity and mortality attributed to influenza, since many of the residents in LTC facilities have multiple chronic conditions [4-8]. Influenza is also known to exacerbate chronic medical conditions, specifically cardiac or pulmonary disorders, cancer, other immune compromising conditions, kidney disease, anemia or hemoglobinopathy, diabetes or other metabolic conditions, conditions that compromise the management of respiratory secretions, and morbid obesity [1]. Therefore, any reduction in illness during an annual influenza outbreak, especially in LTC facilities, would be expected to reduce both the morbidity and mortality associated with that annual epidemic.

In Manitoba, if an influenza outbreak is detected in a LTC, the standard protocol is that all symptomatic residents are to receive five days of oral oseltamivir at the *therapeutic* dose and all other residents receive 10 days of oseltamivir chemoprophylaxis at the *prophylactic*

dose [9]. This same approach is described in many studies, used in other countries, and is also very similar to the recommendations of the Infectious Diseases Society of America (IDSA) [5, 7, 9-12]. Though the IDSA guideline recommends different neuraminidase inhibitors depending on the type or subtype of influenza detected [10], all influenza outbreaks in LTC facilities in Manitoba are controlled with oseltamivir regardless of type or subtype [9].

In the 2014/2015 influenza season, Manitoba administered over 50,000 doses of oseltamivir for LTC outbreak chemoprophylaxis [13] at an approximate cost of $5.72 per dose [14]. This one seasonal total of almost $300,000 does not include any other associated costs, such as nursing time, nor does this include doses prescribed in the community or the hospital setting. Given that this single intervention is being highly relied upon and at significant cost, the evidence of its effectiveness should be strong and convincing so that health care providers can be confident that they are making an evidence-based decision. However, the studies that the IDSA has relied upon to make the recommendation [6, 8, 11, 15-17], and those published since the recommendation [5, 7, 12, 18, 19], have significant limitations, with low quality evidence and mixed results for the effectiveness of prophylactic oseltamivir in LTC facilities.

To better understand if there is utility in following the portion of the IDSA guideline relating to oseltamivir use in LTC facility outbreaks, the current study examines the effect of the timing of administration of oseltamivir chemoprophylaxis for the control of influenza A H3N2 and influenza B outbreaks among residents in LTC facilities in Manitoba, Canada during the 2014/2015 influenza season, after controlling for other institutional factors. The results of this study can be used to guide provincial policy relating to the influenza chemoprophylaxis timing

within LTCs as well as contribute to the literature examining the secondary attack rate, or odds of becoming ill, in LTC facilities.

# Background

### *What is Influenza?*

Influenza is a virus that causes respiratory infections ranging from asymptomatic to life-threatening in consequences [1]. The virus can be divided into two main epidemic types, A and B, of which there are many different subtypes, lineages and strains. The influenza A subtypes are named according to serotype differences in two viral surface proteins, neuraminidase (N) and hemagglutinin (H), and the two main subtypes of influenza A that have been circulating in recent years are H1N1 and H3N2, though each of these subtypes can be further differentiated into antigenically-distinct lineages and strains [1]. Each year there are slight differences in the composition of the circulating strains of influenza, which is why a new vaccine is needed every year. This means that the infectivity, virulence, and populations most affected by the virus will change from year to year, making it difficult to directly compare effectiveness of influenza prevention programs from year to year.

### *What is Oseltamivir?*

Oseltamivir belongs to a class of drugs called neuraminidase inhibitors (NIs). The N protein on the surface of the influenza virus works by helping to release viral progeny from the surface of an infected cell after replication [20]. Therefore, NIs work to stop this process by preventing the release of these viral progeny and stopping the infection from progressing [20].

In this way, NIs are considered useful for both treatment of influenza infection and prophylaxis to prevent clinically-apparent influenza infection.

### *What is an Attack Rate, and Why is it Important?*

An attack rate is defined as the number of new cases of a specific disease reported during a time interval divided by the total population at risk of the disease at the start of the time interval [21]. It is used to measure of the spread of a disease. This is different from the secondary attack rate which is "a measure of the frequency of new cases of a disease among contacts of cases" [21]. The important part of this definition which differentiates it from the overall attack rate is that it excludes the initial cases of infection. This is important because, by definition, none of the initial cases can be prevented by responsive interventions (such as post-exposure prophylaxis) once an outbreak has been detected. Therefore, when reporting the overall attack rate, instead of the secondary attack rate, interventions of smaller institutions may seem less effective, since initial cases will likely contribute disproportionately more to the overall attack rate, relative to a larger institution's. This makes the calculation of the secondary attack rate paramount.

### *Why the 2014-2015 Influenza Season, and Why Influenza A H3N2 and Influenza B?*

The 2014-2015 influenza season was chosen for this analysis because this season presented a highly unique opportunity to assess non-vaccine interventions due to the almost null effect of vaccine on the dominant H3N2 strain [22], the large number of documented outbreaks in LTC facilities in that season, and the high number of interventions that ensued. This created the setting for an excellent natural experiment.

Influenza A H3N2 and influenza B were selected because these were the dominant circulating influenza viruses in Manitoba during the 2014-2015 influenza season. Manitoba's Cadham Provincial Laboratory (CPL) only detected influenza A H1N1 from one specimen out of the 699 sub-typed influenza specimens reported by the CPL that season [13].

### *Manitoba and the IDSA Guidelines*

In 2009, the Infectious Diseases Society of America (IDSA) published its guidelines for the treatment and prevention of influenza in children and adults [10]. The guideline recommended that all residents in LTC facilities should be given either oseltamivir or zanamivir, both neuraminidase inhibitors, for chemoprophylaxis if two or more residents become ill with an influenza-like illness (ILI) within 72 hours of each other and influenza A virus or influenza B virus is detected in at least one ill person [10]. In Manitoba, all residents are given oseltamivir if two or more residents become ill with an ILI within seven days of each other and influenza virus is detected in at least one ill person [9]. The regimen provided to each resident is dependent on if the resident is ill or not ill.

### *Evidence behind the IDSA Guidelines*

IDSA based their guidelines on a review of six available studies: Bowles et al, Peters et al, Hayden et al, Monto et al, van der Sande et al. 2006, and Welliver et al [6, 8, 11, 15-17]. All six of the studies informing the guideline reported a benefit of oseltamivir use in controlling influenza outbreaks. The IDSA reported the level of evidence for its recommendation as I-A [10], meaning that it is derived from a systematic review of randomized control trials. I-A is also the highest level of evidence available for recommendations. Yet the evidence supporting the recommendation for oseltamivir is much weaker than these guidelines suggest.

The IDSA guidelines recommend the use of either oseltamivir or zanamivir, which are both neuraminidase inhibitors [10]. However, each is administered in different ways, have different pharmacokinetics, and different *in vitro* activity against the different types and subtypes of influenza virus [20]. Therefore, when evaluating the strength of the evidence for oseltamivir, it is critical to exclude studies based only on zanamivir (n = 2).

Additionally, in considering the six referenced publications, there exist several relevant weaknesses in design or conduct to base such strong concluding recommendations as found in the IDSA guidelines. These include using an incomparable study population [11, 17], using an incomparable intervention [8], being a descriptive study [16], relying on small sample sizes [6, 15], and varying timing [6, 15]. Additionally, not one of the studies included any analysis of secondary attack rates.

*An incomparable study population*. Hayden et al. and Welliver et al. studied the effect of neuraminidase inhibitor administration in average households [11, 17]. An average household contains mostly children and young to middle aged adults, as seen by the ages of the participants in these two studies [11, 17]. This population is very different from that of a LTC facility and the IDSA guideline recognizes the significant difference in immune competence of the elderly relative to younger individuals [10]. Thus, the ability to respond to infection fighting and preventing medication may be very different in the elderly population compared to the younger, often much healthier, population [2]. Therefore, the findings in these studies, though favourable for the effect of chemoprophylaxis on preventing influenza infection, cannot be assumed to be the same in an elderly population in LTC facilities.

*An incomparable intervention*. Peters et al. used a completely different intervention [8]. In this study, oseltamivir prophylaxis was given for 6 continuous weeks at the start of the influenza season in the experimental group and not given to the control group. So, though the study had a randomized design, the intervention is not comparable to only giving oseltamivir for 10 or 14 days once the exposure to influenza has occurred, as is the practice in Manitoba and the recommendation from the IDSA guidelines [9, 10].

*Descriptive study*. The study performed by van der Sande et al. 2006 was descriptive in nature [16]. This study only examined which LTC facilities used oseltamivir for post-exposure prophylaxis, and under which circumstances oseltamivir was and was not used. No conclusions about the effectiveness of oseltamivir should be drawn from this type of study; at best it provides a III level of evidence.

*Small sample sizes*. Bowles et al. and Monto et al. had small sample sizes [6, 15]. Monto et al. analyzed eight outbreaks [15], and Bowles et al. had ten [6]. Moreover, neither made a distinction between overall attack rate and secondary attack rate, which is critically important to evaluating a post-detection intervention, and both had other aspects of their procedures which made it difficult to assess the impact of oseltamivir. For example, in Monto et al., some of the LTC facilities did not give the oseltamivir to all unaffected residents, while others did, and some of those who did not receive prophylaxis were exposed to ill residents while others were not [15].

*Timing of oseltamivir use*. Lastly, some facilities gave their residents oseltamivir immediately, as in Hayden et al. and Welliver et al. [11, 17], while in others there was a delay, for example Bowles et al. and Monto et al. [6, 15]. Yet, these differences were not accounted

for when comparing the infection rate of those who received oseltamivir and those who did not. In Bowles et al, two outbreaks occurred in the same institution [6]. This would likely change the expected secondary attack rate due to immune response among residents, but this was not accounted for. Consider also that half of the facilities initially attempted to control the outbreaks with Amantadine, a different drug from a different class that works in a different way from oseltamivir, making the overall results again more difficult to interpret.

Many potential problems existed with the evidence that was used to inform the IDSA guidelines. These confounders and others can also be found in the studies published since these guidelines. When inconclusive or mixed evidence is produced, this weakens the generalizability of a stated guideline and calls into question the scope of applicability of recommended clinical or preventative actions.

