Using Spatial Epidemiology as a Tool to Better Understand Influenza-like Illnesses

by

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Abstract

Influenza is a population health issue in Canada, with an annual infection rate of 10-25% of the population. The purpose of this thesis was to analyze influenza-like illnesses (ILI) for the fiscal years (April 1 to March 31) from 2004-05 through to 2008-09, both spatially and temporally, throughout the province of Manitoba. ILI, for the purpose of this study, included diagnoses of pneumonia and influenza and acute respiratory infection as determined by ICD-09 and ICA-10 codes. As with other published studies and the accepted definitions of ILI, repeat cases within a season were included. The analysis used a framework specific to spatial analysis, and incorporated the principles of population health and ecological frameworks. The underlying objectives of the research were to better understand the patterns of ILI diagnoses as well as the characteristics of those diagnosed.

The data were explored in three ways: employing methods of data visualisation, exploration and modeling, with the incorporation of the determinants of health to inform the results and guide the choice of regression variables. Different maps were created to show the results from various perspectives and negative binomial regression analysis was used to test which, if any, of the chosen variables (including household density, co-morbidity score, income quintile and age) were significant.

Based on this research, one could conclude that although clusters of ILI do exist in the province of Manitoba, a clear relationship does not exist between the determinants of health and ILI as was expected. Although the age variable yielded predictable results, higher risk of diagnoses amongst the high density households or in the lowest income

quintiles was not observed. It is however unclear as to how these results were affected by the limitations of the study, particularly the inclusion of repeat cases.

Acknowledgements

Although I am the author of this thesis, I feel confident saying it was a group effort. There were so many people who offered their support in various ways and I can honestly say that everyone in my life while completing this adventure deserves recognition. I thank you all.

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I would like to acknowledge the Manitoba Centre for Health Policy for use of data contained in the Population Health Research Data Repository under project # 2010/2011-06. The results and conclusions are my own and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred.

I would also like to acknowledge my thesis committee and offer all of you a heartfelt thank you. Each of you provided me with a very distinct area of expertise that truly helped shape my thesis. I cannot imagine having completed this venture without any of you. I am so grateful to you- Alan, Carol and Chris – for the constructive feedback and guidance that you provided along the way.

My committee was led by my advisor, Michelle; this is as much your accomplishment as it is mine. Your encouragement and support were paramount in the

completion of my degree. Thanks to you I was given opportunities to travel and take part in conferences that I would have otherwise not had. You made a great difference in my development in the area of Community Health Sciences that will reflect on my future projects throughout my career.

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Chapter 1 - Introduction

Influenza ('flu') is a communicable disease characterized as a respiratory illness that affects millions of Canadians annually. It is suspected that 10-25% of Canadians get infected with influenza each year, with approximately 4000-8000 deaths associated with the illness and its complications (Health Canada, 2009). The high number of people infected each year makes the flu an important public health issue. While the level of risk of developing more serious complications as a result of influenza varies from person to person, studying the epidemiology of how influenza cases are spatially distributed may help to better target resources towards its management. This thesis will examine the spatial epidemiological aspects of influenza-like illnesses (ILI) in the province of Manitoba, Canada, using a population health framework.

Epidemiology refers to the study of health-related states or events, including their distribution and determinants (Last, 2001) and is a necessary component to mitigate health-related adverse events (Young, 2005). The importance of space, and consequently time, when studying the distribution of disease is often referred to as spatial epidemiology. Space and time are important factors when considering health-related adverse events within a given population, particularly when investigating infectious or communicable diseases such as influenza (Knorr-Held & Besag, 1998). Although spatial epidemiology is a logical lens with which to study ILI, a gap in the literature exists. This thesis will help fill that void, particularly in Manitoba where its population is widespread over a large geographic area.

Purpose

The purpose of this thesis is to analyze influenza-like illnesses (ILI) retrospectively, both spatially and temporally, throughout the province of Manitoba. ILI, for the purpose of this study, will include diagnoses of pneumonia and influenza, and acute respiratory infection as determined by ICD-09 and ICD-10 codes. Acute respiratory infections and ILI share similar symptoms; consequently it is not uncommon to see acute respiratory symptoms counted as cases of ILI. The literature available supports the choice of these classifications for a broad-based definition of influenza-like illnesses (Menec, Black, MacWilliam, & Aoki, 2003; Yiannakoulias, Russell, Svenson, & Schoplocher, 2004). The data will be analyzed for the fiscal years (April 1 to March 31) from 2004-05 through 2008-09, and will most often be aggregated to create one dataset. This will allow for a greater sample population, stengthening the results obtained.

Study Objectives and Hypotheses

For the combined influenza seasons from 2004-05 to 2008-09, the three research questions and hypotheses are:

Research Question 1: How does the incidence of ILI vary spatially and temporally in Manitoba?

Hypothesis 1: A higher incidence will be observed in areas with lower socio-economic status, with the highest incidence occurring in the mid-season.

Research Question 2: Are there any significant (high or low) clusters of ILI cases in Manitoba?

Hypothesis 2: Both high and low clusters will be identified consistent with areas of

higher and lower socio-economic status, as demonstrated by premature mortality rates for the different Health Districts and Neighbourhood Clusters.

Research Question 3: Is ILI incidence significantly related to a select group of determinants of health variables (age, gender, dwelling density, co-morbidities, education and income) and influenza immunization status?

Hypothesis 3: ILI incidence will be significantly higher in populations with low incomes, living in crowded housing conditions, and in very young and very old individuals having significant co-morbidities.

This research will be undertaken using administrative data and various geographic information systems (GIS) tools and software. Administrative health service utilization data is routinely collected and housed at the Manitoba Centre for Health Policy. The data will be used to develop a better understanding of the characteristics and patterns of influenza-like illness in Manitoba.

The research questions aim to better understand the epidemiology of ILI incidence in Manitoba, exploring the spatial and temporal distribution through the identification of variables that may make ILI more common for some people over others. A better understanding of the distribution of ILI will occur as unusually high or low clusters of ILI cases will be sought. Patient characteristics will include qualifiers such as age, sex and co-morbidities. Some of the characteristics that will be analyzed spatially will include average neighbourhood income level, average number of people per dwelling, and education levels. Patterns of illness will be sought in terms of clusters of cases by Health District and Neighbourhood Clusters; commonalities of characteristics

(i.e., age, sex, co-morbidities, vaccination, average number of people per dwelling); and date of reported illness. This will be achieved through an analysis of the administrative data using statistical and, where appropriate, geostatistical tests.

A better understanding of the patterns of illness and characteristics of those affected across five flu seasons should identify the locations and populations with higher rates throughout the province. Many policies are guided by assumptions that have neither been confirmed nor disproved. The results provided by this research will help to inform assumptions with regards to influenza policies specific to the at-risk population and where they are located.

Chapter Synopsis

Chapter 1 – Introduction.

The purpose of the first chapter is to present a brief introduction to the thesis, focusing on its purpose and research objectives. An outline of the thesis and chapters to follow is also presented.

Chapter 2 – Theoretical Frameworks.

Chapter 2 presents the theoretical frameworks that served as a foundation for the development of the research questions and guided all aspects of the research. The population health framework is presented and described, with emphasis placed on the determinants of health. The determinants of health are outlined, as proposed by the Public Health Agency of Canada, as they are often referred to throughout the thesis and form an important element of the population health framework. Next the ecological framework is explained, highlighting its connection to population health as a parallel to

the determinants of health. Finally, the spatial framework of Bailey and Gatrell (1995) is presented as it was used to guide the spatial aspects of the research.

Chapter 3 – Background and Literature Review.

The third chapter serves to provide the reader with the necessary background information to fully understand the thesis. This includes an overview of influenza and influenza-like illnesses, as well as more specific details pertaining to the existing surveillance practices in Manitoba and Canada. A brief history of pandemic influenza is discussed to further explain the burden of influenza illness, and the principles of spatial epidemiology are presented.

Chapter 4 – Methods and Analysis.

This chapter provides the reader with a step-by-step guide to how the research was conducted. The study population is described and the inclusion/exclusion criteria explained. To assist with setting the spatial context of the study, maps of Manitoba and other relevant geographies are shown. The chapter introduces the different data that were used and how they were obtained.

The methods to address each research objective is presented separately and in sufficient detail so the study could be replicated in the future. The first objective of data visualisation explores the temporal and spatial patterns of ILI in Manitoba using epidemic curves and standarized rates. The second objective focuses on data exploration and examines, using the Spatial Scan statistic, whether visual clusters (made apparent by the first objective) are in fact true clusters. Finally, the third objective of data modeling seeks to identify which variables are most important in terms of ILI diagnoses using negative binomial regression tests.

Chapter 5 – Results.

The fifth chapter presents the results from the analysis performed in Chapter 4. Each objective is reviewed individually with necessary tables and maps shown when appropriate. An overview of the final study population is presented to provide the reader with an understanding of who was ultimately included to answer the research questions.

The results of the data visualisation objective show that similar temporal patterns exist within the study population as with the Manitoba population as presented by Manitoba Health. It is seen that ILI do not occur in all areas of the province at the same time; a different spread pattern is evident in the Health Districts than is apparent in the Neighbourhood Clusters. The Blue Water Health District and the Point Douglas Neighbourhood Cluster have consistently higher rates of ILI than elsewhere in the province.

The apparent spatial patterns are confirmed following the data exploration analysis. The Spatial Scan statistic also identifies other clusters throughout the province that were not obviously clustered based on data visualisation alone. With regards to the Health Districts, the areas most likely to cluster are found alongside the east side of the province, with the west side showing the areas that are least likely to cluster.

The data modeling identifies some variables that are statistically significant for ILI diagnoses at the various geographies, but the expected relationship between the ecological variables (determinants of health) and ILI diagnoses is not apparent. Surprisingly, a higher rate of household density was shown to be a protective factor as did a high unemployment rate, with income quintiles not being a significant variable overall. Although there were some variables that behaved as expected (age group,

season group, co-morbidity score), the overall results of the regression resulted in more questions than explanations. These unexpected results are potentially due to the inherent limitation of using the case definition for ILI which includes repeat cases, and should be interpreted with caution.

Chapter 6 – Discussion.

Chapter 6 serves to interpret the results of the analysis and offers some explanation to their importance. Comparisons are made to existing literature, where available, to support or highlight results that are unique to this research. The population health and ecological frameworks are used to provide insight to the results and help to explain what is shown.

The hypotheses of the first two objectives were supported by the findings. However, the results of the third objective were not clear in establishing the role of the determinants of health as factors in the diagnoses of ILI among the study population, as was hypothesized. The role that the inclusion of repeat cases may have played in these results was not explored but should be considered. The chapter concludes with a description of study limitations and assumptions, including those related to the inclusion of repeat cases, and those that are inherent when using administrative datasets.

Chapter 7 – Conclusion.

The final chapter of the thesis summarizes and concludes the research by providing an overview of the previous chapters. Each objective is revisted and their hypotheses examined. Although the results of these research questions do not fully support the idea that an association exists between health outcomes and the determinants of health, it should not be infered that there is no association between ILI and the

determinants of health. Future applications of the research are presented, including more in-depth research ideas that could enhance the study that was conducted.

Chapter 2 – Theoretical Frameworks

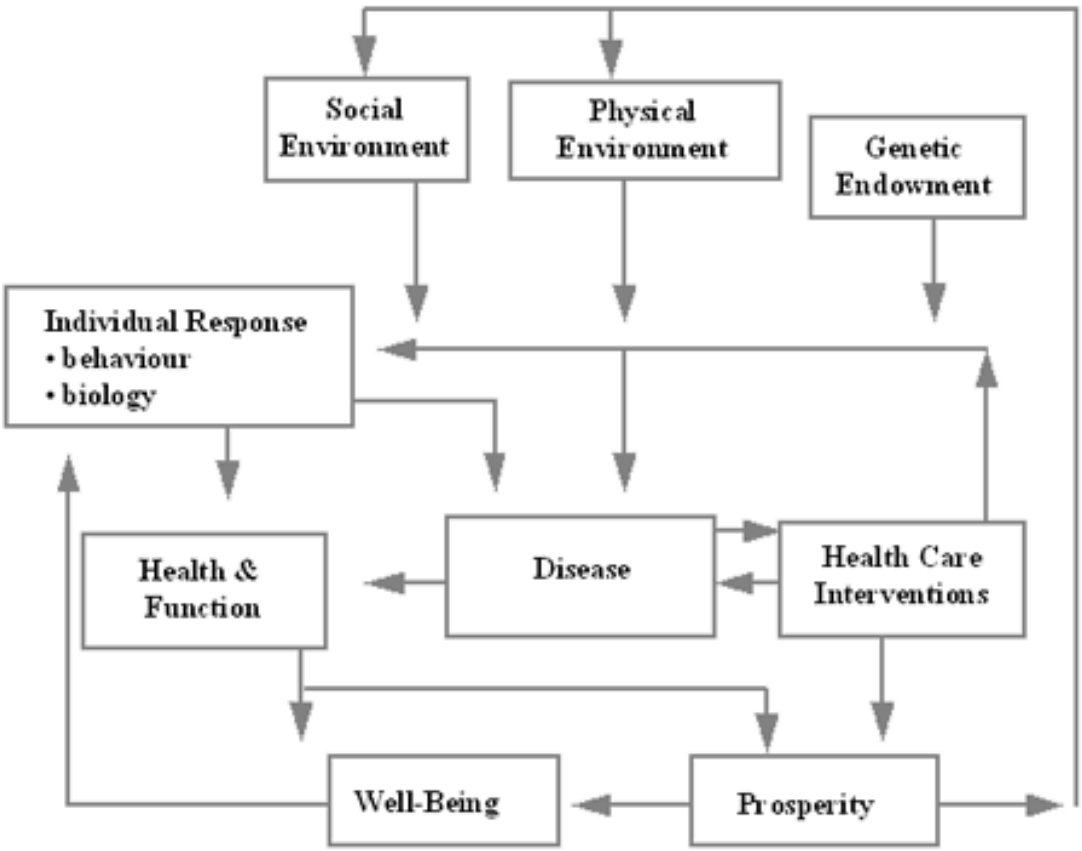
Theoretical frameworks or approaches are the structure on which something is formulated or built. In the case of this thesis the population health and ecological frameworks provide the rationale for the prescribed research questions, the methods in which they are answered, the interpretation of the results and their application in a practical context.

As a principle element of this thesis is its spatial component, a framework to guide those aspects is also needed. This foundation will be set using the principles of the Bailey and Gatrell (1995) spatial framework. Population health and ecological frameworks compliment Bailey and Gatrell's principles of spatial analysis. All three lenses will be used to guide and inform this research for the perspective and knowledge they will add to the study. Each will be described in this chapter and referred to throughout the thesis.

Population Health Framework

Population health focuses on public health and health promotion. It emphasizes the importance of health and health equity at the population level. A population health framework, as demonstrated in Figure 1 (Evans & Stoddart, 1990), stipulates that a focus on a complete and broad range of personal and ecological factors, along with their interactions, is essential to understanding the health and well-being of a population (Public Health Agency of Canada, 2009).

Figure 1 - A population health framework



Evans & Stoddart (1990). Producing health, consuming health care. *Social Science and Medicine*, 1347-1363. © Used with permission by Elsevier Limited on January 28, 2013.

The population health framework represents an integrated approach to the thesis and understanding of disease in a population. It assumes that many, if not all, aspects of life are interconnected and therefore play a role in health as well as disease, as seen in Figure 1 (Evans & Stoddart, 1990). The population health framework is widely used in areas of public health research (Etches, Frank, Di Ruggiero, & Manuel, 2006; Green, Elliott, Beaudoin, & Bernstein, 2006; Heaman, Green, Newburn-Cook, Elliott, & Helewa, 2007), including studies focusing on influenza and ILI (Crighton, Moineddin, Kanaroglou, & Upshur, 2007; Menec, Black, MacWilliam, & Aoki, 2003; Schanzer,

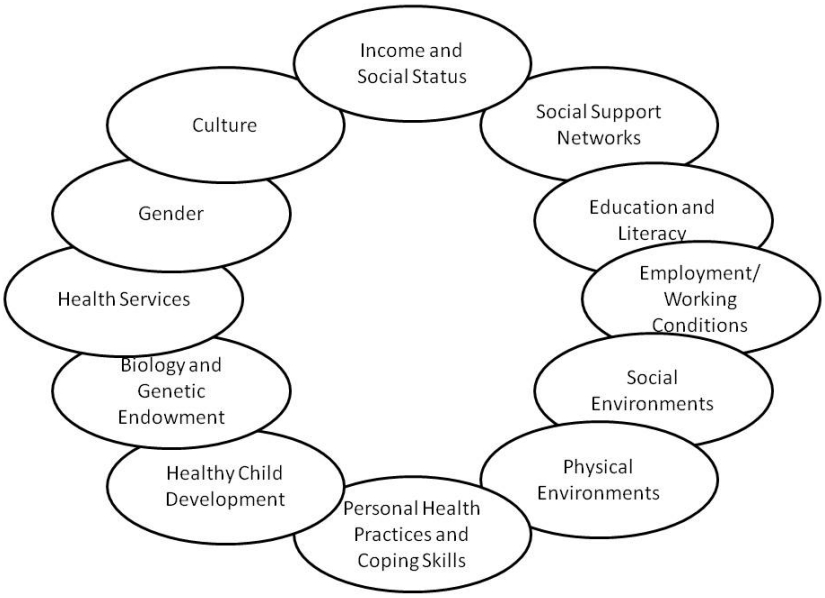
Langley, & Tam, 2008) as it seeks to understand illness in the broad context of a population.

A population health lens recognizes that many illnesses are not only the consequence of factors operating at the level of the individual, and that a population-based approach can better serve to identify public health concerns. A key element of the interconnectivity described is the determinants of health. Although not a theoretical approach or framework, the determinants of health play such a prominent role in population health and its framework that their understanding go hand in hand.

The determinants of health.

The determinants of health represent factors that can affect health at a population level, without exclusively being related to health. The Public Health Agency of Canada lists 12 key determinants of health that guide public health in Canada, as can be seen in Figure 2 (Public Health Agency of Canada, 2011). These determinants can affect everyone differently.

Figure 2 - The determinants of health

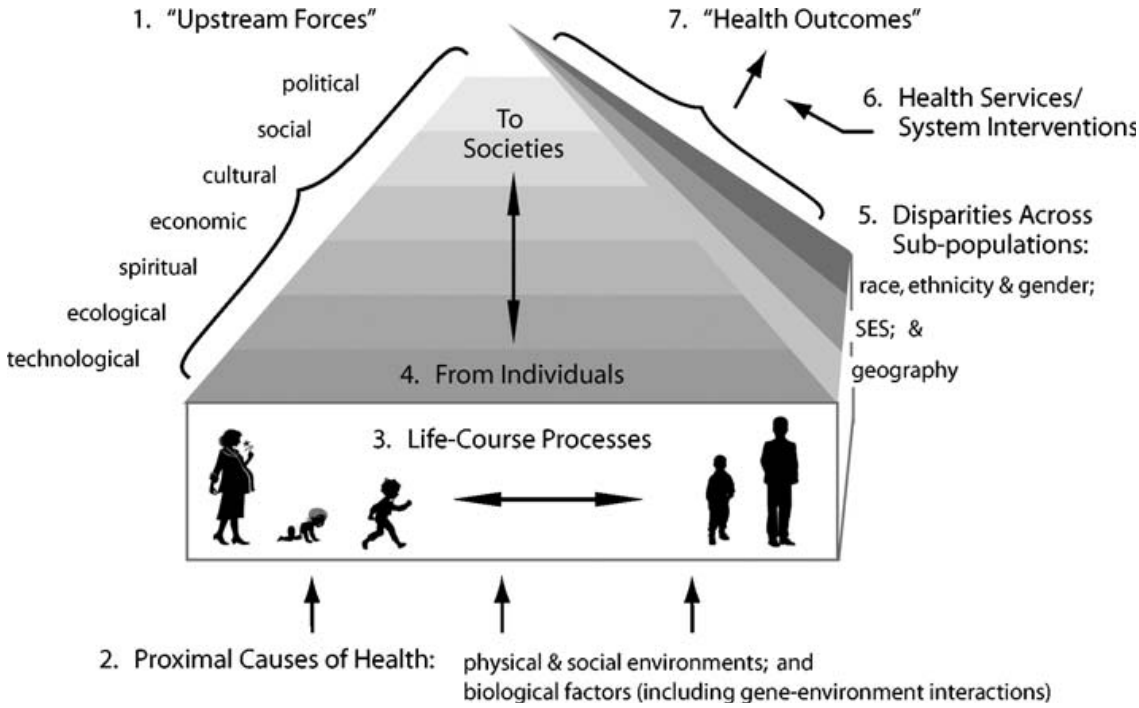


The determinants of health are intended to help explain some of the inequalities that exist in the health of populations with the hope that a better understanding of these will help reduce health disparities. Many of the determinants of health have inherent geographical and spatial elements that lend themselves to be examined from that perspective, as they will be in this study. For the purpose of this research some of the determinants of health will be used as ecological variables to test for their significance related to ILI in Manitoba, and will be further discussed in the Methods and Analysis chapter.