*Published Research Post-publication of the IDSA Guidelines*

To evaluate the evidence published since the publication of the IDSA guidelines, a search of both the database PubMed and a hand search were conducted.

PubMed was searched using both free text (terms used: (oseltamivir OR Tamiflu) AND (outbreak OR epidemic OR cluster) AND (long term care OR nursing home OR institution)) and MeSH terms ("Disease Outbreaks"[Mesh] AND "Oseltamivir"[Mesh] AND "Long-Term Care"[Mesh]). An initial search was conducted in October 2015, and updated in December 2016. This produced 137 studies, 106 of which were published after January 1, 2009.

All the abstracts of these studies were examined for relevance. Then the references of all relevant studies were examined further for relevance.

The references from a 2014 systematic review of neuraminidase inhibitors for the prevention and treatment of influenza in adults and children in the Cochrane database was used to evaluate the search strategy for articles published prior to July 22, 2013 (the date up to which the review evaluated) to determine the validity of the PubMed and hand searches [23]. No relevant articles included in the 2014 systematic review were missed by the PubMed and hand search.

Lastly, the search was repeated in August 2017 to determine if any new studies had been added to the PubMed database from December 2016 to August 2017. One study had been added during this time and was included in this review.

There were six relevant studies published since the IDSA guideline was released, Booy et al, Miksic et al, van der Sande et al. 2014, Millership & Cummins, Ye et al, and Singh, Robinson & Hilderman. Booy et al, Millership & Cummins, and Singh, Robinson & Hilderman reported a benefit [5, 18, 24]; Miksic reported mixed results [7], and van der Sande 2014 and Ye et al. reported no benefit [12, 19] with oseltamivir prophylaxis. As before, these studies also have significant limitations, including relying on small sample sizes, analyzing the data inappropriately, grouping infections from all types or subtypes of influenza virus, and inappropriately inferring conclusions from a descriptive study.

Booy et al, Miksic et al, van der Sande et al. 2014, and Singh, Robinson & Hilderman analyzed a small number of outbreaks. The number of outbreaks in these studies ranged from three to 15 [5, 7, 12, 24]. Van der Sande et al. 2014, which had 15 outbreaks and was a randomized control trial, represents one of the studies that showed no difference between the infection rate in the placebo and intervention groups [12]. As well, Miksic et al, the study with

the smallest number of outbreaks, had a mixed result in terms of whether oseltamivir prevented infection or not [7]. Millership & Cummins was a descriptive observational study and should not be used to draw conclusions about oseltamivir effectiveness [18]. Ye et al. grouped influenza outbreaks from multiple years into the final analysis, which is a problem as the virulence of the circulating strain changes from year to year [19]. This study also did not indicate the date of oseltamivir administration, simply the date that oseltamivir chemoprophylaxis was recommended, which may not be the same. As well, four studies, Booy et al, van der Sande et al. 2014, Millership & Cummins, and Ye et al, did not separate the analysis of the results by influenza type or subtype in the final analysis [5, 12, 18, 19]. This is problematic because oseltamivir has varying levels of activity *in vitro* depending on the type and subtype of influenza virus [20].

Only van der Sande et al. 2014, Ye et al, and Singh, Robinson & Hilderman took into account the secondary attack rate, which excluded those individuals who became ill before the outbreak was detected [12, 19, 24], and only one other study, Millership & Cummins, recognized that not using the secondary attack rate was a potential limitation [18]. None of the studies, except for Singh, Robinson & Hilderman, used a hierarchical regression analysis to analyze the results. This will have resulted in an over estimate of the standard error in Booy et al. and Ye et al, the studies that only analyzed the outbreaks at the institutional level [5, 19], and an inability to control for confounders in Miksic et al. and van der Sande et al. 2014, the studies that did not use a regression analysis [7, 12].

When Singh, Robinson & Hilderman looked at the question of the effect of timing of oseltamivir chemoprophylaxis on the secondary attack rate for influenza A H3N2 [24], a

significant effect was noted by delaying the administration of oseltamivir in LTC facilities in one Regional Health Authority in Manitoba. The odds of infection for residents were increased by approximately 50% for each day oseltamivir prophylaxis was delayed. However, interpretation of these results was limited by sample size, with only 11 outbreaks.

A comprehensive description of all 12 of these studies published before (n = 6) and after (n = 6) the IDSA guidelines can be found in Appendix A.

Given these limitations, there is both questionably applicable and conflicting evidence for the use of oseltamivir chemoprophylaxis for influenza A H3N2 or influenza B outbreaks in LTC facilities; the current IDSA guidelines in this regard are arguably both out of date and not adequately supported. No referenced study had an appropriate sample size (one in which the power was above 80%), an appropriate intervention, or appropriate analysis applied to a relevant (LTC or elderly) patient population. As well, none of the studies mentioned specifically looked at the effect of timing of oseltamivir chemoprophylaxis on the secondary attack rate of any influenza type or subtype in LTC facilities. Therefore, further investigation is necessary to determine the effectiveness of oseltamivir for use as chemoprophylaxis in this population.

## Research Questions

This study has two quantitative research questions:

1) *Is there an association between the odds of secondary infection from influenza A H3N2 and the amount of time between when an outbreak begins and when oseltamivir*

*chemoprophylaxis is initiated in long term care facilities during influenza A H3N2 outbreaks, after controlling for other institutional factors?*

We hypothesize that the time to initiate oseltamivir chemoprophylaxis after the outbreak begins is positively associated with secondary infection from influenza A H3N2.

2) *Is there an association between the odds of secondary infection from influenza B and the amount of time between when an outbreak begins and when oseltamivir chemoprophylaxis is initiated in long term care facilities during influenza B outbreaks, after controlling for other institutional factors?*

   We hypothesize that the time to initiate oseltamivir chemoprophylaxis after the outbreak begins is positively associated with secondary infection from influenza B.

# Methods

A retrospective cohort design was used to examine the effect of timing of oseltamivir chemoprophylaxis in controlling influenza A H3N2 and influenza B outbreaks in long term care facilities in Manitoba for the 2014-2015 influenza season. The benefits of a retrospective design are that one can determine a sample size large enough to power the study, the cost is minimized, and the time required to conduct the study is also reduced [25].

## *Data Sources*

Four data sources were used in this study: 1) epidemic curves, 2) hand hygiene audits, 3) lists of private and public LTC facilities in each studied region, and 4) Statistics Canada census data.

*Epidemic curves.* In Manitoba, all LTC facilities monitor for influenza-like illness (ILI). Nursing staff at each facility complete an influenza preparation toolkit each October and are instructed to keep watch for respiratory symptoms in residents. An institutional influenza outbreak is defined as "two or more cases of ILI (including at least one laboratory –confirmed case) occurring within a seven-day period in an institution" [9]. If an institutional ILI outbreak is suspected, an Outbreak Code is typically established. Then nasopharyngeal swabs are conducted on a sampling of up to six ill residents or staff to identify the causative pathogen.

Influenza is detected by growth of influenza virus on viral culture, detection of influenza-specific amplified nucleic acid or detection of influenza viral antigens from a clinical sample [9]. In Manitoba, these specimens are sent to Cadham Provincial Laboratory for testing. Once an institutional outbreak is confirmed, an Outbreak Code is assigned to the LTC facility (if not already done) which is used to track the progress of the outbreak, and is typically followed by Medical Officer of Health authorization to commence oseltamivir prophylaxis.

Staff also keep records of daily case counts and symptoms present during outbreaks to monitor their development and resolution. Once no new cases have occurred for two incubation periods of the infecting organism, which for influenza is up to eight days [1], the outbreak can be declared over. Outbreak summaries are then submitted to the Surveillance Unit within provincial government health department, Manitoba Health, Seniors, and Active Living (MHSAL).

*Hand hygiene audits.* As a part of the accreditation process that Accreditation Canada performs for Manitoban health care facilities, all health care facilities are required to evaluate hand hygiene compliance [26]. This information then informs the reports that Regional Health

Authorities (RHAs) publicly report. Hand hygiene compliance is reported as a percentage, which represents how often proper staff hand hygiene was observed in the institution. MHSAL delegates the responsibility for delivering all publicly funded health services in the province to five semi-autonomous, mutually exclusive (non-overlapping) RHAs.

*Private vs Public facilities.* The RHAs have a list of all publicly administered and privately administered LTC facilities in their region.

*Statistics Canada census data.* Canadian Census data from 2011 is used to determine the size of the cities and towns in which the LTC facilities are located.

### *Inclusion Criteria*

Based on provincial surveillance reports produced by the Epidemiology and Surveillance Unit of Manitoba Health, Seniors and Active Living, during the 2014/2015 influenza season, there were 94 outbreaks caused by influenza A H3N2 and 11 outbreaks caused by influenza B in LTC facilities in Manitoba [13]. Outbreaks were included in the analysis if: 1) they occurred between October 2014 and May 2015, 2) they occurred in a LTC facility in Manitoba, and 3) a type of influenza was determined to be the causative organism. Note that only the first outbreak of each influenza type in an institution was included in the analysis since a prior outbreak during the same influenza season with the same virus may significantly alter the immunity of the residents to that strain of influenza and thus alter the attack rate of the virus, and the subsequent likelihood of symptomatic infections.

Outbreaks were only excluded from the analysis if either the *independent variable* (how many days passed between the start of the outbreak and commencement of oseltamivir chemoprophylaxis) or the main *dependent variable* (whether the exposed person in the

institution developed ILI after outbreak detection (yes or no)) could not be determined. Therefore, institutions with more than one date indicated for oseltamivir chemoprophylaxis were excluded since the circumstances of this entry would not be known (the entry may have been made in error or the outbreak may have spread to a group that did not receive prophylaxis and was subsequently administered prophylaxes).

## *Procedures*

### Ethics

All the data obtained was administrative data. It is standard protocol that the data is anonymized by facility so the researcher cannot identify individuals. Typically this type of study does not need ethical approval as indicated in the latest edition of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans [27]. However, since this study was for a Master of Science (M.Sc.) degree, University of Manitoba ethics approval from the Human Research Ethics Board was obtained.