The Canadian Institutes of Health Research- Institute of Population Health (CIHR-IPPH) endorses the population health framework that incorporates the aforementioned determinants of health and aspects of everyday life. CIHR-IPPH supports and encourages health research that employs this framework in order to draw attention to important aspects of health and disease that may otherwise be ignored.

Although health outcomes are the area of interest for researchers, they should not be studied without taking into account the entire population health pyramid, as seen in Figure 3 (Etches, Frank, Di Ruggiero, & Manuel, 2006) which is continuously affecting and informing future outcomes.

Figure 3 - Population health pyramid



Etches, Frank, Di Ruggiero, & Manuel (2006). Measuring Population Health: A Review of Indicators. *Annual Review of Public Health*, 27:29-55. © Used with permission by Annual Reviews on January 24, 2013.

"The Public Health Disparities Geocoding Project," led by Nancy Krieger at Harvard University, also emphasizes the importance of the role that socio-economic status (SES) has on health (The Public Health Disparities Geocoding Project Monograph, 2004). The project examines seven health outcomes (including mortality, cancer,

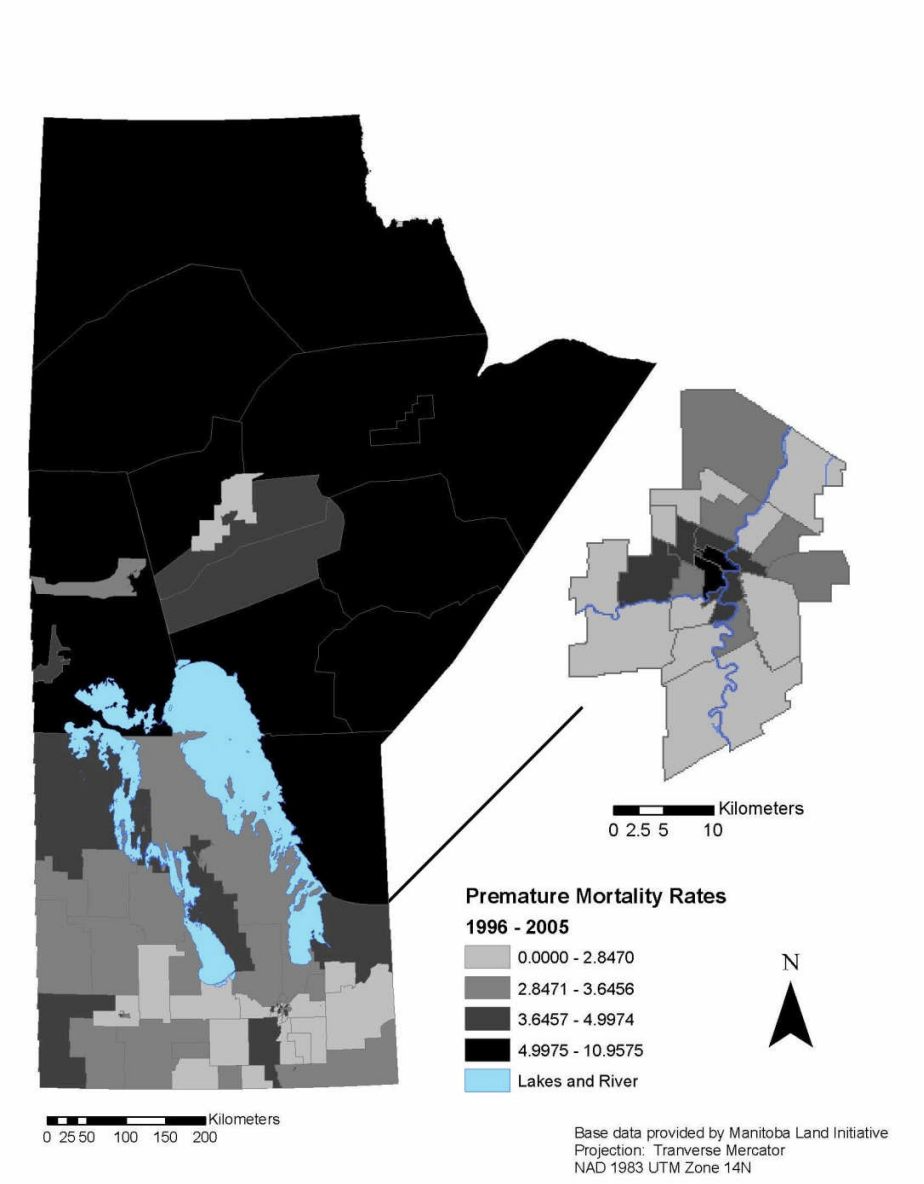
tuberculosis and sexually-transmitted infections) in two states (Massachusetts and Rhode Island), linking the outcomes to SES at different geographic levels (census block group, census tract and zip code). The results from that research identify a link between SES and health outcome, with the subsequent recommendations that this kind of analysis should be conducted for other health outcomes. This thesis attempts to meet the spirit of these recommendations in the province of Manitoba with ILI.

The *Developmental Health and the Wealth of Nations* (Keating & Hertzman, 1999) also recognizes the importance of the determinants of health and their role in the population health framework. This work focuses on a socio-economic health gradient, identifying that those with greater socio-economic wealth are in better health. For example, countries with greater wealth enjoy inherent benefits, such as the likelihood of greater health at birth. However, wealth is not evenly distributed in any country, and a gap often exists at the population level as well. National comparisons of health are often made by the World Health Organization (WHO) using the Premature Mortality Rate (PMR) to evaluate the health of a country.

The Manitoba Centre for Health Policy (MCHP) uses this same method within the province of Manitoba to compare Health Region Health Districts and Neighbourhood Clusters. The 2010 report on health inequities in Manitoba produced by the MCHP examined 18 health measures amongst Manitobans and compared them across different income quintiles (Martens, et al., 2010). The Premature Mortality Rate was one of the outcomes measured. The report showed that the PMR was one of the many indicators whose gap is widening over time, with greater variation in urban versus rural Manitoba, though widening in both.

Using the PMR as a proxy for the overall health of a community at any level confirms the notion that place is an important determinant of health in itself. Figure 4 geographically shows the premature mortality rates for the province of Manitoba as calculated by the MCHP (Fransoo R. , Martens, Burland, Prior, & Burchill, 2009).

Figure 4 – Manitoba Premature Mortality Rates by Health District and Neighbourhood Cluster



Ecological Framework

The ecological framework is often linked with population health as it is based on the notion that outcomes, in this case, population health outcomes – specifically ILI, are not the result of a single factor, but rather due to a collection of variables or characteristics, such as the determinants of health. Ecological characteristics are

potentially modifiable and can be greatly influenced by their interactions as well as by the spatial location in which they take place (Arya, et al., 2009). The ecological framework also fits well with the notion of an epidemiologic triad (including an agent of disease, a susceptible host and suitable environment) that is necessary for disease (Last, 2001). Disease presence has the ability to change as any one of the elements of the triad is modified. The population health approach will complement these assumptions as it emphasizes the importance of understanding things at the population level rather than at the individual level, which is the very essence of public health.

An advantage to incorporating an ecological framework to examine illnesses or medical conditions, such as ILI, is that the framework allows the analysis to go beyond statistics of disease prevalence and incidence. This framework also answers questions about why numbers and rates are occurring, potentially offering greater opportunities for intervention and prevention (Smith, et al., 2005; Wilson, 2009; Green, Elliott, Beaudoin, & Bernstein, 2006).

Both population health and ecological frameworks recognize that health does not take place simply in the body of an individual, and thus the study of illness and disease cannot be studied without a consideration of the communities in which people live (Wilson, 2009; Smith, et al., 2005). The setting or environment in which health or illness occurs is imperative to understand population and public health; these settings can be best displayed spatially with geographic information systems (GIS) (Nykiforuk, 2011; Crighton, Moineddin, Kanaroglou, & Upshur, 2007; Heaman, Green, Newburn-Cook, Elliott, & Helewa, 2007).

Spatial Framework

Bailey and Gatrell's spatial framework will be used with GIS in conjunction with the population health and ecological frameworks. This framework analyzes the data from three perspectives - data visualisation, data exploration and data modeling- and is often used with spatial analysis and spatial epidemiology (Bailey & Gatrell, 1995). This framework has been used in other areas of public health (Gatrell, Collin, Downes, Jones, & Bailey, 1995), though minimally with influenza research (Crighton, Moineddin, Kanaroglou, & Upshur, 2007; Crighton, Elliott, Moineddin, Kanaroglou, & Upshur, 2007).

Epidemiological measures such as incidence, prevalence and standardized mortality/morbidity ratios are common tools used for data visualisation. Data exploration analysis is most often an attempt to detect patterns, identify any outliers of significance, and highlight any clusters (whether high or low). The distinction between these two elements is often blurred because some of the aspects confirmed by data exploration are often seen with data visualisation.

Data modeling allows for the incorporation of risk factors, whether known or hypothesized, that can be tested for significance to the outcome of interest in a study. The risk factors are then linked to a spatial component and the results modeled in a GIS to detect areas of predicted higher vulnerability (Gatrell, 2000; Bailey & Gatrell, 1995).

Taking into account the population health, ecological and spatial frameworks will allow for a broad look at the Manitoba population and whether the different spatial elements influence the burden of illness caused by influenza-like illnesses. The concepts of population health appreciate that there are many extrinsic factors (ecological

characteristics) beyond the personal, genetic and biological characteristics that affect health (Etches, Frank, Di Ruggiero, & Manuel, 2006; Wilson, 2009; Nykiforuk, 2011). This study will examine ILI in Manitoba spatially and will explore whether the chosen determinants of health are associated with its diagnosis.

Chapter 3 - Background and Literature Review

Influenza and Influenza-like Illnesses

Influenza refers to “a respiratory infection caused by the influenza virus” (Public Health Agency of Canada, 2007, para. 1). Influenza is an acute febrile disease that affects the nose, throat and lungs. The influenza virus is highly contagious and spread through the regular acts of coughing and sneezing. Although generally an acute illness, its ease of spread, short incubation period and ability of the virus to shift are among the chief reasons ‘the flu’ is considered an important public health issue both in Canada and around the world, and is the subject of ongoing research. Populations most susceptible to complications of influenza and typically referred to as high-risk populations, include children, pregnant women, the elderly and those whose immune systems are compromised. For these individuals influenza can be serious and even fatal. Approximately 10-25% of Canadians are infected with influenza annually resulting in 4000-8000 deaths (Health Canada, 2009).

In Canada, influenza is monitored through the Annual FluWatch surveillance program. This program is overseen by Immunizations and Respiratory Infections Division (IRID), Centre for Infectious Disease Prevention and Control (CIDPC) at the Public Health Agency of Canada (PHAC). FluWatch provides weekly reports on the PHAC website and is primarily intended for health-care professionals. The program includes various laboratories, hospitals, sentinel physicians, as well as provincial and territorial health departments. Its purpose is to provide early detection of influenza outbreaks nationwide, to provide timely, updated information with regards to influenza and ILI activity in Canada and the rest of the world, to monitor the current strains of the

virus and the virus' sensitivity to antiviral medications used to treat the illness, and to provide information to the World Health Organization to help inform decisions concerning annual vaccine programs (Public Health Agency of Canada, 2010).

Although a clear clinical case definition exists for influenza, which can then be confirmed through laboratory testing, monitoring and surveillance programs do not rely exclusively on confirmed cases. Influenza is generally not tested for, thus it is recognized that most cases are not confirmed. When a case is clinically diagnosed but not laboratory confirmed, it is referred to as an influenza-like-illness (ILI). ILI includes both influenza viruses and other respiratory illnesses which present the same symptoms and are therefore indistinguishable without laboratory testing. During a regular flu season, ILI clinical diagnosis is considered to be sufficient and a more cost-effective form of surveillance. ILI cases are monitored and treated with antiviral medications when warranted (Public Health Agency of Canada, 2007).

In Canada, the clinical case definition of ILI is an "acute onset of respiratory illness with fever and cough and with one or more of the following - sore throat, arthralgia, myalgia, or prostration, which could be due to influenza virus but has not been confirmed by laboratory testing. In children under five, gastrointestinal symptoms may also be present. In patients under five or 65 and older, fever may not be prominent" (Public Health Agency of Canada, 2010, para. 4).

During the study period (2004-2009), the College of Family Physicians of Canada, National Research System (NaReS), was tasked with securing sentinel physicians and nurses, and overseeing their participation in surveillance reporting for most of Canada, including Manitoba (Public Health Agency of Canada, 2006).

Representation from each of the census divisions, or per 250,000 population, across the country was sought. Participating physicians were asked to report the total number of patients seen on a specific day of the week, and the corresponding number specific to the ILI definition identified for the season (Public Health Agency of Canada, 2006).

There are three types of influenza viruses, labelled A, B and C. Types A and B are the viruses that routinely occur among humans (Stamboulian, Bonvehi, Nacinovich, & Cox, 2000). The different Influenza A viruses are categorized into subtypes based on the two proteins that occur on the surface of the virus. There are 16 different kinds of hemagglutinin (H) subtypes and nine different neuraminidase (N) subtypes. The combination of the type and subtype identify the specific strain of virus. The Influenza B virus is not divided into subtypes, although there are different strains of Influenza B. Increased risk for widespread illness occurs when a new virus evolves, making everyone vulnerable as prior immunity has not been developed (Centres for Disease Control and Prevention, 2010).

Influenza A viruses are present every year and many people have successfully built up some immunity to the virus, The virus is always mutating, making it difficult to protect against all strains. As the influenza virus spreads easily from person to person, new strains have resulted in pandemic outbreaks. If the virus mutates into a different strain such that there is little immunity in the population and no protection from the influenza vaccine, then substantial challenges for public health response may arise. This type of scenario could potentially affect more people, spread very quickly and potentially present more severely (Public Health Agency of Canada, 2007).

There are two ways in which the Influenza A virus changes. The first way is called “antigenic drift”. This occurs gradually over time, with small changes in the virus that gradually change its genetic make-up. As the changes occur, influenza antibodies that exist in the human body are no longer effective protection mechanisms. The influenza vaccine is periodically updated to accommodate this “antigenic drift”.

The second change is referred to as “antigenic shift”. This is a more sudden change that occurs when new proteins (hemmagglutinin and/or hemagglutinin and neuraminidase), emerge from an animal host form a new virus, for which most humans do not have immunity (Centers for Disease Control and Prevention, 2010). The clinical relevance of the new virus is initially unknown. This viral shift typically occurs too quickly for a vaccine to be immediately readily available. The novelty of the virus makes it unclear whether existing antiviral medications will be effective or not.

In Canada, the influenza vaccination is recommended annually for high-risk populations, however at-risk population eligibility changes as research is conducted and disease susceptibility is identified. The vaccine generally includes circulating strains of influenza and is intended to protect individuals against these (Public Health Agency of Canada, 2010). In Canada, the vaccine is available by prescription only, is administered by a physician or public health nurse, and represents the primary prevention strategy against influenza each season (Public Health Agency of Canada, 2009).

The procurement of the vaccine is handled at the federal level, in part to secure the lowest price from the manufacturers, and then distributed to (and paid for by) the provinces and territories as needed. While NACI provides recommendations, the provinces and territories decide to whom it will offer the vaccine and whether it will be

provided free of charge. Variations in influenza vaccine programs exist across the country. Ontario, Alberta and Nunavut have universal programs, whereas Yukon only subsidizes the vaccine for individuals 18 years old and older (Public Health of Agency of Canada, 2011). In Manitoba during the study years, only those who are most at risk of severe illness and complications due to the flu are offered free influenza vaccines (Manitoba Communicable Disease Control Unit, 2006).

A national study found that influenza vaccine coverage in Canada more than doubled from 15% in 1996-97 to 34% in 2005 (ICES, 2007). Despite this increase, the vaccination rate continues to fall short of the national target of 80% as identified by the National Advisory Committee on Immunization (NACI) for adults aged 65 and over (71%) and all adults with chronic medical conditions (42%) (Kwong, Rosella, & Johansen, 2007). Vaccine rates have improved from 1996-97 to 2005 among those aged 12 to 64 with chronic conditions (18% to 38%) and those aged 65 and older (52% to 71%), but continue to be below the targets set by NACI for those in the latter categories (Kwong, Rosella, & Johansen, 2007).

The at-risk groups targeted in Manitoba have remained reasonably consistent throughout 2004-2009. The at-risk groups identified included all those citizens 65 years and older; healthy children aged six to 23 months; people living in personal care homes or other chronic care facilities, regardless of age, anyone with chronic heart or lung disease, people with cancer, anemia, or a weakened immune system whether due to disease or medication, anyone with chronic conditions including diabetes, kidney disease, inflammatory bowel disease, celiac disease, rheumatoid arthritis, lupus, alcoholism or multiple sclerosis, and children on long-term aspirin therapy.

The eligibility list also includes those in household contact with small children up to 23 months of age, people providing care to infants up to 23 months of age, health-care workers, staff or volunteers providing care in personal care homes, as well as first responders, including police officers, firefighters and ambulance workers.

For the 2005-06 season adults and children with chronic respiratory conditions were added to the eligibility list (Communicable Disease Control Unit, 2005). The eligibility list for the 2006-07 season remained unchanged (Communicable Disease Control Unit, 2006). For the 2007-08 season, Manitoba Health followed NACI's recommendation to include pregnant women to the eligibility list (Communicable Disease Control Unit, 2007). The final study year for this research, 2008-09, saw the addition of those individuals who have household contact with pregnant women (Communicable Disease Control Branch, 2008). The complete eligibility criteria for Manitoba for the study years from 2005-06 to 2008-09 is included in Appendix B; similar information was not available for the 2004-05 season.

In order to better understand the at-risk population for influenza, research has been undertaken to identify various risk factors including morbidity, age and hospitalization leading to consequential deaths (Schanzer, Langley, & Tam, 2008). Predictive symptoms of influenza in adult (Monto, Gravenstein, Elliott M, & Schweinle, 2000) and child populations have been identified (Ohmit & Monto, 2006), as have the influence of vaccines within these groups (Figaro & Belue, 2005). Researchers found that co-morbid conditions play an important role in determining who gets sick. These results confirm those people identified by NACI are the most at risk for the vaccination program.

Pandemic Influenza

During the past century there were four identified influenza pandemics occurring in 1918, 1957, 1968 and 2009. A pandemic is defined as "an epidemic occurring worldwide, or over a very wide area, crossing international boundaries, and usually affecting a large number of people" (Last, 2001, p.131). An influenza pandemic occurs when the virus is sufficiently changed due to a quick antigenic shift without sufficient time for the population to adapt and develop antibodies to the virus.

The 1918-1919 pandemic killed an estimated 40-50 million people worldwide. In 1957 the influenza pandemic took the lives of two million people. In 1968 the Hong Kong Influenza, claimed another one million lives (World Health Organization, 2005). 2009 saw the emergence of influenza pandemic (pH1N1) which claimed over 18,000 lives (World Health Organization, 2010). The ever-changing nature of Influenza A viruses makes it impossible to predict when a pandemic will occur, nor the make-up of the associated virus responsible.

When taking into account the number of people who died in the last four influenza pandemics, it is easy to understand why it is important to have measures in place to deal with the potentially catastrophic nature of influenza pandemics. It is difficult to prepare for an influenza pandemic. A well-developed seasonal influenza program is a good place to start. In the most recent pandemic the at-risk population was discovered to be very different as compared to the usual seasonal influenza at-risk cohort. Previous years of influenza surveillance and data comparison allowed Manitoba to quickly identify the variation of at-risk groups.