There were no obvious risks to the residents in the LTC facilities. However, there are benefits since this study will help to inform policy that will benefit the residents of these facilities and other LTC facilities during future influenza outbreaks.

### Obtaining the Data

The researcher contacted research board representative in each of the five Regional Health Authorities (RHAs) in Manitoba to describe the study and gain consent for participation. An RHA is an arms-length organization responsible for the delivery of publicly administered health care in a defined geographic area. Manitoba is divided into five RHAs: the Winnipeg Regional Health Authority (WRHA), Interlake-Eastern Regional Health Authority (IERHA),

Northern Regional Health Authority (NRHA), Prairie Mountain Health (PMH), and Southern Health – Santé Sud (SH). Once approval for participation was given, the various Infection Prevention and Control (IP&C) departments in the RHAs were then contacted to provide the requested epidemic curves, hand hygiene audits, and management information (about if the facility is publicly or privately operated) for the institutions that experienced outbreaks.

Canadian Census data was publicly available data on the Statistics Canada website and was accessed on June 27, 2017.

### Data Storage

Epidemic curves exist in either paper or electronic format. All other data sources were electronic. Paper records were transcribed into an electronic record and the paper copies were destroyed. The electronic records were encrypted and stored on a computer in a locked room with restricted access in the department of Community Health Sciences at the University of Manitoba. A Universal Serial Bus (USB) backup of these electronic records was made to ensure the data was not lost. This USB backup was encrypted with 128-bit encryption software and kept on the person of Dr. Davinder Singh or safely stored in his personal residence. All the names of the LTC facilities were removed and replaced by numbers.

All data will be deleted after three calendar years to allow time for completion of the manuscript of this study, publication in a peer reviewed scientific journal, and conference presentations.

### Communication of Findings

All RHAs will be informed of the results of the study after completion of the study manuscript. The findings will also be presented and defended in a public forum for the M.Sc.

thesis defence. The findings will also be published in a peer reviewed scientific journal. Acknowledgement of collaborations and assistance received from all authors, RHAs and funding sources will be included at every stage of communication.

### *Measures and Variables*

The information extracted from the epidemic curves was:

1) the number of residents who became ill during the outbreak,
2) the number of staff who became ill during the outbreak,
3) the total number of residents in the facility,
4) the total number of staff in the facility,
5) the number of secondary cases among residents,
6) the date that each resident became ill,
7) the date that each staff person become ill,
8) the percentage of residents vaccinated,
9) the percentage of staff vaccinated,
10) the date of commencement of oseltamivir chemoprophylaxis, and
11) the date of declaration of the outbreak.

The main *independent variable* was how many days passed between the true start of the outbreak (the date that the second person became ill) and commencement of oseltamivir chemoprophylaxis. The main *dependent variable* was whether each person in the institution developed ILI (yes or no). The control variables were:

1) the number of days between declaring an outbreak and the start of oseltamivir chemoprophylaxis,

2) the number of days between the first and second cases,
3) the prevalence of symptomatic infection among residents at the start of the outbreak,
4) the prevalence of symptomatic infection among staff at the start of the outbreak,
5) the number of at-risk residents at the start of the outbreak,
6) the percentage of residents vaccinated,
7) the percentage of staff vaccinated,
8) rural (yes or no),
9) publicly operated facility (yes or no), and
10) percent compliance during hand hygiene audit.

The definition of rural is the one used by the Canadian Institute for Health Information of rural being 10,000 people or less [28] based on the Canadian Census conducted closest to the study period. The hand hygiene audit conducted closest to the study period was used to determine percent hand hygiene compliance.

*Data analysis*

For each outbreak, the secondary attack rate is calculated by determining the number of people who became ill, subtracting those who became ill on or before the day that the second person became ill, and dividing this number by the total number of occupants minus the number subtracted from the numerator [21]:

$$2^0\ attack\ rate = \frac{(Total\ \#cases - \#\ Cases\ on\ or\ before\ day\ of\ 2nd\ case\ of\ illness)}{(Total\ \#\ residents - \#\ Cases\ on\ or\ before\ day\ of\ 2nd\ case\ of\ illness)}$$

The number of days until oseltamivir prophylaxis was started was calculated by determining the date of chemoprophylaxis and subtracting the date that the second person became ill in the institution.

The data was analyzed at the individual and institutional level by using a hierarchical (also known as multi-level) logistic regression model with Laplace Maximum Likelihood approximation. A hierarchical model was required because not all the observations in the study were independent. All the individuals in a LTC facility have several factors in common which influence their likelihood of becoming infected, such as the specific facility design and procedures. Therefore a simple logistic regression could not be used as it would significantly underestimate the standard error of the estimate of each independent variable [29, 30]. As well, using only the overall secondary attack rate in each facility would not be the ideal analysis either because it ignores the difference in the number of observations between small and large facilities, and overestimates the standard error of the estimate of each independent variable [29, 30]. Therefore, the hierarchical regression model is the best design since it takes both factors into account [29, 30]. This analysis was conducted in the following stepwise approach.

1) First, an empty model was used to determine the intra-class correlation (ICC). This is a measure of how dependent the observations are within each institution. It is used to determine if a hierarchical model is required for the data analysis, or if a simple logistic regression can be used [30].

2) Then, the 11 independent variables listed above were included in the model as level two (institutional level) variables and individually modeled with the outcome variable.
3) They were then added in a stepwise forward modelling strategy to determine the best multiple variable main effects model, including both statistically significant and clinically significant variables.
4) The continuous variables were then assessed for linearity to determine if any variable transformations were needed.
5) As well, model variables were assessed for co-linearity.
6) Lastly, the final main effects model was extended by adding any significant interactions between the time to oseltamivir prophylaxis and other main effects model variables: 1) the number of days between declaring an outbreak and the start of oseltamivir chemoprophylaxis, 2) the number of days between the first and second cases, 3) the prevalence of symptomatic infection among residents at the start of the outbreak, 4) the prevalence of symptomatic infection among staff at the start of the outbreak, 5) the number of at risk residents at the start of the outbreak, 6) the percentage of residents vaccinated, 7) the percentage of staff vaccinated, 8) rural (yes or no), 9) publicly operated facility (yes or no), and 10) the hand hygiene compliance score.

All analyses were two tailed and conducted at an alpha level (α) of 0.05. This means that the cut-off for the acceptability of making a Type 1 error, rejecting the null hypothesis when the null hypothesis should be accepted, was 5 percent (%).

*Power Calculations*

The power calculations presented are conservative estimates and only calculated at the institutional level, not the individual level. That is, they only use the number of outbreaks during the 2014-2015 influenza season, not the number of individuals in each LTC facility. As indicated in the literature,

$$\frac{Effect\ Size}{Standard\ Error} \approx \left(Z_{1-\alpha} + Z_{1-\beta}\right) \quad [30]$$

Therefore, if the effect size, standard error and alpha levels are known, beta (β) can be estimated. If β is known, then the power of the study can be calculated since,

$$Power = 1 - \beta \quad [29, 30]$$

The power of a study relates to Type 2 error, or accepting the null hypothesis when the null hypothesis should be rejected.

Based on the recent study conducted in Manitoba [24], the estimates and standard errors of the independent variables for a sample size of 11 outbreaks can be seen in Table 1.

Table 1: Estimates and Standard Errors of Model Predictors of Influenza

| Independent Variable | Estimate | Standard Error |
|---|---|---|
| **Days between Second Case and Chemoprophylaxis** | 0.47 | 0.18 |
| **Days between First and Second Case** | -0.74 | 0.33 |
| **Days between Declaring an Outbreak and Chemoprophylaxis** | 0.30 | 0.23 |
| **Prevalence of Influenza at Start of Outbreak** | 0.12 | 0.06 |
| **Number of At Risk Individuals at Start of the Outbreak** | -0.03 | 0.01 |

Therefore, using the equation which relates sample size to standard error,

$$Standard\ Error\ \propto \frac{Standard\ Deviation}{\sqrt{n}}$$

where n = sample size, or in this case number of outbreaks, one can estimate the power of the current study [31]. The power of this study to detect a statistically significant difference in the *dependent variable* associated with the main *independent variable* for each of the two type and subtype of influenza, A H3N2 and B, can be seen in Table 2 and Table 3.

Table 2: Estimate of power of current study for main Model Predictor for Influenza A H3N2

| Independent Variable | Estimate of Power |
|---|---|
| **Days between Second Case and Chemoprophylaxis** | > 0.99 |

Table 3: Estimate of power of current study for main Model Predictor for Influenza B

| Independent Variable | Estimate of Power |
|---|---|
| **Days between Second Case and Chemoprophylaxis** | < 0.50 |

This study was extremely highly powered for determining the effect of the variables relating to influenza A H3N2. However, the power is very low for determining the effect of the variables relating to influenza B, due to the much smaller number of outbreaks.

# Results

There were 105 influenza outbreaks in long term care facilities during the 2014-2015 influenza season. In 93 of these outbreaks, the sub-type of influenza was H3N2, in 11 of these outbreaks it was influenza B, and in one outbreak both influenza H3N2 and influenza B were detected. The outbreak with both agents detected was excluded from analysis as this was a confounding co-occurrence that could not be controlled for. Seven of the influenza A outbreaks

reported occurred in acute care facilities, not long term care facilities. Acute care has a different patient population than long term care, so these seven outbreaks were excluded from the analysis. Of the 86 remaining influenza A outbreaks, no information was available for 12 of these outbreaks. Then of the 74 remaining influenza A outbreaks, 15 had incomplete epidemic curves, and an additional six outbreaks were the second outbreak that occurred in those facilities. That left 53 influenza A outbreaks for analysis (Figure 1).

Of the 11 remaining influenza B outbreaks, no information was available for six of these outbreaks. Two of the remaining outbreaks were the second outbreak that occurred in those facilities. That left three influenza B outbreaks for analysis (Figure 1).