The pH1N1virus was most dangerous for those aged 5 to 19, followed closely by those aged 30 to 59 (Communicable Disease Control Branch, 2009). Another noticeable difference between the seasonal influenza and pH1N1 in Manitoba was the geographical distribution of the cases. Seasonal influenza typically affects higher numbers in the Winnipeg Regional Health Authority (RHA), representing approximately 70% of the cases, which parallels the proportion of the Manitoba population (Communicable Disease Control Unit, 2006; Communicable Disease Control Unit, 2007; Communicable Disease Control Branch, 2008; Communicable Disease Control Branch, 2009).With pH1N1, fewer than half the cases were reported in the Winnipeg RHA. The increased rates of Influenza during pH1N1 were seen in most of the other regional health authorities around the province, regardless of population size (Communicable Disease Control Branch, 2009). This variation could be explained by the uneven distribution of the sentinel physicians in Manitoba. This difference may be a result of differentials in general reporting practices, which can include both over and under use of ILI diagnoses in surveillance data.

Epidemiology of Influenza in Manitoba

Surveillance of influenza and ILI in Manitoba is the responsibility of the Communicable Disease Control (CDC) Branch at Manitoba Health. Manitoba Health uses CDC, or 'epi', weeks as the unit of time for influenza surveillance and reports. CDC, in this case, refers to the USA governments' Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, 2010). Although there are typically 52 CDC weeks each year, these weeks do not necessarily represent the same calendar dates. CDC week 1 for any given year begins on the first Sunday of the week of the New Year.

The influenza season, as tracked by Manitoba Health, begins on July 1 and ends on June 30 of the following year. This surveillance involves the tracking of laboratory confirmed influenza cases by collection date, age and RHA, as well as ascertaining serotype information for as many cases as possible. Suspected and confirmed outbreaks are also reported to the CDC, along with any influenza-related deaths.

An important component of the influenza surveillance performed by Manitoba Health is the reporting of data to the national FluWatch program, including reporting of ILI on a weekly basis (Manitoba Communicable Disease Control Unit, 2006). Reports are produced weekly and at the end of each season. The reports are made publicly available on the Manitoba Health website. The following tables and paragraphs summarize the data from the 2005-06 to 2008-09 seasons relevant to this research; similar data was not always available for the 2004-05 season.

Table 1 shows the CDC week of the first and last laboratory confirmed case in Manitoba for each of the study years (Manitoba Health - Communicable Disease Control Branch; Communicable Disease Control Unit, 2006; Communicable Disease Control Unit, 2007; Communicable Disease Control Branch, 2008; Communicable Disease Control Branch, 2009). Note that the 2008-09 season appears twice: once depicting the number of laboratory confirmed cases excluding pH1N1*, and one depicting pH1N1 laboratory confirmed cases**.

The 2008-09 season was unusual as the novel pandemic H1N1 (pH1N1) virus was detected. The detection of a new strain and the subsequent attention that it received may have triggered a bias in testing practices, thus resulting in an increased number of reported cases. Although the end of season report does separate those cases that were

pH1N1 from those that were not, it is possible that both physicians and patients were more sensitive to ILI which may have resulted in more tests. There were 803 confirmed cases of pH1N1 during the 2008-09 influenza season in Manitoba (Communicable Disease Control Branch, 2009).

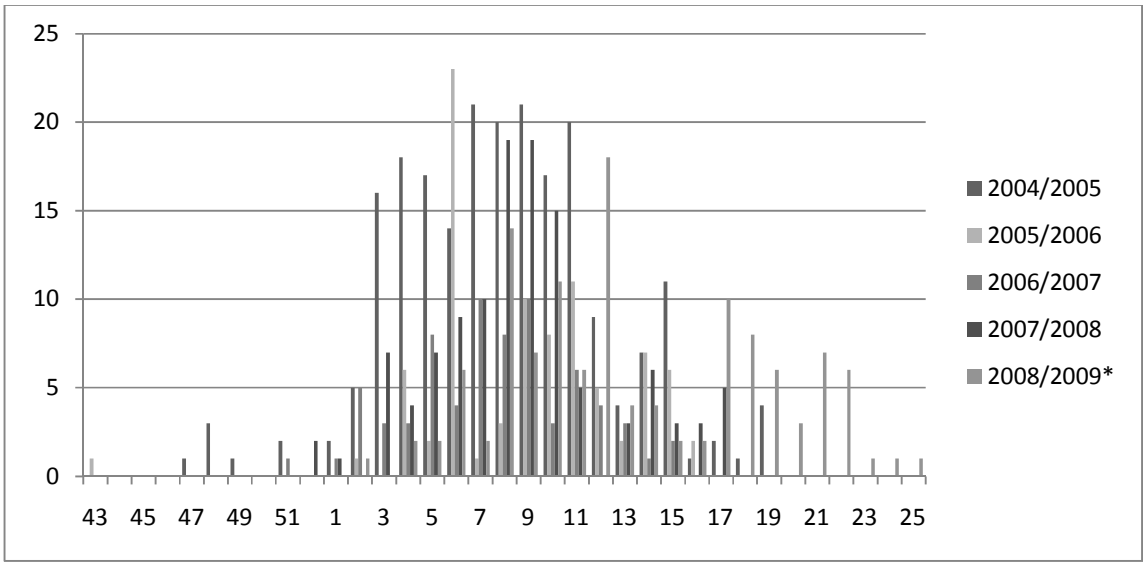
Table 1 – CDC Week of First and Last Laboratory Confirmed Cases by Study Year

Season	CDC Week of First Laboratory Confirmed Case	CDC Week of Last Laboratory Confirmed Case
2004/2005	CDC Week 47	CDC Week 19
2005/2006	CDC Week 40	CDC Week 16
2006/2007	CDC Week 51	CDC Week 15
2007/2008	CDC Week 52	CDC Week 17
2008/2009*	CDC Week 2	CDC Week 25
2008/2009**	CDC Week 2	CDC Week 26

It is easiest to compare the temporal distribution of the cases across the seasons using the CDC weeks by displaying the data as an epidemic curve, as shown in Figure 5. Although the peaks occur in different weeks across the seasons, laboratory confirmed cases were always present by CDC week 4 and typically end by CDC week 15 (Communicable Disease Control Unit, 2006; Communicable Disease Control Unit, 2007; Communicable Disease Control Branch, 2008; Communicable Disease Control Branch, 2009; Manitoba Health - Communicable Disease Control Branch). Note that the data

presented in Figure 5 does not include any pH1N1 cases during the 2008-09* season, as those cases occurred outside of the typical influenza season in Manitoba. Epidemic curves for each of the seasons, based on laboratory confirmed cases including the pH1N1 cases, are available in Appendix A.

Figure 5 - Laboratory confirmed influenza cases by CDC week by season



Influenza in Manitoba, based on laboratory confirmed cases and ILI, is not evenly distributed across the various age groups. The age group breakdown of cases per season is depicted in Figures 6 and 7. The age groupings were changed for the 2008-09 season. Figure 7 depicts the distribution for the 2008-09 season excluding pH1N1* cases and exclusively pH1N1 cases**. The data shown in these graphs is based on the absolute numbers of laboratory confirmed cases, as Manitoba Health does not present age standardized rates (Communicable Disease Control Unit, 2006; Communicable Disease Control Unit, 2007; Communicable Disease Control Branch, 2008; Communicable Disease Control Branch, 2009).

Figure 6 - Age distribution of laboratory confirmed influenza cases by season

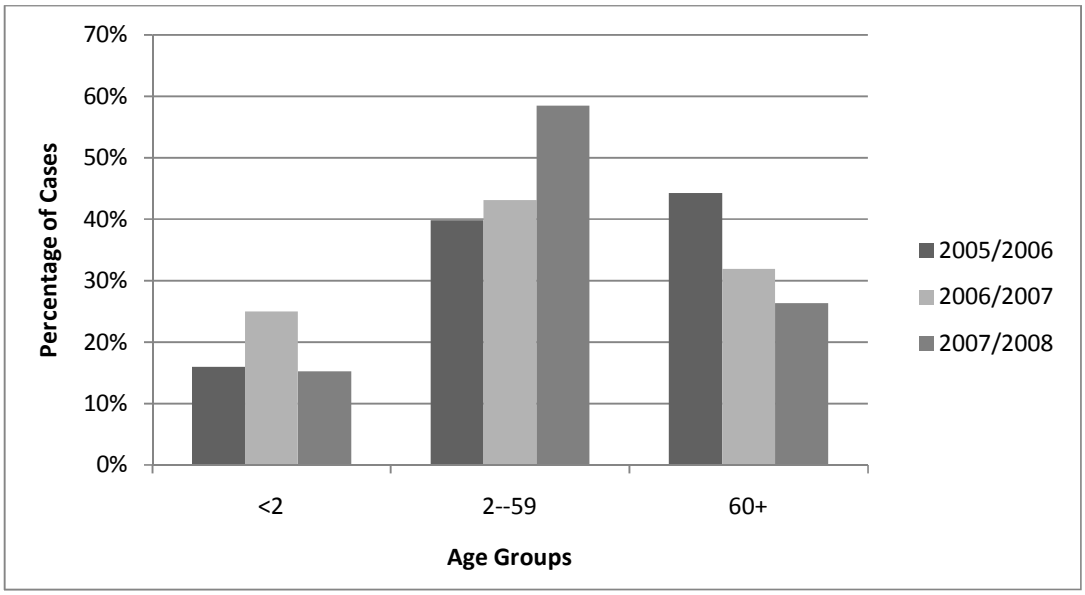
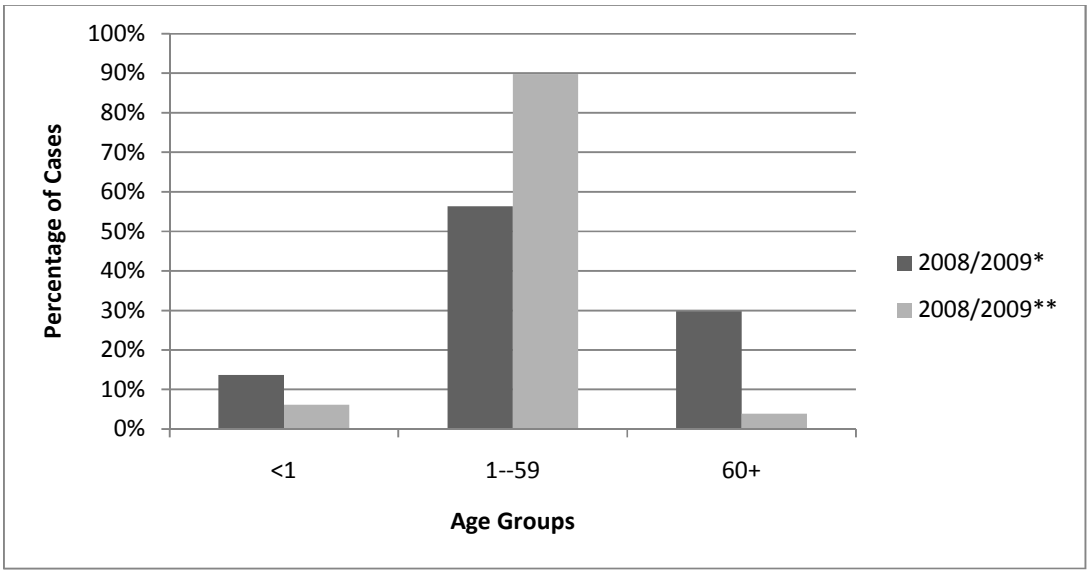


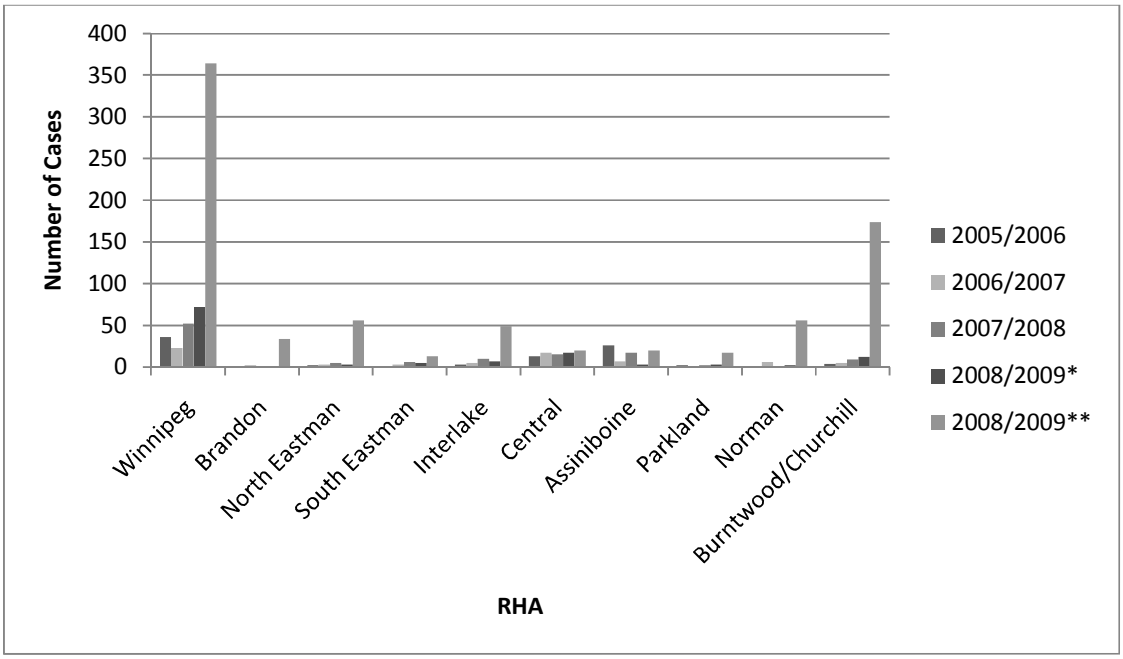
Figure 7 - Age distribution of laboratory confirmed influenza cases for 2008/2009 season



The distribution of laboratory confirmed influenza cases by RHA by season, as presented by the CDC in the annual end of season reports (Figure 8), only shows absolute case numbers and does not account for the difference in population size of each RHA

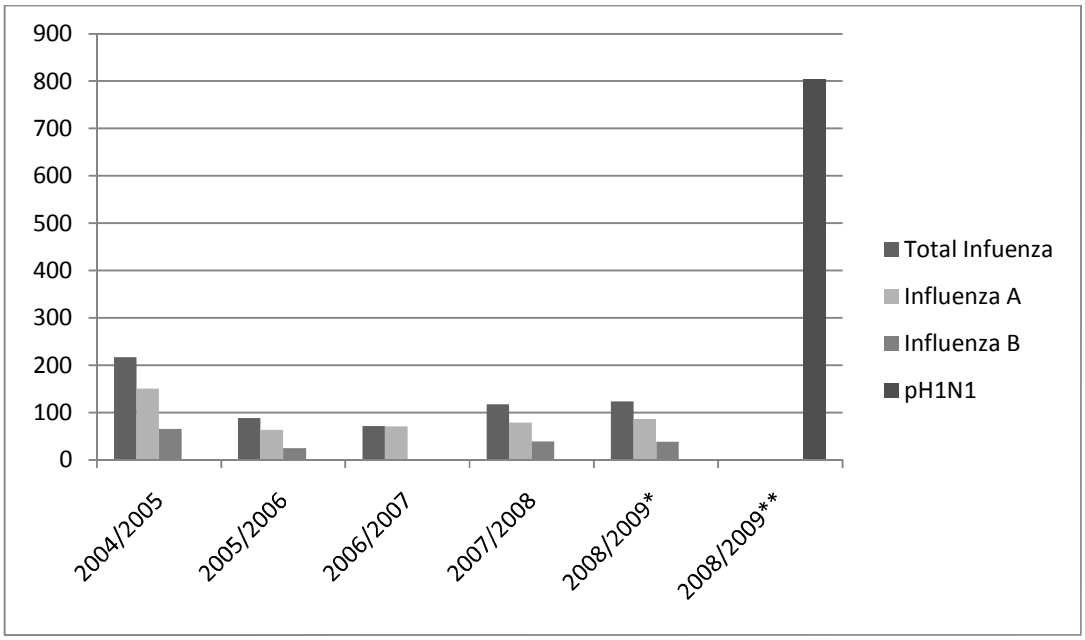
(Communicable Disease Control Unit, 2006; Communicable Disease Control Unit, 2007; Communicable Disease Control Branch, 2008; Communicable Disease Control Branch, 2009)**.** Again, note that the 2008-09 season is presented twice: once for cases excluding pH1N1* and once for only cases of pH1N1**.

Figure 8 - Laboratory confirmed influenza cases by regional health authority by season



The distribution of total laboratory confirmed influenza cases, divided into serotypes A and B for each of the study years using available data, is depicted in Figure 9 (Communicable Disease Control Unit, 2006; Communicable Disease Control Unit, 2007; Communicable Disease Control Branch, 2008; Communicable Disease Control Branch, 2009; Manitoba Health - Communicable Disease Control Branch). Note that the 2008-09 season appears twice: once showing the number of laboratory confirmed cases excluding pH1N1*, and one showing the volume of pH1N1 laboratory confirmed cases**.

Figure 9 - Laboratory confirmed influenza cases by season and serotype



The rate at which ILI occur in Manitoba is tracked by the CDC with the help of sentinel physicians also collecting data for the FluWatch program. The distribution of these physicians is slightly different each year. For the 2005-06 and 2006-07 seasons there were 14 sentinel physicians distributed across eight regional health authorities: South Eastman, Central, Brandon, Winnipeg, Assiniboine, Interlake, Nor-Man and Burntwood (Communicable Disease Control Unit, 2006; Communicable Disease Control Unit, 2007). For the 2007/2008 and 2008/2009 seasons, 15 sentinel physicians were reporting ILI cases across nine regional health authorities: North Eastman, South Eastman, Central, Parkland, Winnipeg, Assiniboine, Burntwood, Brandon and Interlake (Communicable Disease Control Branch, 2008; Communicable Disease Control Branch, 2009). Surveillance of ILI is not population-based in Manitoba. The rates of ILI for the study seasons are available in Appendix A.

ILI rates, which are also tracked as part of the national and international influenza surveillance programs (WHO Global Influenza Surveillance Network, 2011; Public Health Agency of Canada, 2010; Manitoba Communicable Disease Control Unit, 2006), are accepted as reflective of influenza activity when influenza is known to be present in the community; i.e., when laboratory confirmed cases have been documented (Vega, et al., 2012; Westheimer, et al., 2012; Western Pacific Region Global Influenza Surveillance and Response System, 2012).

Place, Space and Time

Flu vaccination campaigns, as well as influenza reporting procedures account for some of the characteristics of at-risk populations, these often neglect to take into account the role that 'place and time', or space, have in modifying the risk of infection. At present, the vaccination campaign is launched at the same time throughout the province at the beginning of the fall. Those individuals identified by vaccination campaigns as "at risk" are more likely to experience severe illness from influenza. If consideration of space and time was to occur, a greater understanding of what makes a person more susceptible to severe illness may be obtained. This in turn could help structure intervention strategies more effectively.

There are several examples that highlight the role of place, space and time play when studying the epidemiology of a communicable disease. Perhaps the most famous case is the cholera outbreak in London in 1854 when Dr. John Snow found an association was discovered between the proximity of the Broad Street pump and cholera case clusters (Paneth, 2004). Snow plotted cases on a map, identified the cluster and eventual source of

the outbreak. This correlation was identified even before any epidemiological recognition that water was the vector for the disease.

In May 2000, the community of Walkerton discovered that an illness affecting its citizens was due to contamination of the water supply. A strain of E. coli bacteria was identified as responsible for the outbreak (Salvadori, et al., 2009; Arya, et al., 2009). In this case, the element of space became important, not necessarily for its specific characteristics, but rather in more absolute terms – a person must have been in, or had some relationship to, the community in order to have been exposed to the bacteria. Similarly the spatial epidemiology of a food-borne illness outbreak must focus on the distribution of the contaminated product in order to locate potential cases, as was the case with the national Listeriosis outbreak in 2009 (Public Health Agency of Canada, 2008).

Understanding how quickly a virus can spread globally, as well as locally is important to consider in pandemic preparedness, and an area that requires further research. The 2002-03 SARS outbreak was a prime example of how quickly and how far a communicable disease can spread when movement of the population is prominent. Whereas the two previous pandemic influenza outbreaks in the twentieth century spread over a number of years (Public Health Agency of Canada, 2007), the SARS outbreak claimed nearly 800 lives, beginning with one individual in China and within a matter of weeks, infecting individuals in 37 countries (Public Health Agency of Canada, 2008; Berry, Wharf-Higgins, & Naylor, 2007). Although the current spread of a pandemic is facilitated by rapid and more accessible travel (an important element in the spread of communicable diseases), technological advances may be used to better prepare for, and hence deal with, the next pandemic.