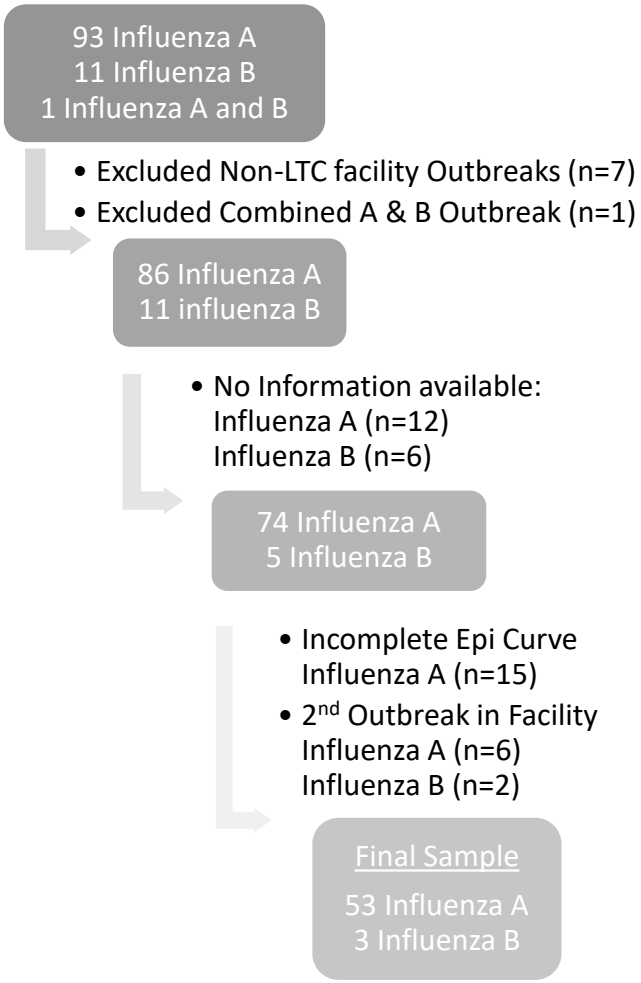


Figure 1: Outbreaks included and excluded from analysis

The summary of the characteristics of the 53 influenza A outbreaks that were included in the analysis can be seen in Table 4. The summary of the characteristics of the three influenza B outbreaks that were included in the analysis can be seen in Table 5. In total, there were 5,258 residents total in the 53 facilities with influenza A outbreaks and 261 residents total in the three facilities with influenza B outbreaks.

Table 4: Summary of Influenza A H3N2 outbreak characteristics

| Characteristic (number of facilities with information) | Average | Minimum Value | Maximum Value | Standard Deviation |
|---|---|---|---|---|
| # of Cases (n=53) | 14.57 | 3 | 81 | 13.41 |
| Total # of Residents (n=53) | 99.21 | 16 | 431 | 76.72 |
| $2^0$ Cases (n=53) | 10.38 | 0 | 77 | 12.23 |
| Residents excluding $1^0$ cases[1] (n=53) | 95.02 | 13 | 427 | 76.46 |
| $2^0$ attack rate (%) (n=53) | 14.24 | 0 | 67 | 13.73 |
| Days till chemoprophylaxis[2] (n=53) | 3.85 | 0 | 11 | 2.52 |
| Days1-2[3] (n=53) | 1.17 | 0 | 6 | 1.65 |
| Days to Declare OB[4] (n=53) | 2.08 | 0 | 10 | 2.20 |
| Prev Res Flu (%)[5] (n=53) | 6.29 | 0.9 | 19 | 5.03 |
| Prev Staff Flu (%)[6] (n=26) | 0.55 | 0 | 6.6 | 1.42 |
| % Staff Vacc[7] (n=27) | 34.07 | 8 | 96 | 22.16 |
| % Res Vacc[8] (n=40) | 82.73 | 3 | 100 | 16.71 |
| Hygiene Score[9] (n=27) | 74.29 | 49 | 100 | 14.23 |
| Rural[10] (Y/N) (n=53) | 0.51 | 0 | 1 | 0.50 |
| Private[11] (Y/N) (n=53) | 0.30 | 0 | 1 | 0.46 |

[1] Primary cases are defined as cases occurring on or before the day that the second case occurred

[2] Number of days between the second case and start of chemoprophylaxis

[3] Number of days between the first and second cases

[4] Number of days between the second case and declaring an outbreak

[5] Prevalence of influenza among residents in the institution at the start of the outbreak

[6] Prevalence of influenza among staff in the institution at the start of the outbreak

[7] Percentage of staff vaccinated for influenza during current influenza season at the start of the outbreak

[8] Percentage of residents vaccinated for influenza during current influenza season at the start of the outbreak

[9] Hand hygiene score in the facility during the 2014-2015 influenza season. If more than one audit occurred during this time, scores were averaged

[10] Rural is defined as a community having a population less than 10,000 people based on the Health Canada census in 2011 (1=Yes, 2=No)

[11] Facilities that are not directly operated by the Regional Health Authority (1=Yes, 2=No)

Table 5: Summary of Influenza B outbreak characteristics

| Characteristic (number of facilities with information) | Average | Minimum Value | Maximum Value | Standard Deviation |
|---|---|---|---|---|
| # of Cases (n=3) | 8 | 3 | 12 | 4.58 |
| Total # of Residents (n=3) | 87 | 50 | 120 | 35.17 |
| $2^0$ Cases (n=3) | 2 | 0 | 3 | 1.73 |
| Residents excluding $1^0$ cases[1] (n=3) | 81 | 41 | 114 | 37 |
| $2^0$ attack rate (%) (n=3) | 3.31 | 0 | 7.32 | 3.71 |
| Days till chemoprophylaxis[2] (n=3) | 1.67 | 0 | 4 | 2.08 |
| Days1-2[3] (n=3) | 0 | 0 | 0 | 0 |
| Days to Declare OB[4] (n=3) | 0 | 0 | 0 | 0 |
| Prev Res Flu (%)[5] (n=3) | 8.8 | 3 | 18 | 8.04 |
| Prev Staff Flu (%)[6] (n=2) | 0 | 0 | 0 | 0 |
| % Staff Vacc[7] (n=3) | 44 | 19 | 84 | 34.79 |
| % Res Vacc[8] (n=3) | 95 | 92 | 100 | 4.16 |
| Hygiene Score[9] (n=2) | 82 | 70 | 93 | 16.26 |
| Rural[10] (Y/N) (n=3) | 0.33 | 0 | 1 | 0.58 |
| Private[11] (Y/N) (n=3) | 0.67 | 0 | 1 | 0.58 |

[1] Primary cases are defined as cases occurring on or before the day that the second case occurred
[2] Number of days between the second case and start of chemoprophylaxis
[3] Number of days between the first and second cases
[4] Number of days between the second case and declaring an outbreak
[5] Prevalence of influenza among residents in the institution at the start of the outbreak
[6] Prevalence of influenza among staff in the institution at the start of the outbreak
[7] Percentage of staff vaccinated for influenza during current influenza season at the start of the outbreak
[8] Percentage of residents vaccinated for influenza during current influenza season at the start of the outbreak
[9] Hand hygiene score in the facility during the 2014-2015 influenza season. If more than one audit occurred during this time, scores were averaged
[10] Rural is defined as a community having a population less than 10,000 people based on the Health Canada census in 2011 (1=Yes, 2=No)
[11] Facilities that are not directly operated by the Regional Health Authority (1=Yes, 2=No)

The characteristics of each of the 53 influenza A outbreaks that were included in the analysis can be seen in Table 10. The characteristics of the three influenza B outbreaks that were included in the analysis can be seen in Table 11.

A plot of the secondary attack rate versus time from the start of the outbreak to initiation of chemoprophylaxis can be seen for influenza A H3N2 and influenza B in Figures 2 and 3 respectively.