It is necessary to first identify important individual (Irwin D. , et al., 2001) and geographic characteristics that may influence the spread of the illness (Crighton, Moineddin, Kanaroglou, & Upshur, 2007). Once individual and geographic characteristics are identified through statistical tests (to be further discussed in the Methods and Analysis chapter), existing relationships can then be highlighted and accounted for within a given exploratory model. The better the understanding of the data as it relates to space, time and illness, the better the model will be (Kanaroglou, & Upshur, 2007). By taking into account ILI rates from previous Manitoba flu seasons, we can examine its characteristics from a different perspective and acquire information that may be useful in predicting or better understanding future outbreaks and potential pandemics.

Spatial Epidemiology: Data Visualisation, Data Exploration, Data Modeling

Spatial epidemiology encompasses the principles of epidemiology with an emphasis on the established importance of place, space and time as related to health and illness (Gatrell, 2000; Rytkonen, 2004). There are many facets of spatial epidemiology with various tests and presentation options available. The chosen tests and analysis conducted within this study are dependent on the study objective as well as available data. Spatial epidemiological analysis will follow the concepts of data visualisation, data exploration and data modeling, as framed by Bailey and Gatrell's spatial framework.

Data visualisation.

Surveillance mapping is a useful tool to display the incidence and prevalence of disease highlighting variations across space. These maps can be created using any number of different software, but represent the most basic capabilities of GIS (Unwin,

1996; Nykiforuk, 2011; Prince, Chen, & Lun, 2005; Gatrell & Bailey, 1996). Surveillance mapping is a form of data visualisation that requires minimal analysis, thus does not take advantage of the many tools and tests that are possible with the assistance of GIS (Gatrell, 2000). Surveillance maps serve as a tool to facilitate communication, display multiple risk factors and provide a spatial context to better understand illness distribution patterns (Barford & Dorling, 2007; Koch & Denike, 2001; Gatrell & Senior, n.d.). They also provide the ability to display the data in a way that facilitates geographic comparisons visually.

One tool of surveillance mapping is spatial smoothing. Smoothing of rates is a method of addressing the possibility of highly variable rates in sparsely populated areas, or where case numbers may be small and can be highly inflated by standardization (Elliott, 2004; Rytkonen, 2004). Smoothing takes data from surrounding areas and borrows information in order to reduce the variability, or noise, created by unstable rates (Gomez-Rubio, 2010). Data points from neighbouring areas are averaged and subsequently create a new piece of data in areas where great variability exists in order to provide an image that is more smooth and stable for interpretation purposes. As rates of ILI are high and variability is not a concern, smoothing techniques are not used in this thesis.

Data exploration

Different statistical tests take into account the importance of space, place and time (Bell, Hoskins, Pickle, & Wartenberg, 2006; Gomez-Rubio, 2010; Rytkonen, 2004). Although there are a number of different techniques that could be employed for data exploration analysis, including LISA (Jerrett, Gale, & Kontgis, 2010), Moan's I (Gomez-

Rubio, 2010) and Model Based Methods (Kulldorff, et al., 2007), the Spatial Scan Statistic (Kulldorff, et al., 2007) is often employed. The Spatial Scan Statistic is a focused statistical method, rather than global or local. It is well respected for establishing whether clusters of cases that occur are in fact 'true' clusters, do not occur by chance, and therefore are significant.

The Spatial Scan Statistic uses circular windows that capture cases within the window to be included in the analysis (Kulldorff, et al., 2007; Onozuka & Hagiahara, 2008). The radius of the circle gets progressively bigger until a threshold number of cases is included. The window with the largest likelihood ratio test is assumed to be the most-likely-to-cluster area. This occurs by comparing the risk inside the cluster to that outside of it.

The identified cluster can then be tested using Monte Carlo statistics methods to determine its significance as a true cluster. Monte Carlo methods simulate random outcomes to detect the likelihood that a cluster has occurred by chance or is significant (Sonesson, 2007). Identifying clusters of an event is important epidemiologically speaking, as a cluster of cases can indicate a higher risk of illness requiring further investigation.

Data modeling

Many different methods could be chosen to conduct the analysis of data modeling, including Bayesian, Logistic or Cox Regression and, Poisson Regression. The latter has been chosen for some of its key advantages (Kulldorff, et al., 2007; Jerrett,

Gale, & Kontgis, 2010) including the ability to conduct Categorical Poisson Regression to analyze data and addresses the concern of spatial auto-correlation.

Spatial auto-correlation is the identification that objects that are closer together are more likely to be similar than those that are farther apart. This idea identifies an inherent bias in studies that consider space as a variable that either must be acknowledged or addressed. Categorical Poisson Regression overcomes spatial auto-correlation to some extent as it aggregates geographic areas into broad categories (i.e., all low income areas, or all urban areas get aggregated together into one geographic unit for the purpose of analysis). These geographic areas are likely to be spread across the larger study area.

Another key advantage of the Categorical Poisson Regression approach is that it is a form of spatial smoothing. By aggregating geographic areas together based upon the predictor categories used (i.e., aggregates all high income neighbourhoods together or rural populations), it helps keep the analysis from being affected by unstable rate estimates. A third advantage is that it allows for the inclusion of independent and ecological variables; a necessary requirement for this study's protocol.

Categorical Poisson Regression has been used in similar studies (Green, Elliott, Beaudoin, & Bernstein, 2006; Heaman, Green, Newburn-Cook, Elliott, & Helewa, 2007). If the distribution of the data is over-dispersed (where the scale factor is greater than one), Negative Binomial Regression can be used in lieu of Categorical Poisson Regression. Negative Binomial Regression has the same advantages as Categorical Poisson Regression but is more flexible, allowing for variability in the data. Negative Binomial Regression relaxes the assumption of the Categorical Poisson Regression model that requires the variance and mean to be the same (Gardner, Mulvey, & Shaw, 1995;

Cadigan & Tobin, 2010; Robinson & Smyth, 2007). This relaxed assumption then removes the concern of over-dispersion or variability in the data.

This chapter provides the necessary background information to fully understand the thesis in terms of its objectives, methods and the discussion of the results. This included an overview of influenza and influenza-like illnesses, as well as details pertaining to the existing surveillance practices in Manitoba and Canada. To help contextualize the importance of ILI from a public health perspective, an overview of the annual morbidity and mortality of influenza in Manitoba and Canada were presented; a brief history of pandemic influenza was also discussed. The principles of spatial epidemiology were presented as the subsequent chapters will refer to data visualisation, exploration and modeling as they relate specifically to the the thesis objectives and methodology.

Chapter 4 - Methods and Analysis

This chapter outlines how the research was conducted. It describes the study area and time period followed by an explanation of the data sources and the steps used to acquire the data. The inclusion and exclusion criterion for the study are then provided. The steps taken for the analysis of the data are described, employing the framework of Bailey and Gatrell previously discussed to address the three research objectives focusing on data visualisation, exploration and modeling. Statistical analysis conducted using SAS® software were performed using version 9.2, developed in Cary, North Carolina.

Study Area and Study Period

This research focused on the province of Manitoba, Canada. During the study years the province was divided into 11 Regional Health Authorities (RHA), which were further divided into Health Districts (see Figure 10). Health Districts (n=55) were the chosen level of geography in rural Manitoba for the study. In this case, rural Manitoba refers to all areas of the province not including the Winnipeg Regional Health Authority (WRHA). The WRHA was analyzed using the Neighbourhood Clusters (n=25) (see Figure 11).

Health Districts (HD) and Neighbourhood Clusters (NC) were used as they were the smallest areas of analysis possible without experiencing the limitations of small cell numbers. Small cell numbers are a concern when working with geographically-based data as the risk of identifying individual people increases. The Health Information Privacy Committee (see page 53) stipulates that there not be a cell size (of data) smaller than six (records) (unless it is zero) at any time.

Figure 10 - Manitoba Regional Health Authorities and Health Districts

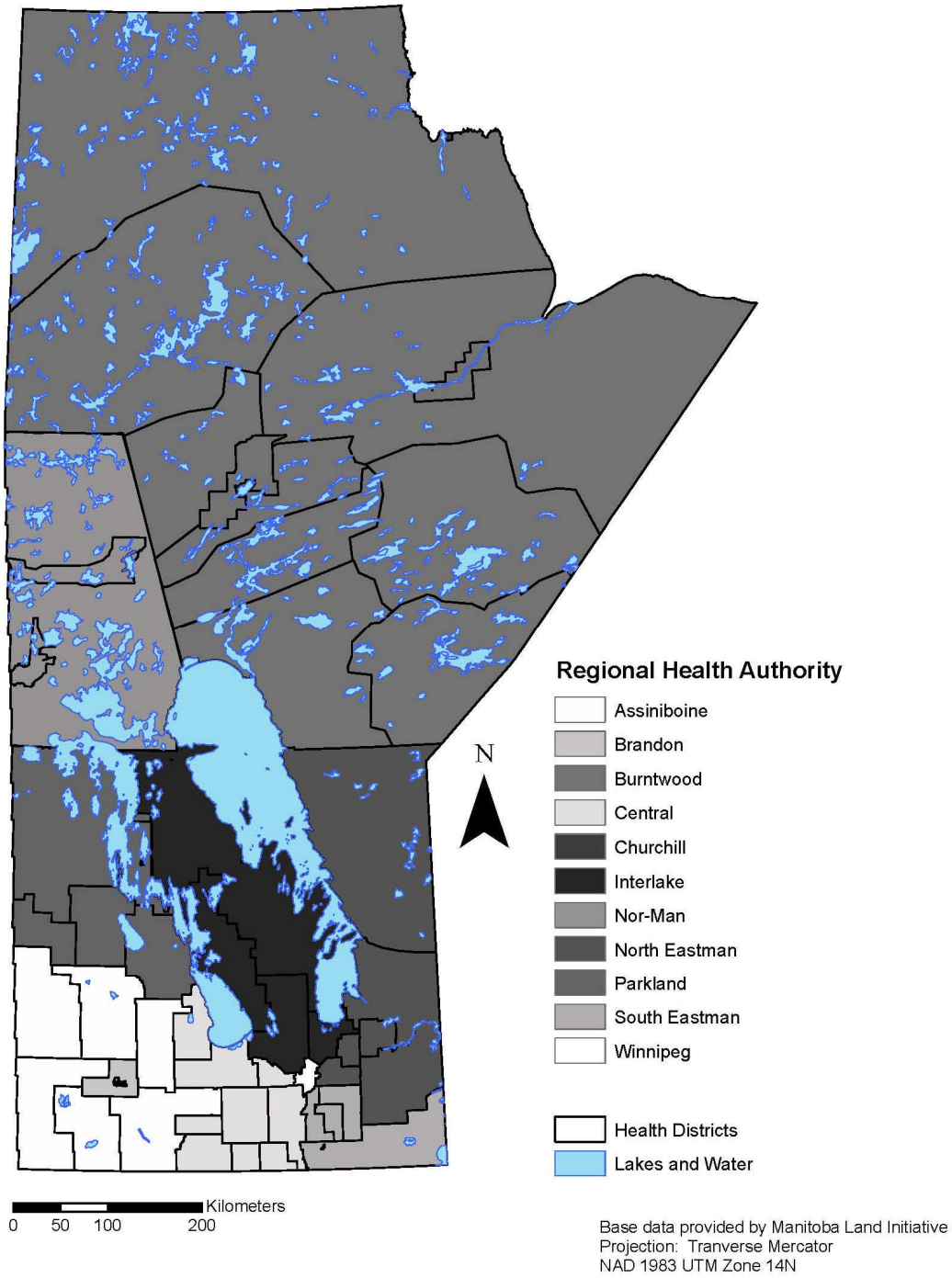
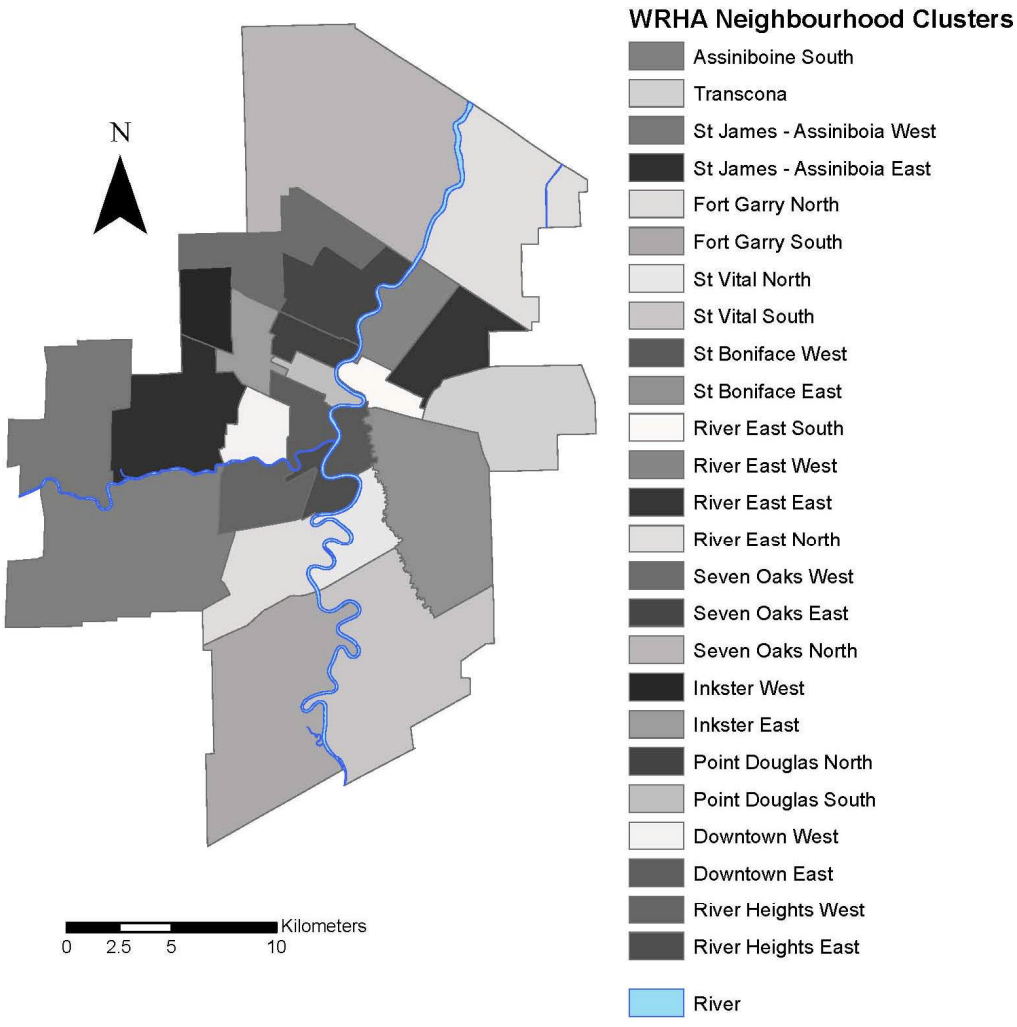


Figure 11 - WRHA Neighbourhood Clusters



Base data provided by Manitoba Land Initiative
Projection: Tranverse Mercator
NAD 1983 UTM Zone 14N

Data was compiled based on routinely collected administrative data for Manitoba for the five-year period from 2004-05 to 2008-09. Health data is compiled using a fiscal year calendar and thus each year of data commences on April 1 and ends on March 31. Case data is represented using the corresponding CDC week for the year in which it occurred to allow for comparison across study years (World Health Organization, 2012).

Data Sources

Data was accessed through the Manitoba Centre for Health Policy (MCHP), the repository for Manitoba Health data at the individual level. Use of the repository data requires a data agreement which is available in Appendix C. Access to this data required approval from the Health Information Privacy Committee (HIPC) (approval number 2010/2011-06, available in Appendix D), which serves to protect the interests of Manitobans with regards to their health information and how it is used. Permission from the Health Research Ethics Board (HREB) (approval number H2010:110, available in Appendix E) was also obtained in order to proceed with the research.

As identified by the existing literature (Crighton, Moineddin, Kanaroglou, & Upshur, 2007; Figaro & Belue, 2005; Irwin D. , et al., 2001; Schanzer, Langley, & Tam, 2008), data included in the thesis comprised of population data related to age and sex to first identify the at-risk population; co-morbidity data to take into account the differing susceptibilities of the population; and immunization data. This data was then aggregated to the Health District and Neighbourhood Cluster levels. The datasets used, how they were used, along with the specific variables are shown in Table 2.

Table 2 - Datasets to be used

Dataset Type	Name	Source	How they were used	Variables requested
Health	Hospital Abstracts	Manitoba Health	To show those hospitalized in which diagnosis of ILI was assigned	Data of admission/discharge Age Sex Scrambled PHIN Postal code of residence ACG with ADG co-morbidities
Health	Medical Services	Manitoba Health	To show all physician visits in which diagnosis of ILI was assigned	Date of visit Age Sex Scrambled PHIN Postal code of residence ACG with ADG co-morbidities
Health	Immunization	Manitoba Health	To show those immunized with seasonal influenza vaccine during study years	Date of immunization Age Sex Scrambled PHIN Postal code of residence
Registries	Insurance Registry	Manitoba Health	To provide denominator data for statistical purposes	Age Sex Postal code of residence
Database Support Files	Tariff and fee tables	Public Data	To assist with the interpretations and understanding of the physician's billing data	N/A
Database Support Files	Mapping/Electronic boundary files	Data Liberation Initiative	For mapping purposes where sufficient data is not available from the Manitoba Land Initiative	N/A

Data not found in the MCHP administrative database were also used, specifically information from the 2006 Canadian census. This database includes over 1,000 variables often used for research purposes. A selection of these variables was used to show income level, unemployment status, highest level of education attained, and number of people per dwelling. The census data is reported by Dissemination Areas (DAs), each containing between 400 and 700 people. These areas were aggregated to the Health Districts and to the Neighbourhood Clusters. The mapping data which served as the various boundaries for analysis were available through the Manitoba Land Initiative (MLI) website (Manitoba Land Initiative, 2009).

Study Population - Inclusion Criteria

The first element of the inclusion criteria was to identify ILI cases. Data requested from the MCHP was at the individual level. Influenza cases were identified by the ICD – 09 - CM code (487) for those who sought care from a physician, and by the ICD – 10 – CA code (J10) for those who were treated in a hospital. Although influenza is a laboratory reportable disease in Manitoba (Manitoba Communicable Disease Control Unit, 2006), the number of confirmed clinical cases is low and the unconfirmed usage of the code is high, as previously discussed.

As a means of enhancing data quantity, in addition to those cases coded as influenza, administrative data documenting symptoms consistent with case definitions of influenza such as fever, cough and dyspnea (Froehling, Elkin, Wahner-Roedler, Bauer, & Temesgen, 2008; Monto, Gravenstein, Elliott M, & Schweinle, 2000; Manitoba Communicable Disease Control Unit, 2006) were also included as cases. These were represented by the broader definition of influenza, influenza-like illnesses (ILI).

ILI codes, using ICD – 09 - CM, included 460 – 466 (acute respiratory conditions), and 480 – 486 (pneumonia and influenza); using ICD – 10 – CA, these codes were J00 – J06 (acute uper respiratory infections), and J09 – J18 (influenza and pneumonia). Cases identified through the Hospital Discharge Abstract were included in the study population if the ILI diagnosis was the primary reason for admittance to hospital, and if the date of admittance occurred after the first date of the study period. The specific diagnoses included in the study are in Tables 3 and 4.