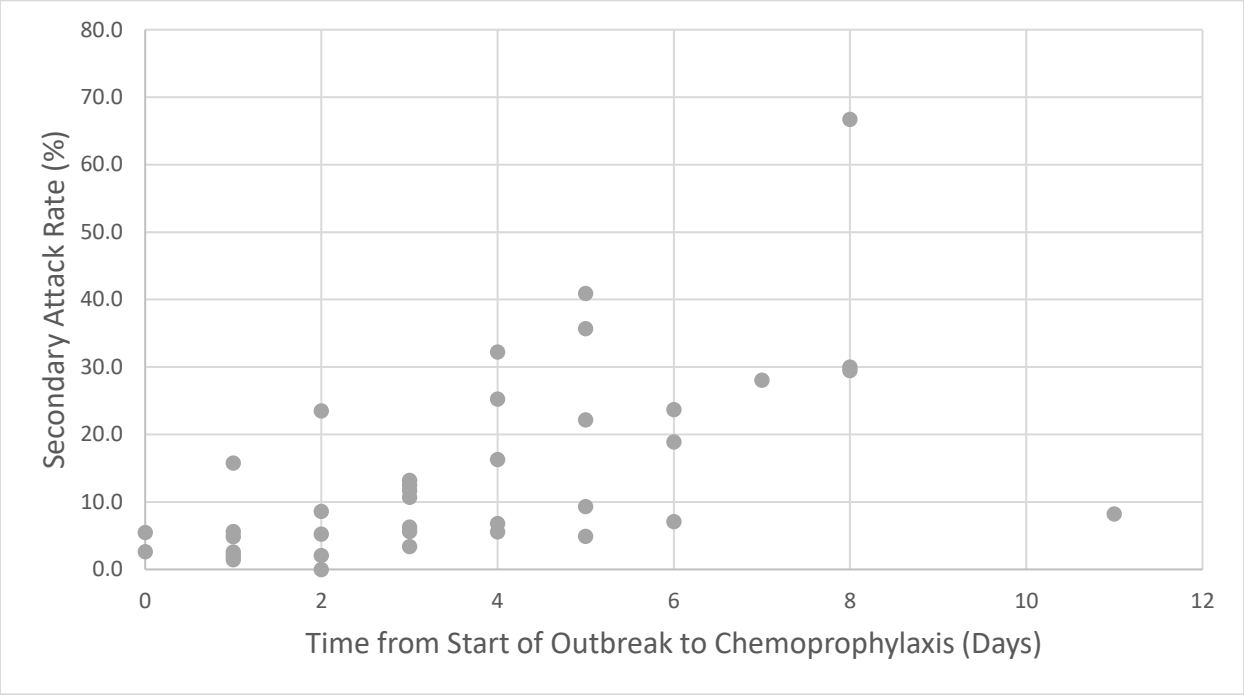


Figure 2: Outbreak secondary attack rate vs time for influenza A H3N2 outbreaks

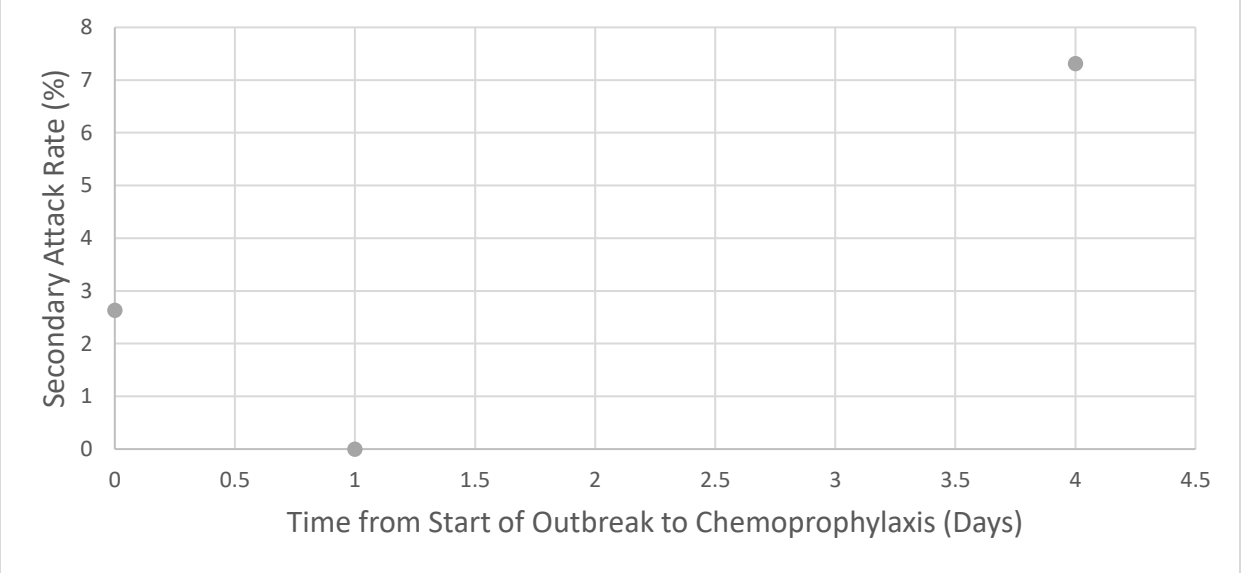


Figure 3: Outbreak secondary attack rate vs time for influenza B outbreaks

One can see in these figures the general trend that as one increases the amount of time to administer oseltamivir chemoprophylaxis, the secondary attack rate, meaning the number of residents who become ill, rises.

*Influenza A H3N2 outbreak data analysis*

The ICC can be calculated by taking an empty model and dividing the between group variance by the sum of the within group variance plus the between group variance. This again is used to determine if the hierarchical model is needed for the analysis. The between group variance is the estimate of the covariance of the intercept in the empty model. The within group variance is fixed in hierarchical logistic regression at $\pi^2 / 3$. With a covariance of 1.21 for the intercept in the empty model, the ICC is 27%. Therefore, the outcomes of infection are significantly correlated with the institutions that the residents reside in and hierarchical logistic regression is needed to analyze this data.

Using a univariate analysis, five of the 11 independent variables are statistically significant (Table 6): the number of days from the second case to starting oseltamivir ($t = 5.41$, $df = 51$, $p < 0.0001$), the number of days from declaring an outbreak to starting oseltamivir ($t = 3.48$, $df = 51$, $p = 0.001$), the prevalence of influenza among residents at the start of the outbreak ($t = 2.04$, $df = 51$, $p = 0.047$), the number of residents at risk at the start of the outbreak ($t = 4.02$, $df = 51$, $p = 0.0002$), and the staff vaccination rate at the start of the outbreak ($t = 2.09$, $df = 25$, $p = 0.047$).

Next, using a stepwise forward modeling strategy, where initial criteria for being included in the model was having a *p*-value less than 0.15 and removal from the model with a p-value greater than 0.20, only three variables were found to be statistically significant (Table 6): the number of days from the second case to starting oseltamivir ($t = 6.04$, $df = 49$, $p <$

0.0001), the number of days from the first case to the second case (t = 3.35, df = 49, p = 0.002), and the number of residents at risk at the start of the outbreak (t = 4.22, df = 49, p = 0.0001).

Some might consider the prevalence of influenza among residents at the start of the outbreak to be clinically significant, but its inclusion in the model did not change the odds ratios of the three statistically significant independent variables. As well, none of the other control variables seriously affected the model since the timing of oseltamivir chemoprophylaxis remained statistically significant (p values ranging from 0.002 to < 0.0001) in all other four variable models with an odds ratio ranging from 1.27 to 1.37 in these other four variable models. Therefore, the final main effects model includes only the three statistically significant variables indicated.

Table 6: Univariate and Final Model Predictor Odds Ratios for Influenza A H3N2 Infection

| Independent Variable | Model Predictions for Influenza Infection | |
|---|---|---|
| | Unadjusted OR (95% CI) | Adjusted OR (95% CI)[1] |
| Days from 2nd Case to Oseltamivir (n=53) | 1.33 (1.20 – 1.47) | 1.33 (1.21 – 1.46) |
| Days from 1st to 2nd Case (n=53) | 0.99 (0.81 – 1.22) | 0.77 (0.66 – 0.90) |
| Days from Declaring Outbreak to Oseltamivir (n=53) | 1.31 (1.12 – 1.53) | - |
| Prevalence of Res Flu at Outbreak (n=53) | 1.07 (1.00 – 1.14) | - |
| # at Risk at Start of the Outbreak[2] (n=53) | 0.44 (0.29 – 0.66) | 0.50 (0.36 – 0.70) |
| Prevalence of Flu among Staff (n=26) | 1.26 (0.90 – 1.78) | - |
| Staff Vaccination Rate (n=27) | 0.98 (0.96 – 1.00) | - |
| Resident Vaccination Rate (n=40) | 1.00 (0.97 – 1.02) | - |
| Rural (Yes or No) (n=53) | 1.83 (0.97 – 3.46) | - |
| Hand Hygiene Compliance (n=27) | 1.00 (0.96 – 1.04) | - |
| Privately Run (Yes or No) (n=53) | 0.57 (0.29 – 1.14) | - |

[1] (-) indicates that this variable was not included in the final model
[2] OR represents change per 100 resident increase in LTC facility
Note: OR = odds ratio

Next, the logit three continuous independent variables in the main effects model, number of days from the second case to the start of oseltamivir, the number of days from the first to the second case, and the number of residents at risk in the facility at the start of the outbreak, were tested for linearity compared to the predictor. As one can see in Figure 4, all three variables are linear. Therefore, no variable transformations are needed.

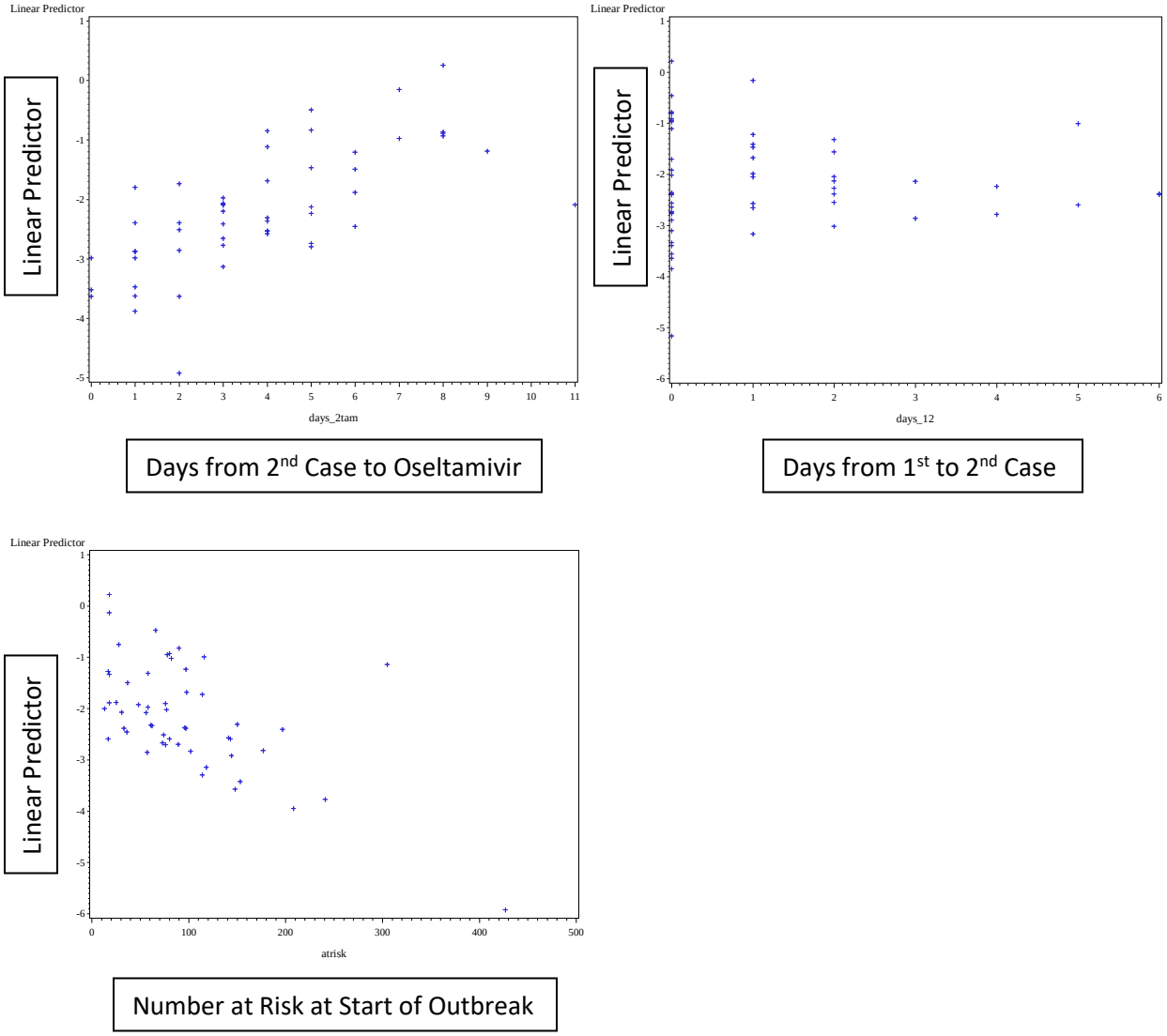


Figure 4: Assessment of linearity of independent variables

Next, the three main effects model independent variables are assessed for co-linearity. This is done by determining the variance inflation of these three variables. As can be seen in

Table 7, the variance inflation is well below 10. Therefore, there is no concern regarding co-linearity of these variables.