Table 3 - ICD - 09 - CM Codes to be included in ILI definition

Category	ICD – 09 – CM Code	Diagnosis
Acute Respiratory Conditions	460	Acute Nasopharyngitis (common cold)
	461	Acute Sinusitis
	462	Acute Pharyngitis
	463	Acute Tonsillitis
	464	Acute Laryngitis
	465	Acute Upper Respiratory Infections of Multiple or Unspecified Site
	466	Acute Bronchitis and Bronchiolitis
Pneumonia and Influenza	480	Viral Pneumonia
	481	Pneumococcal Pneumonia
	482	Other Bacterial Pneumonia
	483	Pneumonia due to Other Specified Organism
	484	Pneumonia in Infectious Diseases Classified Elsewhere
	485	Bronchopneumonia
	486	Pneumonia, Organism Unspecified
	487	Influenza

Table 4 - ICD - 10 - CA Codes to be included in ILI definition

Category	ICD – 10 – CA Code	Diagnosis
Acute Upper Respiratory Infections	J00	Acute Nasopharyngitis (common cold)
	J01	Acute Sinusitis
	J02	Acute Pharyngitis
	J03	Acute Tonsillitis
	J04	Acute Laryngitis and Tracheitis
	J05	Acute Obstructive Laryngitis (croup) and Epiglottitis
	J06	Acute Upper Respiratory Infections of Multiple and Unspecified Sites
Influenza and Pneumonia	J09	Influenza Due to Identified Avian Influenza Virus
	J10	Influenza Due to Identified Influenza Virus
	J11	Influenza, Virus not Identified
	J12	Viral Pneumonia, not elsewhere classified
	J13	Pneumonia Due to Streptococcus Pneumoniae
	J14	Pneumonia Due to Haemophilus Influenzae
	J15	Bacterial Pneumonia, not elsewhere classified
	J16	Pneumonia Due to Other Infectious Organisms, not elsewhere classified
	J17	Pneumonia in Disease classified elsewhere
	J18	Pneumonia, unspecified

Although the chosen ICD codes are supported by the literature (Yiannakoulias, Russell, Svenson, & Schoplocher, 2004; Menec, Black, MacWilliam, & Aoki, 2003; Irwin D. , et al., 2001), they are more commonly used when focusing on clincal diagnosis, as with the physician visits data. As hospitalization usually leads to additional tests, some of the more specific ILI codes that are acceptable when assigned clinically,

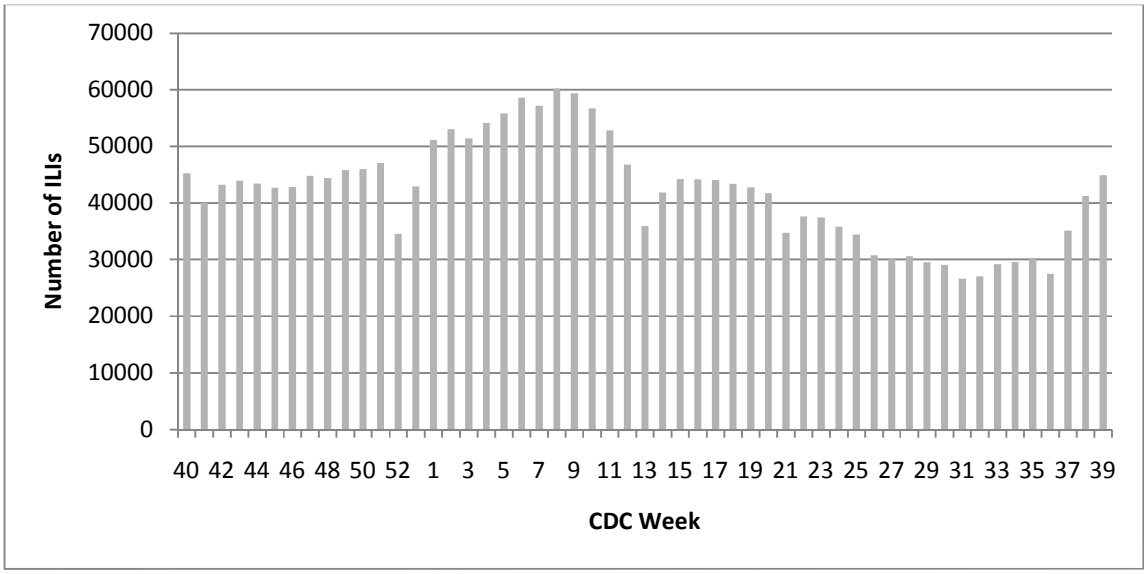
are not necessarily appropriate when the data source is the Hospital Discharge Abstract . These include ICD-10 codes J13, J14 and J15 and were included in this study as occurrences in the data were minimal, as seen in Table 5. The percentage that each contributed to the total population was calculated, including those for the corresponding ICC-9 codes (462 – 464) used in the physician data for comparison purposes. This comparison informed the decision to retain these cases in the study populations.

Table 5 – Percent of Study Population by Specific ICD Code

Category	ICD Code	Percentage of Study Population
ICD – 9 – CM Code	462	13.4%
Sinusitis/ Pharyngitis/	463	6.2%
Tonsillitis	464	2.9%
ICD – 10 – CA Code	J13	0.95%
Pneumonia Due to	J14	3.45%.
Streptococcus,	J15	0%
Haemophilus, Bacteria		

The second element of the inclusion criteria , and also the first objective, was to determine what CDC weeks would be included in the flu season for this thesis. Six epidemiologic curves were created, one for each year (2004/2005 to 2008/2009) as well as one combined for all years. The curve for the combined years is shown in Figure 12; those for the individual years are in Appendix A. As the typical flu season is identified as occurring from November to April (Health Canada, 2009), an epidemiologic curve for ILI is often presented starting with CDC week 40, which typically represents the first week in October when surveillance starts (Martinez-Beneito, Botella-Rocamora, & Zurriaga, 2010).

Figure 12 - Total Number of ILI in Manitoba per CDC Week from 2004/2005 to 2008/2009



Based on the data presented in Figure 12, the flu season for the purpose of this thesis was identified as including CDC weeks 39 to 17 (a total of 31 weeks), consistent with the typical November to April flu season experienced in the northern hemisphere. Although five years of data were used in the study, the timing of the flu surveillance (October to May) and the use of fiscal years (April 1 to March 31) to obtain administrative data meant that only four years of complete flu seasons were used, with a partial year from the 2008-2009 fiscal year of data (see Table 6).

Table 6 – CDC weeks used from each Fiscal Year of Administrative Data

Fiscal Year	CDC Weeks Available and Used	Contribution to Study Period
2004/2005	39-17	Complete season
2005/2006	39-17	Complete season
2006/2007	39-17	Complete season
2007/2008	39-17	Complete season
2008/2009	39-12	Partial season

Study Population - Exclusion Criteria

Any case that did not occur during the influenza season as described above was excluded. A case identified as ILI was excluded if it was an obvious duplicate or if not all the relevant data was available, such as a birth date or postal code, or if the postal code was for another province.

Some patients, as determined by scrambled Personal Health Information Number (PHIN), appeared multiple times in a seven-day period, given season or with more than one physician visit or hospitalization coded as an ILI. If a patient had both a physician visit and a hospitalization visit within a seven-day period, only the hospitalization visit was included as it was deemed to be a more definitive diagnosis. If a patient had multiple visits within a seven-day period, only the first visit was counted.

Although the case definition of ILI includes repeat cases, and many studies count them all (Irwin, Weatherby, Huang, Rosenberg, Cook, & Walker, 2001; Menec, Black, MacWilliam, & Aoki, 2003; Yiannakoulias, Russell, Svenson, & Schoplocher, 2004), the decision not to include all cases coded as ILI in a seven-day period was made to reduce the bias that their inclusion may have on the results. However, as multiple cases within a season, outside the seven-day period, were included the bias was not completey eliminated.

Analysis

As the analysis had a spatial focus, a framework specific to spatial analysis was employed in conjunction with the population health and ecological frameworks, as discussed in Chapter 2. The spatial framework proposed by Bailey and Gatrell (1995;

Gatrell, 2000) explores the data in three steps by employing methods of visualisation, exploration and modeling.

These three methods were used as tools to address the objectives. The first objective focused on descriptive epidemiology and represented the methods of data visualisation. The second objective attempted to identify any clusters in the data and was representative of the methods of data exploration. The third objective served to establish which of the chosen predictor variables were most important in determining an ILI and represented the methods of data modeling.

The data was analyzed respecting the principles of population health-based practices and the assumptions of an ecological framework. As previously described, this latter approach proposes that influences outside of the realm of health care are important in the understanding of the health of the study population. These factors were represented by the Canadian census variables concerning different geographies, income, unemployment status, co-morbidity score, population density per household and education level.

Preparation of the Data

To ensure that analysis could be performed on a combined dataset of both the hospital and physician data, the ICD – 10 - CA codes in the hospital cases were recoded to ICD – 09 – CM codes to coincide with the physician data. The Manitoba Centre for Health Policy (MCHP) has created SAS® code in order to complete the conversion and which was used in this study. The converted cases were then graded to ensure their accuracy (Manitoba Centre for Health Policy, 2012). This process is commonly used in MCHP studies and deliverables (Fransoo R. , et al., 2011; Fransoo R. , Martens, Burland,

Prior, & Burchill, 2009; Martens, et al., 2010). The ICD – 10 – CA codes and their ICD – 9 – CM code equivalents are shown in Table 7.

Table 7 – ICD – 10 – CA Codes Showing ICD – 9 – CM Code Equivalent

Category	ICD – 10 – CA Code	ICD – 9 – CM Code
Acute Upper Respiratory Infections	J00	460
	J01	461
	J02	462
	J03	463
	J04	464
	J05	464
	J06	465
Influenza and Pneumonia	J09	487
	J10	487
	J11	487
	J12	480
	J13	481
	J14	482
	J15	482
	J16	483
	J17	484
	J18	485

The cases were then sorted by patient (based on scrambled personal health information number - PHIN) and date so those with multiple entries in a seven-day period and season could be identified. Although, a true flu infection is likely to occur only once per season (Public Health Agency of Canada, 2010) this is not the case with ILI. Tests were therefore undertaken to identify the frequency of multiple users within a given flu season. As the definition of ILI does not exclude the issue of multiple cases in a season and the literature that addresses this is scarce (Tilston, Eames, Paolotti, Ealden, & Edmunds, 2010; Irwin D. , et al., 2001), the decision to use all cases was made for the purpose of this thesis. It is acknowledged that the inclusion of multiple cases in a season

is a limitation of the study when making generalizations specific to the flu, which is likely to occur only once per season. Repeat cases could potentially highlight characteristics that are not necessarily as a result of having ILI or flu, but that may be representative of chronic over-users of the health care system.

As the data did not have a variable placing them in a specific Health District or Neighbourhood Cluster, the postal code field was used to place each case in its appropriate geographical grouping. The new geographic variable was created using SAS® code established by the MCHP and commonly used in other studies (Fransoo R. , et al., 2011; Martens, et al., 2010; Martens, Frohlic, Carriere, Derksen, & Brownwell, 2002).

Objective 1 – Data Visualisation

It is usual for the first step of spatial analysis to focus on basic principles of descriptive epidemiology (Rytkonen, 2004; Gomez-Rubio, 2010; Bailey & Gatrell, 1995; Gatrell, 2000). In keeping with this idea, the first objective of this study sought to explore and better understand the distribution and frequency of ILI cases, both spatially and temporally (Green, Elliott, Beaudoin, & Bernstein, 2006; Public Health Agency of Canada, 2009). Examining the ILI data spatially, thus appreciating the importance of space and place, is a fundamental principle of the ecological framework (Arya, et al., 2009).

Temporal distribution.

The first analysis was undertaken to observe the temporal distribution of the ILI cases in Manitoba. The data was first separated by fiscal year and the dates of recorded illness placed into the corresponding CDC week; the standard method for reporting

epidemiological data (World Health Organization, 2012). An epidemiological curve showing the 52 weeks of cases was then created for each year. This analysis served to show what, if any, variation existed across the selected years in terms of when peak cases of ILI occurred.

A combined epidemiological curve was then created based on all the cases in each of the CDC weeks for the five study years. This analysis was used to determine which weeks should be classified as making up the flu season. Typically this occurs from approximately October to May (Manitoba Communicable Disease Control Unit, 2006; Centers for Disease Control and Prevention, 2010) in the northern hemisphere. The combined dataset including the five study years was used for all subsequent analysis.

Spatial distribution.

Maps were created showing the age standardized rate (per 1,000 population) of cases in each Health District and Neighbourhood Cluster. Rates were divided into quintiles based on Natural Jenks. Natural Jenks create a user-defined number of categories based on natural breaks that occur in the dataset (Harlow, Pfaff, & Minami, 2004).

Rather than creating a map for each CDC week, the season was divided into four groups with four standardized maps being created. Mapping these rates by CDC week shows the spread of illness across the province and over time for the combined study period. The denominator for the standardized rates of the first three season groups included the total at-risk populations for the five fiscal years as per the requested registry data. The denominator for the standardized rate of the fourth season group did not include the complete 2008-09 population as only a portion of the data was used.

Standardization is a tool commonly used in epidemiology as it allows for the comparison of populations with varying demographic characteristics (Green, Elliott, Beaudoin, & Bernstein, 2006; Crighton, Elliott, Moineddin, Kanaroglou, & Upshur, 2007). A rate is first calculated based on the observed number of cases and the number of people at risk of illness (Last, 2001). This rate is then standardized, either directly or indirectly, using one common population. The 2006 Manitoba population was used to directly standardize this dataset. The direct method of standardization is appropriate in this study as the rate of cases is high and the population counts great (Last, 2001). The 2006 Manitoba population not only serves as the middle year of the study but also represents a census year. Due to small cell numbers this analysis was not completed for each individual year of the study.

Maps were also created showing the age standardized rates using a consistent equal interval scale (as opposed to using Natural Jenks) for each season group to make it easier to compare between season groups. In order to see the total progression of the ILI throughout the season, a set of maps, using an equal interval scale, was also created to show the cumulative age standardized rates of cases. Finally, a map showing the age standardized rates for the combined years and the entire season was created to show the overall burden of illness based on ILI diagnosis.

In addition to the epidemiological curves and maps produced, a table summarizing the data was also created. This table shows the number of cases in the study population, along with counts by age category, sex, Health District and Neighbourhood Cluster.

Objective 2 – Data Exploration

As a continuation from the data visualisation, this objective sought to confirm whether any observed clusters of ILI cases that were previously mapped were random or representative of true clusters. This analysis was completed using the combined season data from 2004-05 to 2008-09. For this analysis, indirectly standardized rates were calculated for each cluster, using the maximum population allowable (50%) for cluster identification.

SaTScan ® software was used to calculate the Spatial Scan Statistic and used 999 Monte Carlo simulations, and was set to detect age-adjusted clusters. This was based on previously used Monte Carlo statistical methods to determine if they were representative of true clusters, not those solely occurring by chance (Sonesson, 2007). Relative risk rates of the statistically significant clusters were also derived. Maps depicting the statistically significant clusters, whether high or low, were then created using ESRI® mapping software.

Objective 3 – Data Modeling

The third goal of this research was to identify whether there was an association of the personal variables and/or the ecological variables with the development of ILI, and if so, which variables were most significant. Categorical Poisson Regression was first employed for this analysis as it overcomes concerns of spatial auto-correlation, as previously discussed, and allows for the inclusion of independent and ecological variables. These factors have resulted in the use of Categorical Poisson Regression in other similar studies (Green, Elliott, Beaudoin, & Bernstein, 2006; Heaman, Green, Newburn-Cook, Elliott, & Helewa, 2007).

The Categorical Poisson Regression was run using the Proc Genmod command in SAS®. The results of the analysis showed the data was over-dispersed, as the Value/Degrees of Freedom was greater than one. This meant that Negative Binomial Regression would be more appropriate for this analysis. This regression was also run using the Proc Genmod command in SAS®.

The variables chosen to be modeled were reflective of the broader determinants of health that were highlighted in the literature, including socio-economic status, household density, unemployment status, education level and geographic placement (urban versus rural versus remote). These determinants of health were chosen as they represent factors commonly associated with communicable diseases, such as ILI (Keating & Hertzman, 1999; Marmot & Wilkinson, 1999; Martens, et al., 2010; Fernandez, MacKinnon, & Silver, 2010); these were measured using the Canada census data at the Health District and Neighbourhood Cluster levels. The variables were modeled for the Health Districts and Neighbourhood Clusters separately, to highlight any differences that may exist in urban verses rural setting; they were also combined as it is understood that communicable diseases do not respect political boundaries.

Study Variables.

There were two kinds of variables used for this analysis. The first was the personal characteristics unique to each case in the study population. The second was the ecological variables, represented by factors that may contribute to the diagnosis of an ILI that can be measured at the population (or geographic) level.

First, a simple regression analysis was run in which each variable was modeled individually controlling for age and sex. This method was used as the objective was to

determine which characteristics were significant factors in determining ILI diagnosis (how each specific variable affects the outcome), not which combination of factors best predict the outcome. This method ensures that an interaction of variables does not occur, causing variables to be deemed insignificant or resulting in issues of confounding variables. Using the simple regression method, each of the variables was categorized and tested for significance as a predictor of developing ILI (see Table 8). This analysis took place using the Proc Genmod command in SAS®. Rate ratios for each of the categorical predictor variables were derived.

As it is understood that the determinants of health are interconnected, it was also justifiable to conduct a multiple regression analysis. This analysis assumes that multiple variables affect the outcome and should be modeled together. Not all the variables were used in this analysis; only those variables identified by the literature as greater predictors were used (Figaro & Belue, 2005; Monto, Gravenstein, Elliott M, & Schweinle, 2000). Variables used for the multiple regression analysis are also shown in Table 8.

The multiple regression model was run twice; once with the vaccine variable and once without it to ensure that its inclusion did not render the other variables insignificant. Interaction plots were created to ensure that there were no issues of covariance amongst the selected variables. This analysis was also conducted using the Proc Genmod command in SAS®. Rate ratios for each of the categorical predictor variables were also derived.

Table 8 - Study variables included in analysis

Type	Variable	Source	Categories	How they were be categorized
Individual Variables	Date of illness	Administrative data	Early, Early-Mid, Mid or Late flu season	Based on peaks of CDC weeks during the flu season
	Age at diagnosis**	Administrative data	0 – 2, 2 – 65 and 65 plus	Based on the established at risk age groups
	Sex**	Administrative data	Male or Female	N/A
Ecological Variables	Vaccinated or not**	Administrative data	Percent of the population immunized then categorized to Low, Moderate and High	Based on natural jenks algorithm to find natural cut-offs of vaccination rates
	Co-morbidity score+**	Administrative data	Low, Moderate and Severe	Based on natural jenks algorithm to find natural cut-offs for overall population
	Postal code	Administrative data	Urban, Rural or Remote	Based on avg. population over study years where Urban =10,000+, Rural =1,000 – 10,000, Remote≤1,000
	Avg. neighbourhood income quintile (based on family income)**	MCHP census data	Quintiles 1 – 5, where 5 represents the highest avg. neighbourhood income	Based on dissemination areas then cross-walked to the Health Districts or Neighbourhood Clusters and weighted for different population sizes
	Avg. number of people per dwelling**	MCHP census data	Low, Moderate or High	Based on natural jenks algorithm to find natural division for dissemination areas then cross-walked to the Health Districts or Neighbourhood Clusters
	High School Completion Rate	MCHP census data	Low, Moderate or High	Based on percentage of the population aged 25 – 64 who have completed High School in the dissemination areas then cross-walked to the Health Districts or Neighbourhood Clusters and then categorized using natural jenks algorithm to find natural cut-offs
	University Certificate, Diploma or Degree	MCHP census data	Low, Moderate or High	Based on percentage of the population aged 25 – 64 who have achieved a University Certificate, Diploma or Degree in the dissemination areas then cross-walked to the Health Districts or Neighbourhood Clusters and then categorized using natural jenks algorithm to find natural cut-offs
	Unemployment rate	MCHP census data	Percentage of the employable population that is unemployed	Based on the average rate for the dissemination areas then cross-walked to the Health Districts or Neighbourhood Clusters

[+] Aggregated Diagnosis Groups (ADGs) (John Hopkins) were developed at John Hopkins University. There are 32 ADGs, each of which is a grouping of ICD-9 codes that are similar in terms of severity and likelihood of persistence of the health condition over time. They are often used as morbidity marker.

**Denotes variables that were used for the multiple regression analysis.

The methods and analysis described in this chapter were used to address the three objectives of this research. The specific statistical tests and methods were chosen based on existing literature and common practices previously identified in Chapter 3: Background and Literature Review. It was determined that these methods would be best used in this analysis and would yield results that could further inform the existing literature in the area of spatial epidemiology and ILI.

Chapter 5 - Results

The final dataset included for analysis consisted of 2,189,537 cases of influenza-like illnesses, as determined by physician and hospital visits during the fiscal years of 2004-05 to 2008-09. A high-level summary of this population is available in Table 9. This dataset was used for the analyses to address the first objective.

Table 9 - Initial Case Data for Total Population

Geography	Diagnosis Location	Male	Female	Totals
Health Districts (Rural Manitoba)	Physician Visits	360954	479116	840070
	Hospitalization	5004	4753	9757
Neighbourhood Clusters (WRHA)	Physician Visits	560377	774010	1334387
	Hospitalization	2587	2736	5323
Totals		928922	1260615	2189537
Geography		00-02	02-65	65+
Health Districts (Rural Manitoba)	Totals by Age	92082	660855	96890
Neighbourhood Clusters (WRHA)	Totals by Age	91446	1082274	165990
Totals		274974	285403	428870

The crude breakdown of the cases is seen in Table 9. As expected, there are many more cases identified from physician visits than hospitalizations, with higher numbers of women being reported than men. The age breakdown of cases is also as anticipated.

It was found that 297,395 of those included in the initial study population sought services for ILI more than once in a seven-day period, and 1,042,905 sought services more than once in the same fiscal year. These numbers represents 61.21% of the total

cases. Most of these repeat cases were a result of multiple visits in a fiscal year (77.81%) although some did occur more than once in a seven-day period (22.19%). Cases which occurred within a seven-day period were subsequently excluded.

Objective 1 – Data Visualisation

The initial analysis of the epidemiological curve of cases resulted in the determination that the influenza season for the purposes of this study would include CDC weeks 39 – 17. A summary of the cases occurring during CDC weeks 39 to 17 for the 2004-05 to 2007-08 seasons and those occurring during CDC weeks 39 to 12 for the 2008-09 season appear in Table 10. These cases, either in their individual seasons or combined for all seasons, are the data used for the remainder of the analysis. Note that the data represents the crude numbers and the percentage of the total study population for each category.

Table 10 – Case Data for Study Population During Influenza Season 2004/2005 – 2008/20009 (CDC weeks 39-17)

Geography	**Male**	**Female**	**Totals**	
Health Districts (Rural Manitoba)	251982 (16.89%)	327914 (21.99%)	579896 (38.88%)	**Totals by Age**
Neighbourhood Clusters (WRHA)	385762 (25.87%)	525752 (35.25%)	911514 (61.12%)	**Totals by Age**
Totals	637744 (42.76%)	853666 (57.24%)	**1491410**	
Geography		**00-02**	**02-65**	**65+**
Health Districts (Rural Manitoba)	**Totals by Age**	63377 (4.25%)	451823 (30.29%)	64696 (4.34%)
Neighbourhood Clusters (WRHA)	**Totals by Age**	66717 (4.47%)	734875 (49.27%)	109922 (7.37%)
Totals	130094 (8.72%)	1186698 (79.56%)	174618 (11.71%)	

Reducing the population size to only include diagnoses that occurred during CDC weeks 39 to 17 resulted in a total number of 1,491,410 cases of ILI in the province of Manitoba (Table 10). This study population showed that 199,872 of those sought services more than once in a seven-day period, and 830,928 sought services more than once in the same fiscal year, representing 69.12% of the total cases. Most of these repeat cases were a result of multiple visits in a fiscal year (80.61%). These numbers indicate that nearly 70% of documented cases of ILI in Manitoba during the study period were repeat cases and therefore not representative of true influenza cases, however they all met the case definition of an ILI. Multiple cases within a year were included in the study population, however those occurring more than once in a seven day period were excluded. However, the inclusion of repeat cases within a season should be kept in mind when interpreting the following results.

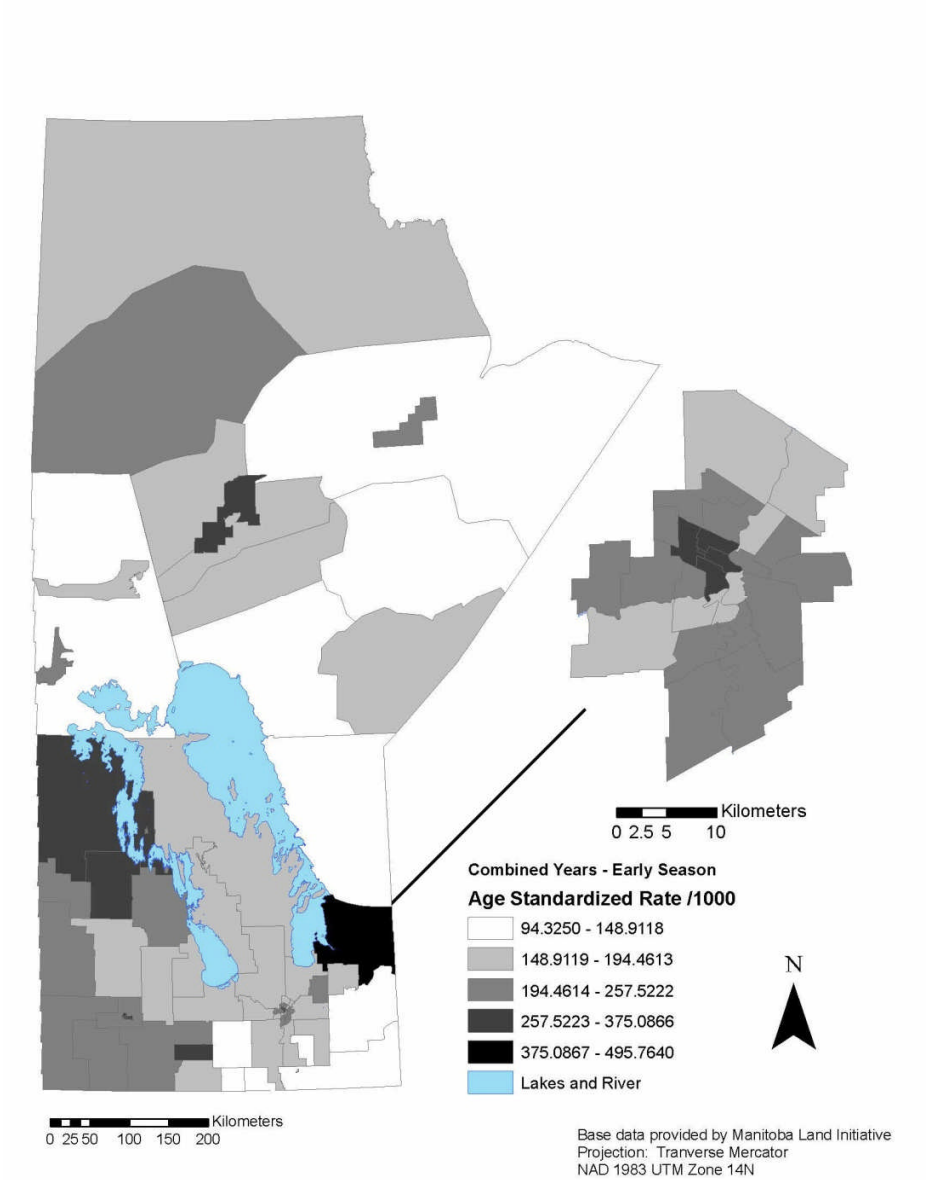
The first specific objective was to answer the question: *How does the incidence of ILI vary spatially and temporally in Manitoba?* It was hypothesized that a higher incidence would be observed in areas with lower socio-economic status, with the highest incidence occurring in the mid-season. This research question was answered by visualising the data using tools of spatial epidemiology.

The temporal distribution of the ILI cases included in the study population in Manitoba, as seen in Figure 12 (see page 50), is consistent with the typical distribution of national cases identified by FluWatch. The CDC weeks were divided into four groups (Early, Early-Mid, Mid and Late) and resulted in four maps for the combined seasons for the Health Districts and Neighbourhood Clusters. The maps appear as Figures 13 to 16, and show the temporal and spatial distribution of ILI cases at each seasonal interval. The

scales for each data map are derived from the cases being shown in each map, with the categories being created by natural breaks in the numbers (using Jenks Natural Breaks).

The Early Season map (Figure 13) shows there is variability of the age standardized case rates among the Health Districts with no obvious patterns. One Health District, Blue Water, is classified as having rates higher (approximately 5 times) than the other Health Districts. The Neighbourhood Clusters of the WRHA have more consistent rates with less variation, and at this point no apparent outliers of high or low cases.

Figure 13 - Temporal and Spatial Variation of Combined Years for the Early Season



The Early-Mid Season results are displayed in Figure 14. An increase in rates throughout the province is evident as the flu season progresses. There are more areas in the top two quintiles, including the entire WRHA.

Figure 14 - Temporal and Spatial Variation of Combined Years for the Early-Mid Season

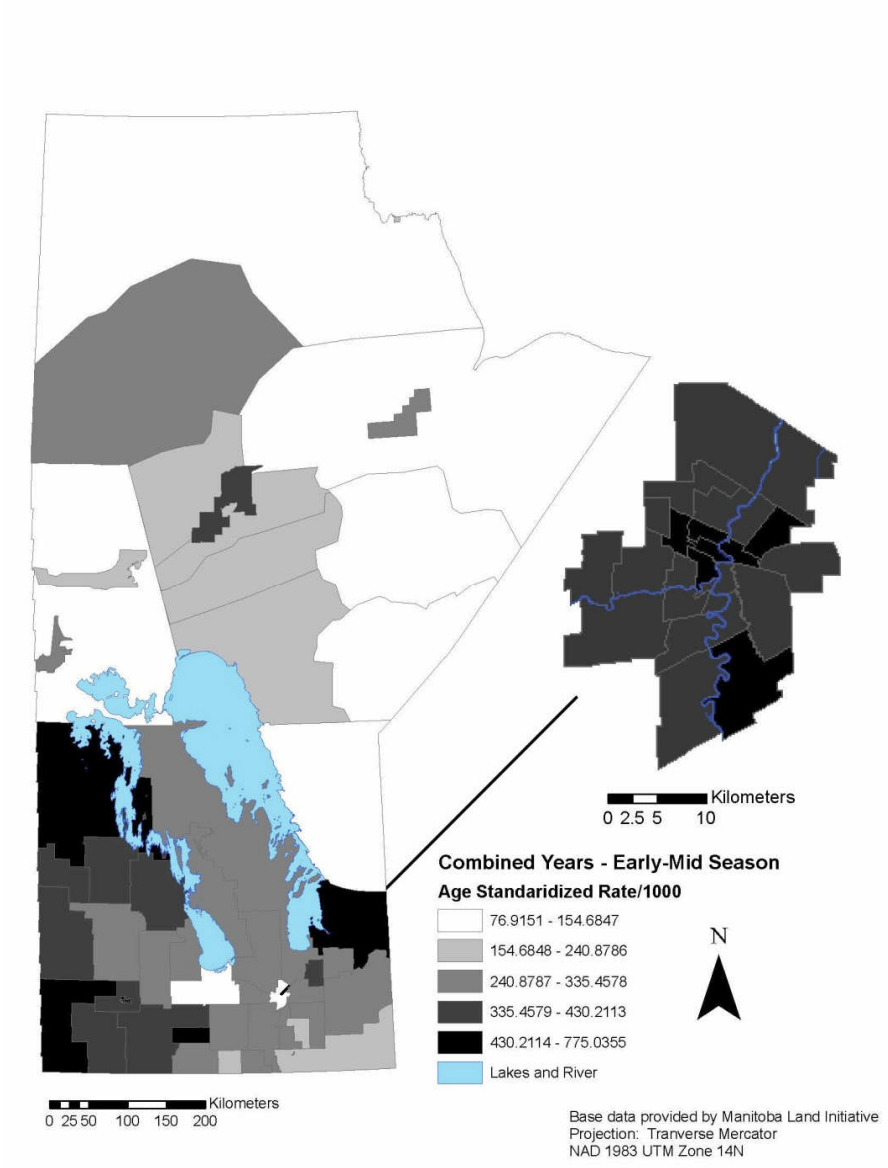
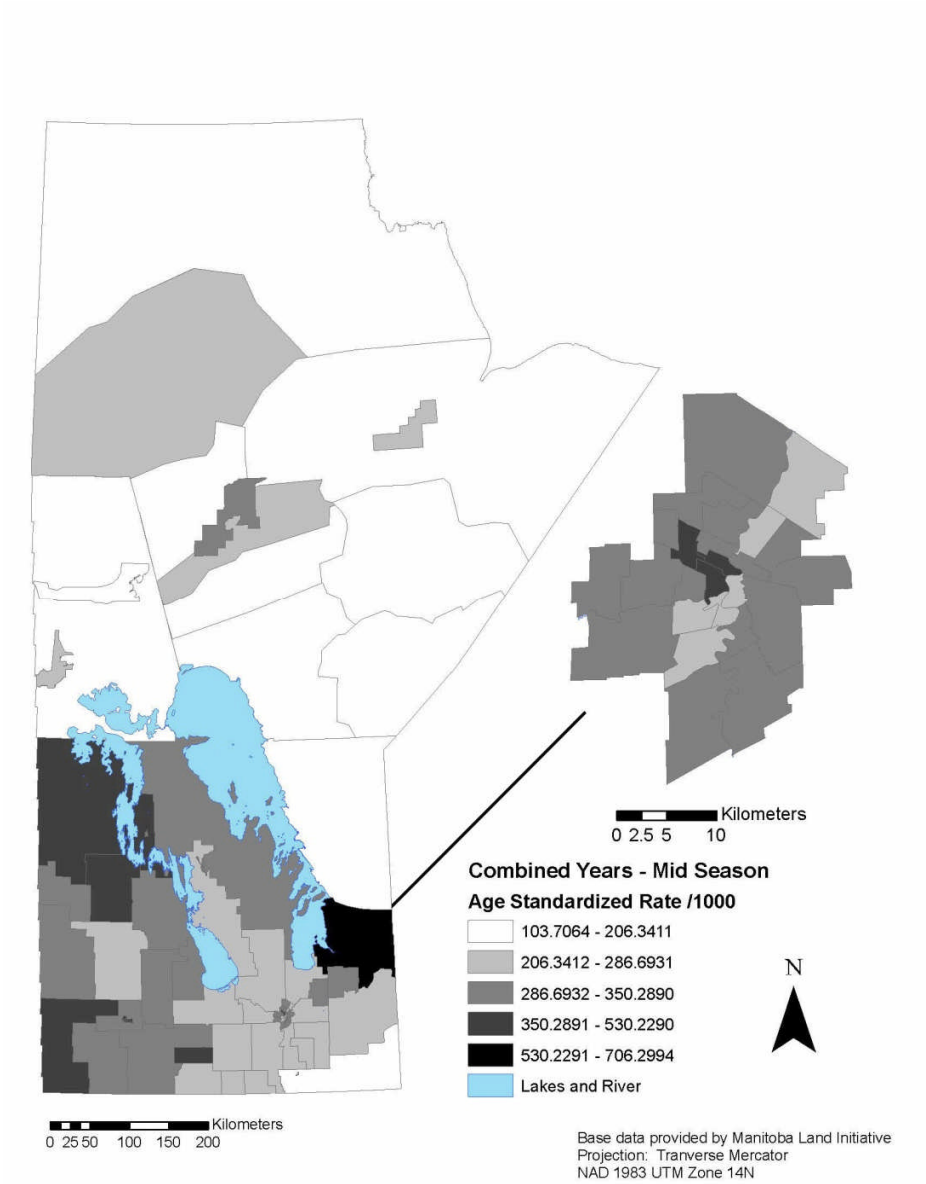


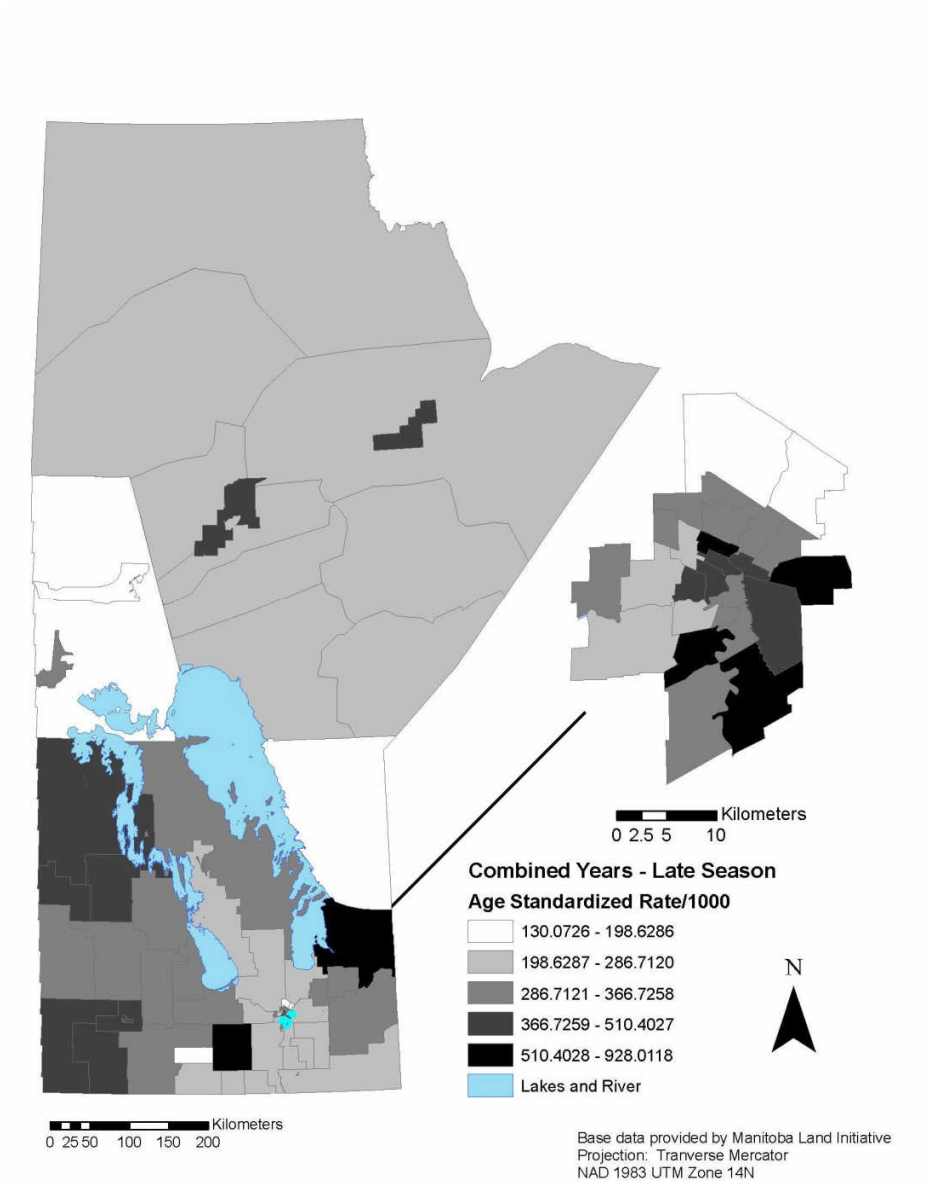
Figure 15 represents CDC weeks 3 – 10, or the Mid Season. Rates appear stable, with the Blue Water Health District (northeast of Winnipeg) continuing to have the highest adjusted rate in the province. Rates are lowest in the north and southeast corner.

Figure 15 - Temporal and Spatial Variation of Combined Years for the Mid Season



The Late Season map (Figure 16) shows far greater variation than the other seasonal maps. Many areas have rates in the highest quintile, with overall rates having increased. Many Neighbourhood Clusters in the WRHA show higher rates.

Figure 16 - Temporal and Spatial Variation of Combined Years for the Late Season



The temporal and spatial variations for the Health Districts and Neighbourhood Clusters are also shown in Figures 17 and 18 respectively, using the same equal interval scale. Displaying the data this way helps to show that rates increase proportionally as the season progresses in the various geographies.

Figures 17 and 18 show that ILI do not occur in all areas of the province at the same time. Variation in the pattern of evolution of the disease can be seen by comparing the Health Districts and Neighbourhood Clusters in the WRHA. The Health Districts show less of an obvious spread than the WRHA. The Blue Water Health District in North Eastman stands out as having a consistently high rate of ILI across all seasons. The subsequent analyses and results will further explain this observation.