Table 7: Assessment of independent variable co-linearity

| Independent Variable | Variance Inflation |
|---|---|
| Days from 1st to 2nd Case (n=53) | 1.41 |
| Days from 2nd Case to Oseltamivir (n=53) | 1.34 |
| # at Risk at Start of the Outbreak (n=53) | 1.17 |

Finally, the model is extended by checking for any statistically significant interactions among the independent variables in the main effects model and the number of day from the second care to the initiation of oseltamivir. There were no statistically significant interactions. Therefore, the final model for the influenza A H3N2 analysis is the same as the main effects model.

The odds ratio for the main independent variable, the number of days from the second case to the start of oseltamivir, in the final model is 1.33 (*95% CI: 1.21 – 1.46*). This means that for every day that passes from the second case to the initiation of oseltamivir, the odds of a resident at risk of infection in the facility becoming infected with influenza A H3N2 increases by 33%.

*Influenza B outbreak analysis*

Only three influenza B outbreaks could be included in the final analysis. Therefore, no meaningful analysis could be done regarding the effect of timing of oseltamivir chemoprophylaxis on the odds of infection among at risk residents in the facilities.

# Discussion

These data indicate that the sooner oseltamivir chemoprophylaxis is initiated, the lower the odds of secondary infection with influenza in long term care facilities during outbreaks caused by influenza A H3N2 in Manitoba. No conclusions could be drawn from the data recorded from influenza B outbreaks in LTC facilities in Manitoba due to the limited number of outbreaks with data recorded for both the timing of oseltamivir chemoprophylaxis and the timing of resident infections.

The data also indicate that the number of residents in a facility and the number of days from the first case to the second case are negatively associated with the odds of secondary infection in LTC facilities with influenza A H3N2 outbreaks. This means that in larger facilities and with outbreaks that have a longer delay between the first and second cases residents have lower odds of secondary infection, compared to smaller facilities, and outbreaks with a shorter time interval between the first and second cases. The causes of these associations are not clear biologically or from previous literature, though the associations have previously been noted in a smaller study previously conducted in Manitoba using a sub-sample of the cohort used in this study [24]. Consider also that the number of residents in a facility and the time interval between the first and second cases are not modifiable factors; therefore, focussing on them is less helpful than focussing on the timing of administration of oseltamivir, which is potentially modifiable.

## *Applicability of the findings*

This study provides the strongest piece of evidence to date for the benefit to reducing the time from identification of an outbreak caused by influenza A H3N2 to administration of

oseltamivir chemoprophylaxis in a LTC resident population. Delays in this process can occur at many key points including: collection of nasopharyngeal specimens, transport of specimens to the laboratory, identification of viruses present, communication of results, making the decision to administer oseltamivir chemoprophylaxis, and the actual administration of oseltamivir. Therefore, these processes should all be examined to create any efficiencies possible. For example, in Manitoba, the machine that conducts a rapid polymerase chain reaction to detect influenza present from nasopharyngeal swabs is housed at the provincial public health laboratory, Cadham Provincial Laboratory. For routine community specimens, it is only operated three days a week, Monday, Wednesday, and Friday during the influenza season, as noted by Dr. Davinder Singh during a rotation at the lab. However, once an outbreak has been declared, the specimens are tested with rapid methods the same day, regardless of the day of the week. Therefore, if an outbreak is not yet suspected, there may be a delay in testing a specimen. It may be more efficient to use this machine five or seven days a week, even for routine community specimens, during influenza season to decrease the time to viral identification. The public health department may also consider empiric administration of oseltamivir chemoprophylaxis in institutions with two or more residents displaying symptoms of influenza-like illness during influenza activity, before getting laboratory confirmation of the presence of the influenza virus. However, this decision will have to weigh the benefits of decreased odds of secondary influenza infection against the risks of unnecessary oseltamivir administration, including negative side effects (mostly gastrointestinal symptoms) and possibly inducing oseltamivir resistance as has been seen with influenza A H1N1 [20].

To date, there have been no studies on the effect of the timing of oseltamivir chemoprophylaxis in influenza A H1N1 outbreaks in LTC facilities, and since no analyses could be conducted on the influenza B outbreak group, the same is true of influenza B outbreaks. This study does not provide any corroborating evidence that the same effect would exist with influenza A H1N1 or influenza B outbreaks. As well, the risks of unnecessary oseltamivir administration are different with different types and sub-types of influenza, as the rate of resistance of oseltamivir in influenza A H1N1 strains has historically been higher than in other influenza strains [20].

*Generalizability of Findings*

The findings presented should be applicable across North America and Europe. All of these areas have similar LTC resident populations, infection control precautions and institutional standards [32, 33], and use oseltamivir for chemoprophylaxis in influenza outbreaks [6, 9, 10, 16, 19]. There is a potential that the institutions that were excluded from the analysis due to unrecorded timing of oseltamivir administration or timing of resident illness are fundamentally different than the institutions that did record these data, but given the variation in institutional characteristics present in the 53 institutions in the analysis, these results are likely widely applicable to LTC facilities.

As well, facilities with multiple influenza outbreaks with the same type of influenza were only allowed to contribute their first outbreak of that influenza type to the analysis so it is possible that these results do not apply to subsequent outbreaks in the same facility. However, the presence of immunity in the resident population from previous outbreaks should only affect

the magnitude of the effect of the timing of oseltamivir, not the presence of an effect, if there is any change at all, as the true number of residents at risk will be affected.

*Strengths and Limitations*

This study has a number of key strengths over previous studies that have been conducted to examine oseltamivir chemoprophylaxis. First, this is the largest study to examine the effect of the timing of oseltamivir chemoprophylaxis in influenza A H3N2 outbreaks in LTC facilities to date; this study has a much larger sample size than the previous study with nearly five times the sample size. As well, it is the second largest study to look at the effectiveness of oseltamivir in any capacity in LTC facilities, being over three times larger than the next largest study, and employs a common provincial approach to oseltamivir prophylaxis. Second, this is one of the only studies in the area to examine secondary attack rate as opposed to total attack rate, which is a much more accurate approach to examine the impact of oseltamivir chemoprophylaxis. Third, vaccination rates were not a significant confounder for infection in the 2014-2015 influenza season for influenza A H3N2 because of lack of effectiveness of the vaccine for that strain of circulating virus [22]. Vaccination rates may have had more of an effect on influenza B outcomes, a significant consideration when evaluating other studies that analysed influenza A and influenza B outbreaks together in 2014-2015. Fourth, some discrepancies between LTC facilities will likely be controlled for by including in the analysis the compliance score on the hand hygiene audits, the percentage of staff that were vaccinated, whether the facility was publicly or privately operated, and the time between declaring an outbreak and the start of chemoprophylaxis. After an outbreak is declared, chemoprophylaxis of its residents should occur immediately. However, many times this is not the case. This may

indicate a difference in the operations and preparedness of these facilities which may account for differences in infection rates among residents. Fifth, several other potentially significant variables are accounted for such as the prevalence of disease among staff and residents at the start of the outbreak, the number of residents as risk, whether the institution was rural or urban, and the number of days' separation between the first and second cases of the outbreaks. Lastly, this study uses a hierarchical model accounting for both the number of outbreaks and the size of the facilities involved.

There are some limitations to the proposed study as well. First, though this study attempts to control for some of the discrepancy between how various facilities are operated and organized, some of these differences may not be accounted for by the control variables, and may confound the results in an unpredictable way. This includes facilities where residents are on different wards and only part of the population receives prophylaxis. However, this limitation was indirectly addressed since any institution with more than one date for oseltamivir chemoprophylaxis would already be excluded; therefore, most (or all) institutions with spread to a group that did not receive prophylaxis and then prophylaxes the remaining residents would not be included in the analysis. Second, there were only 3 outbreaks of influenza B among LTC facilities in Manitoba during the 2014-2015 influenza season after excluding those that were missing crucial information. Therefore, no statistical analysis of those outbreaks could be conducted without an extremely high chance a type II error, thus making the analysis inappropriate. Third, the analysis does not control for individual factors, such as age, co-morbidities, smoking status, or mobility, among the various LTC facility residents. Therefore, differences such as the number and types of co-morbidities and other demographic

differences could theoretically be present and could affect the results. Fourth, this study does not examine hospitalization or mortality from influenza infections during these outbreaks. However, these variables are less sensitive measures of effectiveness and the decision to hospitalize a patient is very subjective. Fifth, a large number of outbreaks were missing data to the extent that they could not be included in the analysis (27 influenza A H3N2 outbreaks out of 93). If these facilities were significantly different in character from those with sufficient information for analysis, the results may not be generalizable to as many LTC facilities.

### *Knowledge Translation*

*Manitoba.* A copy of this manuscript will be submitted to all five Regional Health Authorities in Manitoba through their Infection Prevention & Control coordinators. The findings will also be presented to the Medical Officers of Health in Manitoba, which is an important point of knowledge transfer since they are responsible for deciding when to use oseltamivir chemoprophylaxis during an outbreak. As well, the information will be presented to the Epidemiology & Surveillance Unit at Manitoba Health, Seniors, and Active Living (MHSAL), the Communicable Diseases Unit at MHSAL, and the Cadham Provincial Laboratory as this is an important group for policy decisions regarding use of oseltamivir in long term care facilities.

*Canada.* The findings from this study will be submitted to the Canadian Public Health Association to be presented at their annual conference in May 2018. This conference is well attended by public health professionals from many disciplines from across Canada. A manuscript will also be prepared for publication in a peer reviewed scientific journal, ideally with a high impact factor, such as the Canadian Medical Association Journal.

*International*. If the manuscript is not already published in a peer reviewed scientific journal, the findings will also be submitted to the American Public Health Association annual conference in November 2018 for presentation. Only unpublished findings may be presented at this conference.

## Conclusion

The sooner oseltamivir chemoprophylaxis is initiated, the lower the odds of secondary infection with influenza in LTC facilities during outbreaks caused by influenza A H3N2 in Manitoba during the 2014-2015 influenza season. This study is the largest examination of the use of oseltamivir for chemoprophylaxis for influenza A H3N2 in LTC facilities to date. It provides the strongest piece of evidence for the use of timely oseltamivir chemoprophylaxis in this setting during outbreaks of influenza A H3N2. This study will help inform infection prevention and control policy in LTC facilities in North America and Europe as to the impact of the timing of chemoprophylaxis for outbreaks caused by this subtype of influenza.

Future research regarding the effect of the timing of oseltamivir chemoprophylaxis in LTC facilities should be targeted at influenza B and influenza A H1N1, as these have not yet been studied in a rigorous way. Due to the relatively large amount of missing data common to many retrospective cohort studies, a prospective study may be more beneficial. Though this will need to be weighed against the need for increased time and resources inherent to prospective studies. Eventually, separate strategies regarding chemoprophylaxis may need to be employed based on the circulating type or sub-type of influenza in the community. Other outcomes, such as hospitalization and mortality, could also be used if they are measured in a rigorous way. This

would be very valuable since these are the outcomes that infection prevention and control programs are ultimately striving to prevent.

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# Appendix A

Table 8: Characteristics of Published Research contributing to IDSA Guidelines

| Reference Details | Study Design | Population | Intervention | Sample Size | Use of $2^0$ Attack Rate | Subtypes of Influenza | Control Variables |
|---|---|---|---|---|---|---|---|
| Peters *et al.*, 2001 [8] | Randomized control trial | Residents in long term care facilities in Europe and the United States during single influenza season | Seasonal prophylaxis with oseltamivir 75 mg or placebo once daily for 6 weeks at start of influenza season | 548 elderly occupants from 31 facilities | No | Influenza A and B analysis combined, specific subtype of influenza A not identified | Stratified by vaccine status |
| Welliver *et al.*, 2001 [17] | Randomized control trial | Households with mixed ages, 12 years old and above (mean age 33-34 years), who are contacts of people with influenza infections in Europe and the United States during single influenza season | Post-exposure prophylaxis with oseltamivir 75 mg or placebo once daily for 7 days | 377 index cases with 415 contacts | No | Influenza A and B analysis only partially separated. Influenza A subtype identified (H3N2) | Not stated |
| Bowels *et al.*, 2002 **[6]** | Non-randomized clinical intervention without control group | Residents in long term care facilities and chronic care hospitals in Ontario, Canada during single influenza season | Mixture of oseltamivir and amantadine treatment and prophylaxis for varying periods of time | Ten facilities. 751 residents received oseltamivir prophylaxis | No | Influenza A H3N2 | None |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Hayden *et al.*, 2004 [11] | Randomized control trial | Households with mixed ages, 1 year old and above (median age 14 years – no people over 65 years of age in prophylaxis group), who are contacts of people with influenza infections in Europe and the United States during single influenza season | Post-exposure prophylaxis with oseltamivir 75 mg once daily for 10 days | 298 index cases with 812 contacts | No | Influenza A and B analysis separated. Influenza A subtypes (H1N1 and H3N2) not analyzed separately | Stratified by age greater or less than 12 |
| Monto *et al.*, 2004 **[15]** | Non-randomized clinical intervention without control group | Residents in long term care facilities in Michigan, U.S. during two influenza seasons | Post-exposure prophylaxis with oseltamivir 75 mg once daily for 15 days | Eight outbreaks. 497 of 1164 on prophylaxis | No | Influenza A H3N2 | None |
| Van der Sande *et al.*, 2006 [16] | Descriptive | Long term care facilities in the Netherlands during single influenza season | Not applicable | 194 facilities | Not applicable | Not reported | Not applicable |

Table 9: Characteristics of Published Research Post-publication of the IDSA Guidelines

| Reference Details | Study Design | Population | Intervention | Sample Size | Use of $2^0$ Attack Rate | Subtypes of Influenza | Control Variables |
|---|---|---|---|---|---|---|---|
| Booy *et al.*, 2012 [5] | Random-ized control trial | Residents of long term care facilities in Sydney, Australia during three influenza seasons | Post-exposure prophylaxis with oseltamivir 75 mg once daily for 10 days | Nine facilities with 652 residents | No | Influenza A and B not analyzed separatly. Influenza A subtypes not analyzed separately | Number of residents in facility |
| Miksic *et al.*, 2014 [7] | Non-randomized clinical inter-vention | Residents of long term care facilities in Maribor, Slovenia during one influenza season | Post-exposure prophylaxis with oseltamivir 75 mg once daily for 10 days for all residents or only directly exposed residents | Three facilities with 539 residents | No | Influenza A H3N2 | None |
| Van der Sande *et al.*, 2014 [12] | Random-ized control trial | Residents of long term care facilities in the Netherlands during four influenza seasons | Post-exposure prophylaxis with oseltamivir 75 mg or placebo once daily for 10 days | 15 facilities with 99 non-ill residents | Yes | Influenza A and B not analyzed separatly. Influenza A subtype identified (H3N2) | None |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Millership and Cummins, 2015 [18] | Descriptive | Residents of long term care facilities in Witham, U.K. during three influenza seasons | Not applicable | 75 facilities with 1456 residents | N/A | Influenza A and B not analyzed separatly. Influenza A subtypes not analyzed separately | Not applicable |
| Ye *et al.*, 2016 [19] | Retro-spective cohort study | Residents of long term care facilities in Alberta, Canada during two influenza seasons | Time to recommendation for oseltamivir Post-exposure prophgylaxis | 90 facilities with 127 outbreaks, 11,801 resedents (calculated indirectly) | Yes | Influenza A and B not analyzed separatly. Influenza A subtypes not analyzed separately | Days between 1st ans 2nd case, prevalence of influenza at start of outbreak, number of individuals at risk, urban vs other, other viruses present (yes/no) |
| Singh, Robinson and Hilderman, 2016 **[24]** | Retro-spective cohort study | Residents of long term care facilities in Manitoba, Canada during one influenza season | Time to oseltamivir Post-exposure prophylaxis 75 mg once daily for 10 days | 11 facilities with 610 residents | Yes | Influenza A H3N2 | Days between 1st and 2nd cases, prevalence of influenza at start of outbreak, number of individuals at risk, days between 2nd case and declaring an outbreak, days between declaring an outbreak and starting prophylaxis |

Table 10: Influenza A H3N2 outbreak characteristics

| Outbreak Number | # of Cases | Total # of Residents | $2^0$ Cases | Residents excluding $1^0$ cases[1] | $2^0$ attack rate (%) | Days till chemopro-phylaxis[2] | Days1-2[3] | Days to Declare OB[4] | Prev Res Flu (%)[5] | Prev Staff Flu (%)[6] | % Staff Vacc[7] | % Res Vacc[8] | Hygiene Score[9] | Rural[10] (Y/N) | Private[11] (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 81 | 309 | 77 | 305 | 25.2 | 4 | 0 | 3 | 1.3 | 0.0 | 16 | 88 | * | 0 | 0 |
| 2 | 18 | 154 | 14 | 150 | 9.3 | 5 | 2 | 5 | 2.6 | 1.0 | 8 | 84 | * | 0 | 0 |
| 3 | 11 | 148 | 7 | 144 | 4.9 | 1 | 0 | 1 | 2.7 | 0.0 | 41 | 81 | * | 0 | 0 |
| 4 | 6 | 155 | 4 | 153 | 2.6 | 1 | 0 | 0 | 1.3 | 0.0 | 21 | 93 | * | 0 | 1 |
| 5 | 28 | 84 | 24 | 80 | 30.0 | 8 | 0 | 2 | 4.8 | 0.8 | 12 | 90 | * | 0 | 0 |
| 6 | 4 | 431 | 0 | 427 | 0.0 | 2 | 0 | 0 | 0.9 | 0.0 | 25 | 76 | 67 | 0 | 0 |
| 7 | 6 | 78 | 4 | 76 | 5.3 | 2 | 4 | 2 | 2.6 | 0.9 | 36 | 88 | * | 0 | 1 |
| 8 | 27 | 86 | 23 | 82 | 28.0 | 7 | 5 | 3 | 4.7 | 0.0 | 17 | 75 | * | 0 | 1 |
| 9 | 9 | 120 | 3 | 114 | 2.6 | 0 | 0 | 0 | 5.0 | 0.0 | 84 | 94 | 93 | 0 | 1 |
| 10 | 20 | 116 | 18 | 114 | 15.8 | 1 | 0 | 1 | 1.7 | 0.0 | 50 | 94 | 72 | 0 | 0 |
| 11 | 12 | 80 | 9 | 77 | 11.7 | 3 | 2 | 2 | 3.8 | 0.0 | * | * | * | 0 | 0 |
| 12 | 20 | 200 | 17 | 197 | 8.6 | 2 | 0 | 2 | 1.5 | 0.0 | 36 | 70 | * | 0 | 1 |
| 13 | 18 | 87 | 4 | 73 | 5.5 | 0 | 0 | 0 | 16.1 | 2.3 | 24 | 94 | * | 0 | 0 |
| 14 | 14 | 145 | 10 | 141 | 7.1 | 6 | 2 | 0 | 2.8 | 0.0 | 30 | 59 | 60 | 0 | 0 |
| 15 | 11 | 100 | 8 | 97 | 8.2 | 11 | 6 | 10 | 3.0 | 0.0 | * | 89 | 67 | 0 | 0 |
| 16 | 39 | 100 | 29 | 90 | 32.2 | 4 | 0 | 0 | 10.0 | 0.0 | 25 | 99 | * | 0 | 0 |
| 17 | 11 | 247 | 5 | 241 | 2.1 | 2 | 0 | 0 | 2.4 | 0.0 | 30 | 90 | * | 0 | 1 |
| 18 | 6 | 120 | 4 | 118 | 3.4 | 3 | 1 | 3 | 1.7 | 0.0 | 70 | 90 | * | 0 | 1 |
| 19 | 25 | 80 | 23 | 78 | 29.5 | 8 | 0 | 8 | 2.5 | 6.6 | * | 96 | * | 0 | 0 |
| 20 | 13 | 180 | 10 | 177 | 5.7 | 3 | 0 | 3 | 1.7 | 0.0 | 28 | 98 | * | 0 | 0 |
| 21 | 18 | 100 | 16 | 98 | 16.3 | 4 | 1 | 3 | 2.0 | 0.0 | 13 | 88 | * | 0 | 0 |
| 22 | 7 | 91 | 5 | 89 | 5.6 | 1 | 0 | 0 | 2.2 | 0.0 | 30 | 92 | * | 0 | 1 |
| 23 | 8 | 213 | 3 | 208 | 1.4 | 1 | 0 | 1 | 2.3 | 0.0 | 96 | 94 | * | 0 | 1 |