Figure 17 - Temporal and Spatial Variation of Combined Years of the Health Districts

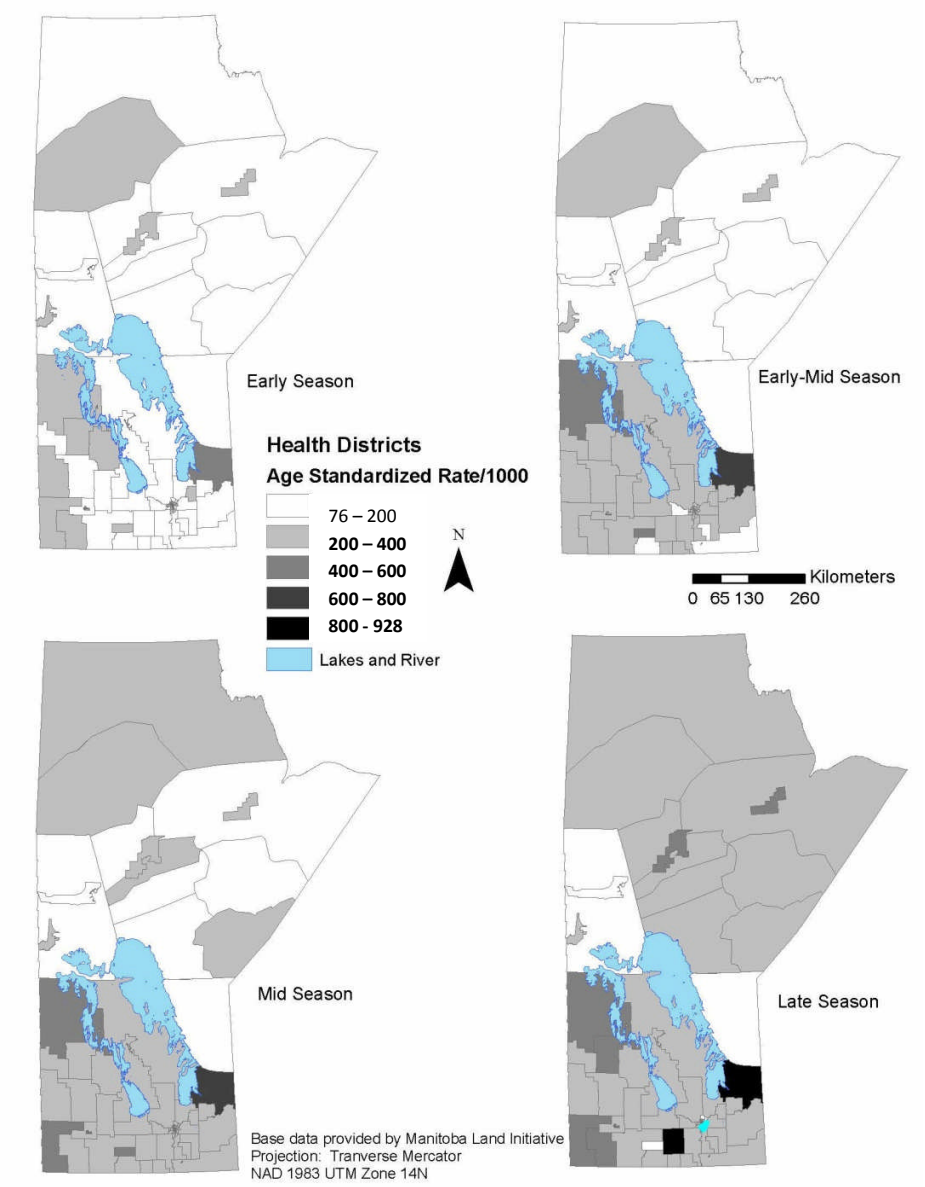
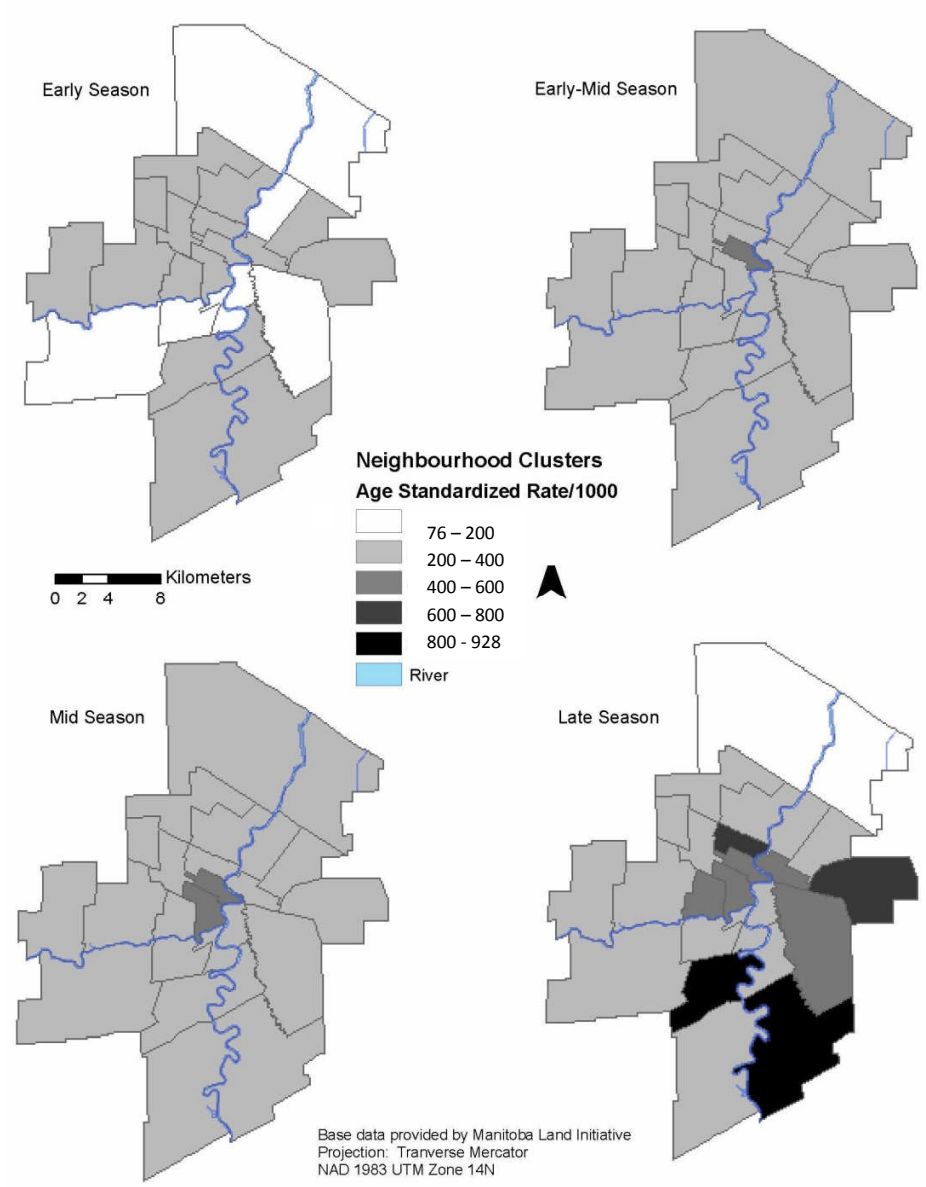


Figure 18 - Temporal and Spatial Variation of Combined Years of the Neighbourhood Clusters



While the previous figures showed each of the season groups individually, Figures 19 and 20 show the cumulative rates for the Health Districts and Neighbourhood Clusters respectively. These figures again show that ILI diagnoses exist throughout the province, but not at the same time or with the same frequency.

Figure 19 - Cumulative ILI Rates for Combined Years by Health District

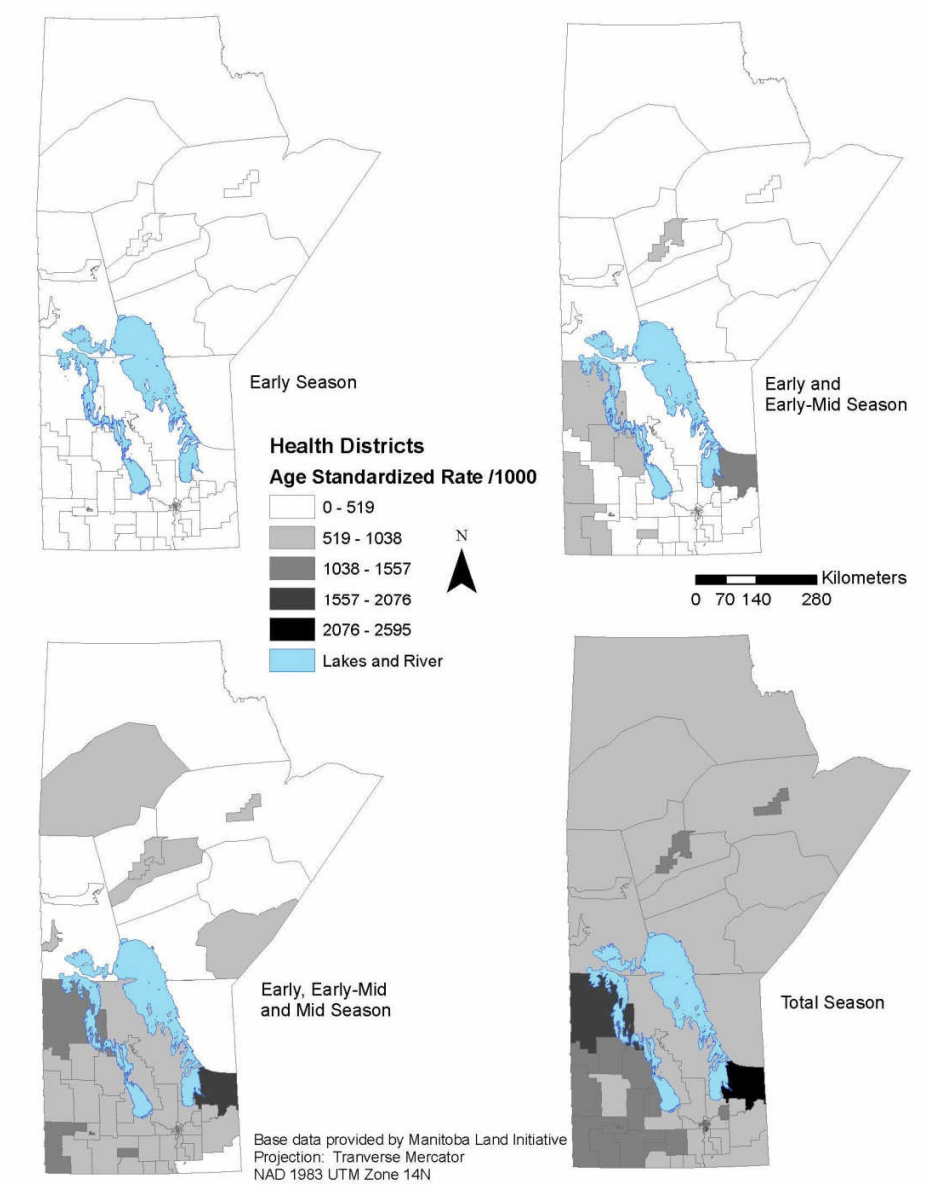
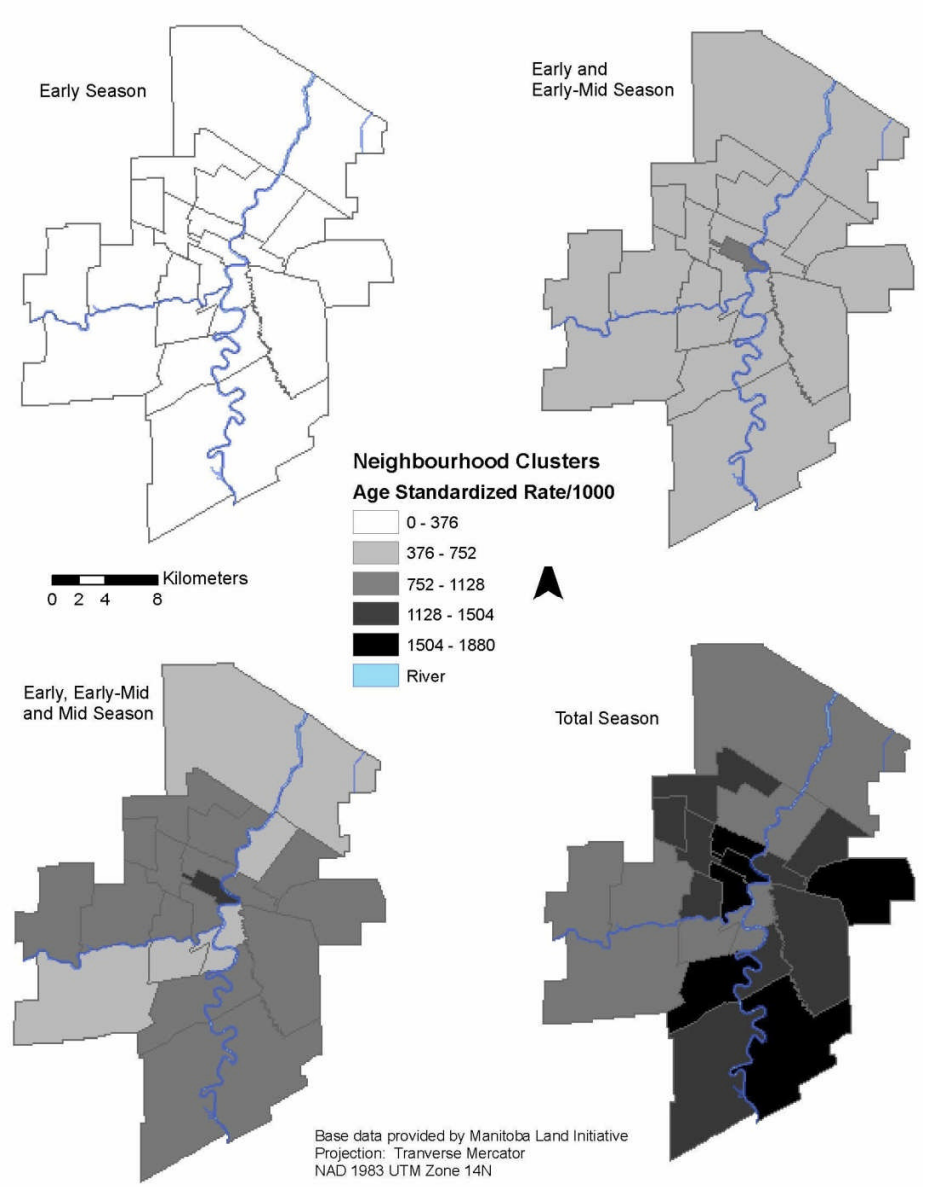
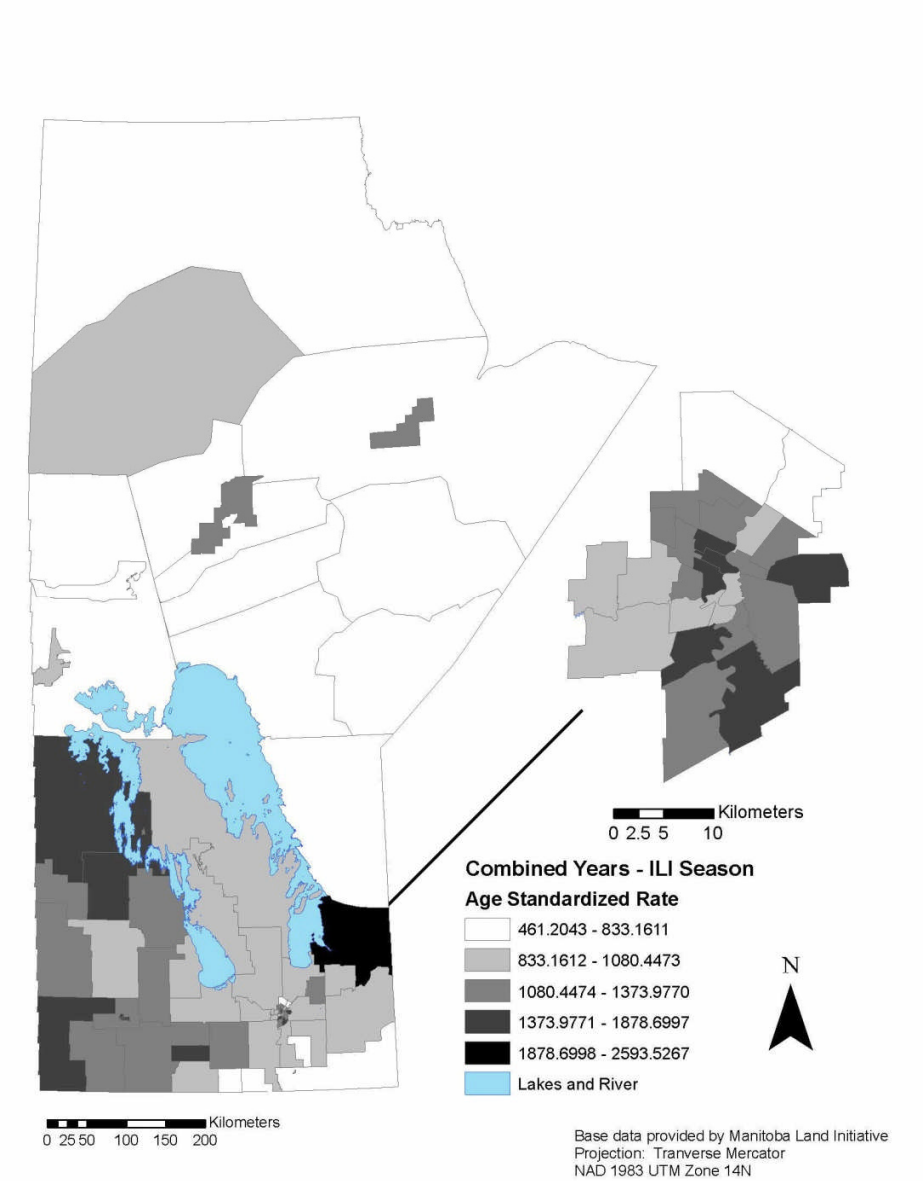


Figure 20 - Cumulative ILI Rates for Combined Years by Neighbourhood Cluster



The overall spatial variation throughout Manitoba is shown in Figure 21. The age standardized rates use Jenks Natural Breaks for classification. These categories show many areas of the province having comparatively low overall rates, and only one Health District - Blue Water - is in the highest income rate quintile category.

Figure 21 - Spatial Variation of Combined Years for the ILI Season



Objective 2 – Data Exploration

The second research question was: *Are there any significant (high or low) clusters in Manitoba?* It was hypothesized that both low and high clusters would be consistent with areas of higher and lower socio-economic status respectively. These clusters were

identified at the Health District and Neighbourhood Cluster levels for the combined seasons of data. The clusters proving to be significantly high or low using the standardized data are shown in Figure 22 at the Health District and Neighbourhood Cluster levels.