| Outbreak Number | # of Cases | Total # of Residents | $2^0$ Cases | Residents excluding $1^0$ cases[1] | $2^0$ attack rate (%) | Days till chemopro-phylaxis[2] | Days1-$2^3$ | Days to Declare OB[4] | Prev Res Flu (%)[5] | Prev Staff Flu (%)[6] | % Staff Vacc[7] | % Res Vacc[8] | Hygiene Score[9] | Rural[10] (Y/N) | Private[11] (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 24 | 26 | 100 | 23 | 97 | 23.7 | 6 | 1 | 2 | 3.0 | 0.0 | 55 | 87 | * | 0 | 1 |
| 25 | 5 | 150 | 3 | 148 | 2.0 | 1 | 0 | 1 | 1.3 | 0.0 | 30 | 95 | * | 0 | 0 |
| 26 | 14 | 80 | 10 | 76 | 13.2 | 3 | 0 | 2 | 5.0 | * | * | 3 | 77 | 1 | 0 |
| 27 | 14 | 20 | 12 | 18 | 66.7 | 8 | 0 | 5 | 10.0 | * | * | 80 | 64 | 1 | 0 |
| 28 | 8 | 50 | 6 | 48 | 12.5 | 3 | 1 | 2 | 4.0 | * | * | 76 | 92 | 1 | 0 |
| 29 | 7 | 76 | 5 | 74 | 6.8 | 4 | 1 | 3 | 3.0 | * | * | * | 91 | 1 | 1 |
| 30 | 12 | 30 | 10 | 28 | 35.7 | 5 | 0 | 4 | 7.0 | * | * | 70 | 86 | 1 | 0 |
| 31 | 7 | 20 | 4 | 17 | 23.5 | 2 | 1 | 1 | 15.0 | * | * | 85 | 63 | 1 | 0 |
| 32 | 7 | 104 | 5 | 102 | 4.9 | 5 | 3 | 2 | 2.0 | * | * | * | * | 1 | 1 |
| 33 | 6 | 40 | 2 | 36 | 5.6 | 4 | 1 | 2 | 10.0 | * | * | 93 | 49 | 1 | 0 |
| 34 | 16 | 91 | 5 | 80 | 6.3 | 3 | 0 | 2 | 12.0 | * | * | 71 | * | 1 | 1 |
| 35 | 40 | 79 | 27 | 66 | 40.9 | 5 | 0 | 1 | 16.0 | * | * | 81 | * | 1 | 1 |
| 36 | 6 | 20 | 4 | 18 | 22.2 | 5 | 1 | 0 | 10.0 | * | * | 100 | 82 | 1 | 0 |
| 37 | 10 | 40 | 7 | 37 | 18.9 | 6 | 2 | 5 | 7.5 | * | * | 65 | 84 | 1 | 1 |
| 38 | 9 | 59 | 6 | 56 | 10.7 | 3 | 3 | 2 | 5.1 | * | * | 65 | 85 | 1 | 0 |
| 39 | 12 | 145 | 10 | 143 | 7.0 | 4 | 0 | 0 | 1.4 | * | 12 | 79 | 67 | 1 | 1 |
| 40 | 51 | 134 | 33 | 116 | 28.4 | 8 | 0 | 0 | 13.4 | * | 11 | 90 | 58 | 1 | 0 |
| 41 | 13 | 69 | 5 | 61 | 8.2 | 4 | 0 | 0 | 11.6 | * | 28 | 68 | 72 | 1 | 0 |
| 42 | 8 | 65 | 5 | 62 | 8.1 | 2 | 0 | 0 | 4.6 | * | 34 | 82 | 79 | 1 | 0 |
| 43 | 4 | 16 | 1 | 13 | 7.7 | 4 | 6 | 4 | 18.8 | * | * | * | * | 1 | 0 |
| 44 | 9 | 60 | 7 | 58 | 12.1 | 3 | 0 | 1 | 3.3 | * | * | * | 100 | 1 | 0 |
| 45 | 5 | 33 | 3 | 31 | 9.7 | 5 | 4 | 4 | 6.1 | 2.6 | 58 | 97 | 52 | 1 | 0 |
| 46 | 3 | 20 | 0 | 17 | 0.0 | 0 | 0 | 0 | 15.0 | * | * | * | * | 1 | 0 |
| 47 | 10 | 65 | 2 | 57 | 3.5 | 5 | 2 | 3 | 12.3 | * | * | * | * | 1 | 0 |
| 48 | 7 | 29 | 3 | 25 | 12.0 | 1 | 1 | 0 | 13.8 | * | * | * | * | 1 | 0 |

| Outbreak Number | # of Cases | Total # of Residents | $2^0$ Cases | Residents excluding $1^0$ cases[1] | $2^0$ attack rate (%) | Days till chemopro-phylaxis[2] | Days1-2[3] | Days to Declare OB[4] | Prev Res Flu (%)[5] | Prev Staff Flu (%)[6] | % Staff Vacc[7] | % Res Vacc[8] | Hygiene Score[9] | Rural[10] (Y/N) | Private[11] (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 | 8 | 39 | 2 | 33 | 6.1 | 1 | 5 | 0 | 15.4 | * | * | * | * | 1 | 0 |
| 50 | 4 | 20 | 2 | 18 | 11.1 | 6 | 2 | 5 | 10.0 | * | * | * | * | 1 | 0 |
| 51 | 12 | 100 | 8 | 96 | 8.3 | 3 | 2 | 1 | 4.0 | * | * | * | * | 0 | 0 |
| 52 | 15 | 60 | 13 | 58 | 22.4 | 9 | 2 | 7 | 3.3 | * | * | * | * | 1 | 0 |
| 53 | 12 | 20 | 10 | 18 | 55.6 | 7 | 1 | 2 | 10.0 | * | * | * | * | 1 | 0 |

[1] Primary cases are defined as cases occurring on or before the day that the second case occurred

[2] Number of days between the second case and start of chemoprophylaxis

[3] Number of days between the first and second cases

[4] Number of days between the second case and declaring an outbreak

[5] Prevalence of influenza among residents in the institution at the start of the outbreak

[6] Prevalence of influenza among staff in the institution at the start of the outbreak

[7] Percentage of staff vaccinated for influenza during current influenza season at the start of the outbreak

[8] Percentage of residents vaccinated for influenza during current influenza season at the start of the outbreak

[9] Hand hygiene score in the facility during the 2014-2015 influenza season. If more than one audit occurred during this time, scores were averaged

[10] Rural is defined as a community having a population less than 10,000 people based on the Health Canada census in 2011

[11] Facilities that are not directly operated by the Regional Health Authority

Table 11: Influenza B outbreak characteristics

| Outbreak Number | # of Cases | Total # of Residents | $2^0$ Cases | Residents excluding $1^0$ cases[1] | $2^0$ attack rate (%) | Days till chemopro-phylaxis[2] | $Days_{1-2}$[3] | Days to OB[4] | Prev of Flu (%)[5] | Prev Staff Flu (%)[6] | % Staff Vacc[7] | % Res Vacc[8] | Hygiene Score[9] | Rural[10] (Y/N) | Private[11] (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 12 | 50 | 3 | 41 | 7.317 | 4 | 0 | 0 | 18 | * | 19 | 100 | 70 | 1 | 0 |
| 2 | 9 | 120 | 3 | 114 | 2.632 | 0 | 0 | 0 | 5 | 0 | 84 | 94 | 93 | 0 | 1 |
| 3 | 3 | 91 | 0 | 88 | 0 | 1 | 0 | 0 | 3.297 | 0 | 30 | 92 | * | 0 | 1 |

[1] Primary cases are defined as cases occurring on or before the day that the second case occurred

[2] Number of days between the second case and start of chemoprophylaxis

[3] Number of days between the first and second cases

[4] Number of days between the second case and declaring an outbreak

[5] Prevalence of influenza among residents in the institution at the start of the outbreak

[6] Prevalence of influenza among staff in the institution at the start of the outbreak

[7] Percentage of staff vaccinated for influenza during current influenza season at the start of the outbreak

[8] Percentage of residents vaccinated for influenza during current influenza season at the start of the outbreak

[9] Hand hygiene score in the facility during the 2014-2015 influenza season. If more than one audit occurred during this time, scores were averaged

[10] Rural is defined as a community having a population less than 10,000 people based on the Health Canada census in 2011

[11] Facilities that are not directly operated by the Regional Health Authority