Figure 22 - Areas of High and Low Likelihood to Cluster According to Spatial Scan Statistic

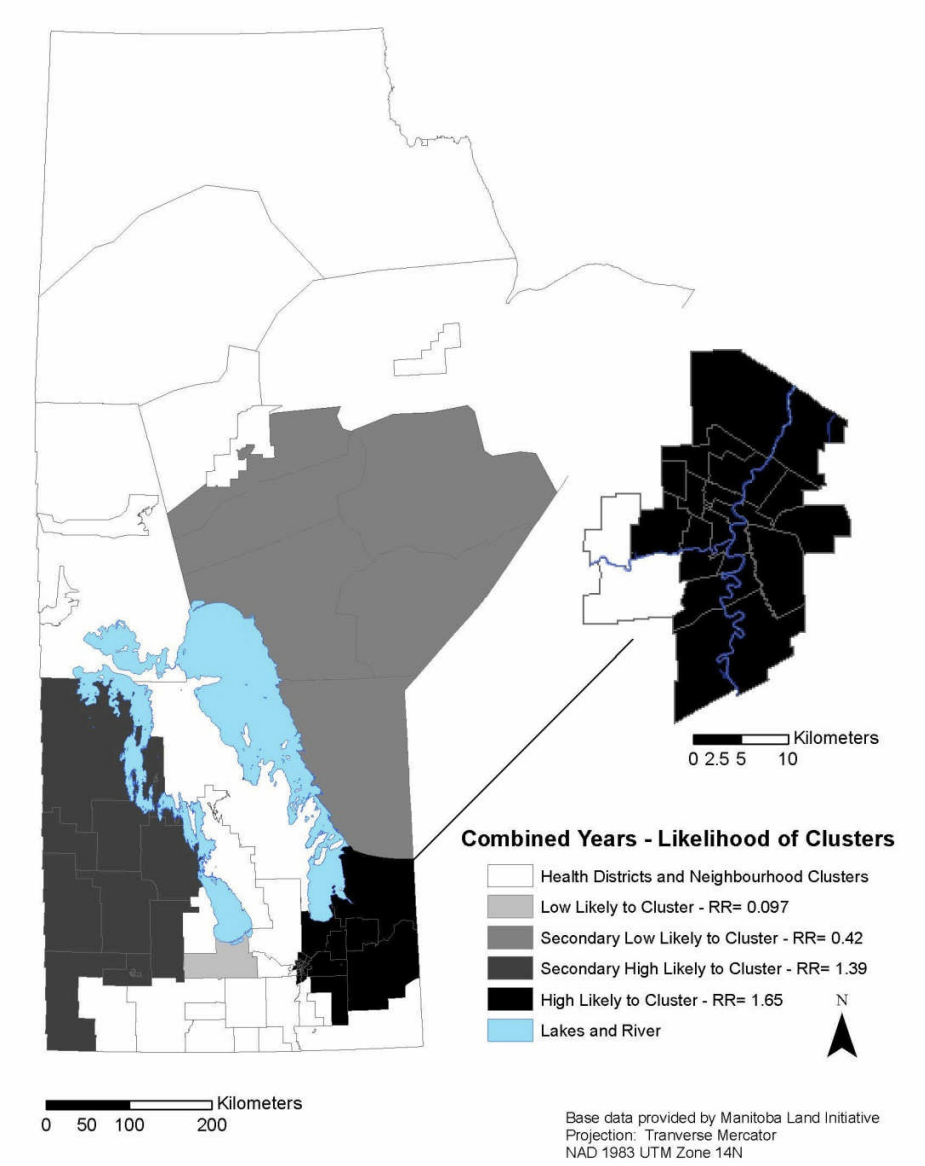


Figure 22 shows a group of Health Districts on the eastern side of the province that are more likely to have clusters of ILI cases based on the study years; these Health Districts have a relative risk (RR) of 1.65 in comparison to the other areas. The Blue Water Health District, previously identified as having visually high rates of cases, is confirmed to have a high likelihood to cluster. This high cluster (RR = 1.65) extends into

most of the WRHA (all but two Neighbourhood Clusters), including the Point Douglas Neighbourhood Cluster. On the western side of Manitoba there is a group of Health Districts identified as being a secondary high likelihood to cluster location, with a RR of 1.39. It should be noted that these areas of high likelihood to cluster could be the result of having many repeat cases that amplify the number of cases and thus artificially highlight these areas as statistically significant clusters.

A geographically large portion of the province is identified as being a secondary low likelihood to cluster (RR = 0.42), with one Health District having a low likelihood to cluster (RR = 0.097). In contrast, there are no Neighbourhood Clusters with a low likelihood to cluster.

Objective 3 – Data Modeling

The third research question was: *Is ILI incidence significantly related to a select group of determinants of health variables (age, gender, dwelling population, immunization status, co-morbidities, education, and income)?* It was hypothesized that ILI incidence would be significantly higher in populations with low incomes, living in crowded housing conditions, and in very young and very old individuals having significant co-morbidities. This final research question was answered using the tools of data modeling. The derived Rate Ratios, along with the lower and upper confidence limits, as modeled by the regression analysis are given.

Each variable had a reference category whose Rate Ratio (RR) is one. To facilitate linear comparisons, the reference category represents the highest rate for each variable. The subsequent category (or categories) has a RR less than or greater than the

reference category (or one). Where the RR is less than one, there is a beneficial effect in comparison to the reference category. The opposite is true if the RR is greater than one.

The regression results were not all as expected and provide some interesting findings, possibly due to the inclusion of repeat cases and the subsequent limitations and biases previously mentioned. Results shown in bold are those found to be statistically significant (where the p value is <0.0001). Such a small p value was used to ensure that only those results that were highly significant were highlighted, as ILI diagnosis is so common. The results for the Health Districts, Neighbourhood Clusters and Combined areas are shown separately, in Table 11 for the simple regression analysis and Table 12 for the multiple regression analysis.

Table 11 – Simple Negative Binomial Regression Results

Predictor	Health Districts			Neighbourhood Clusters			Combined		
Category (data range)	RR~	99.9% CI~		RR	99.9% CI		RR	99.9% CI	
^Household Density									
Low (2.03 – 2.71)	**1.3165**	**1.0718**	**1.6174**	1.0617	0.9235	1.2207	1.0205	0.8832	1.1793
Moderate (2.71 – 3.50)	**1.3243**	**1.0702**	**1.6390**	**1.1668**	**1.0234**	**1.3304**	**1.1838**	**1.0218**	**1.3714**
*High (>3.50)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
#Co-morbidity Score									
Not Severe	**0.4792**	**0.3926**	**0.5849**	0.8091	0.6519	1.0044	**0.7942**	**0.6909**	**0.9130**
Moderately Severe	**0.6650**	**0.5920**	**0.7470**	0.9901	0.8078	1.2137	**0.8850**	**0.8019**	**0.9767**
*Severe	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Gender									
Female	0.9916	0.8888	1.1065	1.0320	0.9440	1.1282	1.0049	0.9240	1.0930
*Male	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Age Group									
0 - 2	**2.3507**	**2.0606**	**2.6816**	**2.3187**	**2.1353**	**2.5178**	**2.2773**	**2.0635**	**2.5133**
2 - 65	**0.7590**	**0.6701**	**0.8596**	1.0207	0.9436	1.1043	**0.8165**	**0.7434**	**0.8969**
*65+	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
®Season Group									
Early (weeks 39 – 46)	**0.8095**	**0.6930**	**0.9454**	**0.8810**	**0.7783**	**0.9972**	**0.8415**	**0.7473**	**0.9475**
Early-Mid (weeks 47 – 2)	0.9925	0.8509	1.1579	1.1204	0.9905	1.2672	1.0453	0.9290	1.1762
Mid (weeks 3 – 10)	1.1557	0.9916	1.3469	**1.2411**	**1.0975**	**1.4035**	**1.1890**	**1.0572**	**1.3372**
*Late (weeks 11 – 17)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
°Area									
Remote	**0.3718**	**0.3186**	**0.4340**	n/a	n/a	n/a	**0.3456**	**0.3113**	**0.3836**
Rural	**0.6740**	**0.5837**	**0.7783**	**0.5917**	**0.4861**	**0.7203**	**0.6329**	**0.5787**	**0.6922**
*Urban	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000

Table 11 –continued

Predictor	Health Districts			Neighbourhood Clusters			Combined		
Category (data range)	RR~	99.99% CI~		RR	99.99% CI		RR	99.99% CI	
°Income Quintile (HD) (NC)									
1 (0 – $41,990) (0 – $51,000)	0.9956	0.8246	1.2021	**1.2829**	**1.1088**	**1.4844**	1.0428	0.9047	1.2019
2 (41,990 – $62,480) (51,000 - $63,080)	0.9344	0.7733	1.1292	**1.1595**	**1.0017**	**1.3422**	0.9658	0.8375	1.1137
3 (62,480 - $73,160) (63,080 – $73,060)	1.0110	0.8324	1.2279	1.0912	0.9468	1.2577	1.0194	0.8824	1.1776
4 (73,160 – $90,020) (73, 060 – $85,970)	0.9791	0.8039	1.1926	0.9641	0.8362	1.1115	0.9563	0.8265	1.1064
*5 ($90, 020 +) ($85,970)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
±Vaccination Rate									
Low (0 – 33%)	0.4331	0.1359	1.3799	0.7056	0.3325	1.4977	0.4819	0.2112	1.0993
Moderate (33-67%)	**0.3017**	**0.0944**	**0.9645**	0.4806	0.2261	1.0215	**0.3553**	**0.1554**	**0.8125**
* High (67 – 100%)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
√Unemployment Rate									
Low (2.17 – 4.96%)	**1.3988**	**1.1402**	**1.7158**	0.9096	0.7410	1.1163	**1.2596**	**1.0683**	**1.4851**
Moderate (4.97 – 7.41%)	**1.4791**	**1.1795**	**1.8547**	1.0327	0.8322	1.2816	**1.4010**	**1.1708**	**1.6763**
*High (7.42 – 12.81%)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
≠High School Completion									
Low (18.39 – 22.65%)	**0.6708**	**0.5607**	**0.8025**	**0.8577**	**0.7554**	**0.9739**	0.7241	0.6524	0.7921
Moderate (22.66 – 27.20%)	0.9828	0.8636	1.1187	**0.8848**	**0.7910**	**0.9896**	**0.9543**	**0.8872**	**1.1976**
*High (27.21 – 33.07%)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
ΩUniversity Certificate, Diploma, Degree									
Low (9.94 – 16.24%)	**0.7456**	**0.6310**	**0.8810**	**1.1482**	**1.0033**	**1.3139**	**0.8314**	**0.7326**	**0.9436**
Moderate (16.25 – 27.98%)	**0.8361**	**0.7340**	**0.9524**	1.0526	0.9554	1.1596	**0.8621**	**0.7831**	**0.9491**
*High (27.99 – 49.62%)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
×Level of Geography									
Neighbourhood Cluster	n/a	n/a	n/a	n/a	n/a	n/a	**1.7217**	**1.5743**	**1.8829**
*Health District	n/a	n/a	n/a	n/a	n/a	n/a	1.0000	1.0000	1.0000

~RR, Rate Ratio; CI, Confidence Interval.
*Denotes a reference category.
^The average number of people per household, categorized using Natural Jenks breaks.
Categorized using ADG scores and Natural Jenks breaks.
® Created by dividing the CDC weeks occurring during the Influenza Season into four groups.
° Based on the classifications used by Statistics Canada.
√ The rate of the population over age 15 that is unemployed
± The percentage vaccinated and categorized using Natural Jenks breaks.
≠ Ω The percentage of the population aged 25 to 64 whose highest level of education is High School, or a University Certificate, Diploma or Degree categorized using Natural Jenks breaks.
× Categorized based on the Average Neighbourhood Income.

Table 12 - Multiple Negative Binomial Regression Results

Predictor	Health Districts			Neighbourhood Clusters			Combined		
Category (data range)	RR~	99.99% CI~		RR	99.99% CI		RR	99.99% CI	
^Household Density									
Low (2.03 – 2.71)	**0.7379**	**0.5476**	**0.9945**	1.0157	0.9102	1.1336	0.9138	0.7876	1.0605
Moderate (2.71 – 3.50)	0.8737	0.6603	1.1559	1.0782	0.9771	1.1897	1.0428	0.9047	1.2021
*High (>3.50)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
#Co-morbidity Score									
Not Severe	**0.3984**	**0.2800**	**0.5670**	**0.8320**	**0.6908**	**1.0021**	**0.5016**	**0.5942**	**0.7168**
Moderately Severe	**0.6332**	**0.5661**	**0.7084**	0.9587	0.8160	1.1264	**0.6526**	**0.4222**	**0.5959**
*Severe	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Gender									
Female	1.0938	0.9919	1.2062	**1.0997**	**1.0339**	**1.1695**	**1.0940**	**1.0176**	**1.1761**
*Male	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Age Group									
0 - 2	**1.5377**	**1.1599**	**2.0387**	**2.5398**	**2.0705**	**3.1155**	**1.7690**	**1.4401**	**2.1726**
2 - 65	**0.4795**	**0.3600**	**0.6385**	1.1143	0.8955	1.3864	**0.6050**	**0.4889**	**0.7486**
*65+	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
ºIncome Quintile (HD) (NC)									
1 (0 – $41,990) (0 – $51,000)	0.8950	0.7533	1.0689	**1.2484**	**1.1233**	**1.3876**	0.9728	0..8568	1.1044
2 (41,990 – $62,480) (51,000 - $63,080)	0.8761	0.7361	1.0427	**1.1177**	**1.0060**	**1.2418**	0.9410	0.8298	1.0672
3 (62,480 - $73,160) (63,080 – $73,060)	0.9179	0.7699	1.0943	1.0671	0.9644	1.1806	0.9527	0.8398	1.0806
4 (73,160 – $90,020) (73, 060 – $85,970)	0.9422	0.7895	1.1245	0.9522	0.8612	1.0528	0.9419	0.8304	1.0683
*5 ($90, 020 +) ($85,970)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
±Vaccination Rate									
Low (0 – 33%)	0.6570	0.2256	1.9132	**0.3954**	**0.2190**	**0.7140**	0.5946	0.2887	1.2245
Moderate (33-67%)	0.4122	0.1438	1.1814	**0.4306**	**0.2473**	**0.7498**	**0.4334**	**0.2143**	**0.8763**
* High (67 – 100%)	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
×Level of Geography									
Neighbourhood Cluster	n/a	n/a	n/a	n/a	n/a	n/a	**2.1654**	**1.9719**	**2.3776**
*Health District	n/a	n/a	n/a	n/a	n/a	n/a	1.0000	1.0000	1.0000

~RR, Rate Ratio; CI, Confidence Interval. *Denotes a reference category. ^The average number of people per household, categorized using Natural Jenks breaks.
#Categorized using ADG scores and Natural Jenks breaks. ± The percentage vaccinated and categorized using Natural Jenks breaks. ºCalculated using the Average Neighbourhood Income.
√ The rate of the population over age 15 that is unemployed and categorized using Natural Jenks breaks. ≠ The percentage of the population aged 25 to 64 whose highest level of education is High School, categorized using Natural Jenks breaks.
×Categorized based on location of occurrence.

The household density variable was significant in both the simple and multiple regression analyses, but its impact was not the same in both regressions models. Modeled as an individual variable, the Low and Moderate categories of household density had an increased risk of ILI diagnosis in comparison to the High category, at all levels of geography. The Low category presented a statistically significant increased risk for only the Health Districts.

The results of the multiple regression analysis for the household density variable show a reduced risk of ILI diagnosis at the Health District level for the Low and Moderate categories, an increased risk for the Neighbourhood Clusters, and varied risk (depending on the category) for the Combined areas. In this model only the Low category for the Health Districts yielded a statistically significant result.

As the co-morbidity score increased in both analyses, so did the risk of being diagnosed with an ILI. This result was statistically significant for both the Not Severe and Moderately Severe categories in the simple regression analysis for the Health Districts and Combined areas. The same was true of the multiple regression analysis; however the Not Severe category was also significant for the Neighbourhood Clusters.

The gender variable did not prove to be significant in the simple regression analysis; however, it was significant in the multiple regression analysis for both the Neighbourhood Clusters and Combined areas. The analyses (both simple and multiple regression) confirmed that being in the age group 0-2 more than doubled the chances of being diagnosed with an ILI in comparison to those in the 65 plus group at all levels; whereas those aged 2-65 had a reduced risk in all but the Neighbourhood Clusters.

The season group variable was only modeled in the simple regression analysis. Of the four season groups identified, only the Early Season was consistently significant. The results for the Health Districts showed that when comparing the Late and Early Seasons, the latter resulted in a reduced risk of ILI diagnoses. At the Neighbourhood Cluster level there was also a reduced risk in comparison to the Late Season, and a significantly increased risk in the Mid Season. When the areas were combined the risk for ILI infection was highest in the Mid Season, and lowest during the Early Season.

The area variable was also only included in the simple regression analysis. The majority of the population of the Health Districts (non-Winnipeg) live in remote or rural areas, with the only urban communities located in the Brandon Regional Health Authority. In the Health Districts, the Remote and Rural communities had a protective effect against ILI, with those living in Remote areas being less likely to be diagnosed with an ILI than someone living in an Urban area, and those living in Rural areas were even more so. All but two of the Neighbourhood Clusters are classified as Urban. As with the results in the Health Districts, those smaller Neighbourhood Clusters had a protective effect against ILI, with those living in Rural areas being less likely to be diagnosed with an ILI than someone living in an Urban area. For the Combined area analysis the Urban areas were most at risk of ILI when compared to Rural (37% reduced risk) and Remote (65% reduced risk).

Both the simple and multiple regression analyses had similar results for the Income Quintile Variable, which was only significant for the Neighbourhood Clusters. The results were as one would expect, with those living in areas in the lowest two income quintiles having a greater risk of illness than those living in the highest income quintile.

The results of the vaccine variable were not consistent between Health Districts and Neighbourhood Clusters in the simple regression analysis. Health Districts with Moderate vaccine uptake were more than 70% less likely to have an ILI diagnosis than those with High uptake. At the Neighbourhood Cluster level however the vaccine variable did not have a significant impact on ILI rates. For the Combined area analysis the predictive value of the vaccine variable showed that areas with Moderate uptake were at a 65% reduced risk of illness compared to those with High uptake.

Although the rate ratios were similar at all the area levels in both the simple and multiple regression analyses, their statistical significance was not consistent. The results of the multiple regression showed that the vaccine rate variable was significant for both the Low and Moderate uptake areas. ILI diagnosis was more than 60% less likely in the Low uptake areas, and just over 45% less likely in the Moderate uptake areas.

The simple regression results of this study showed that Low and Moderate unemployment rates increased the risk of ILI diagnoses at the Health District and Combined geographical areas compared to the High unemployment category. The unemployment rate variable was not statistically significant for the Neighbourhood Clusters.

There were two education variables in the simple regression analysis. The High School Completion variable (where High School was determined to be the highest level of education) showed that having Low rates was, at all levels, significantly protective against an ILI diagnosis. The University Certificate, Diploma or Degree variable significantly reduced the risk of ILI diagnoses at all levels when the classification was

Low, with the Moderate category deemed to decrease the risk significantly at both the Health District and Combined levels.

A variable to examine the relative risk of ILI diagnosis based on the two levels of geography was also measured in the Combined area analysis. In the simple regression analysis, those living in Neighbourhood Clusters were 1.7 times (a statistically significant RR) more likely than those living in the Health Districts of being diagnosed with ILI. Multiple regression analysis showed a similar result with the Neighbourhood Clusters having twice the likelihood of diagnosis in comparison to the Health Districts.

These results are interpreted in Chapter 6: Discussion and have been presented here without explanation or association to the theoretical frameworks guiding this thesis. In summary, the results of the data visualisation and exploration objectives were as expected. The results showed that similar temporal patterns exist within the study population as with the Manitoba population as presented by Manitoba Health and that ILI do not occur in all areas of the province at the same time. The Spatial Scan statistic identified clusters throughout the province that were not obviously clustered based on data visualisation alone. The data modeling identified some variables that are statistically significant for ILI diagnoses at the various geographies, but the expected relationship between the ecological variables (determinants of health) and ILI diagnoses was not apparent.

Chapter 6 - Discussion

Influenza represents an annual threat to public health in Canada (Health Canada, 2009; Public Health Agency of Canada, 2010). However, research studies on influenza often need to use the broad case definition to include all ILI to have a large enough sample size for meaningful analysis (Carrat & Calleron, 1992; Martinez-Beneito, Botella-Rocamora, & Zurriaga, 2010; Tilston, Eames, Paolotti, Ealden, & Edmunds, 2010). This broad definition results in a potential flaw in this and other similar studies (Irwin, Weatherby, Huang, Rosenberg, Cook, & Walker, 2001; Menec, Black, MacWilliam, & Aoki, 2003; Yiannakoulias, Russell, Svenson, & Schoplocher, 2004) that do not adjust for repeat diagnoses of an individual in a single season. Repeat diagnoses were common in this thesis (69.12% of study population), but exclusion of these cases would have made it difficult to proceed with many analyses due to small cell numbers. Having a large sample size was especially important for this study as it explored the data spatially and temporally, counting cases based on geographic location and diagnosis date.

Each of the three objectives was designed to answer specific questions, to complement one another with each result supporting and leading to the subsequent objective. This sequencing was matched to the Bailey and Gatrell framework, and supported by the data visualisation, exploration and modeling methodology used in this thesis.

Objective 1 – Data Visualisation

The first objective was to describe the spatial and temporal variation of ILI incidence in Manitoba. The principles of data visualisation guided this objective as they represent a simple way to display spatial data following the basic concepts of descriptive epidemiology. The hypothesis was confirmed as temporal and spatial variations were

observed by mapping the cases based on when (seasonally) and where (level of geography) the cases occurred.

The seasonal maps (Figures 13 to 16) show a higher incidence of ILI in the WRHA than in the surrounding Health Districts. These maps show the rates classified using Natural Jenks breaks, making it difficult to compare the seasons. The use of Jenks, however, allows for each seasonal map to be examined in terms of spatial patterns during a specific season in relation to other geographies.

As the seasonal maps control for variations in age and population size, the higher incidence in the WRHA is possibly due to more individuals seeking care, as well as greater access to medical care (i.e., access to physician and hospital services is potentially easier for those living within the WRHA). This would likely lead to an increase in the diagnoses of illnesses. While this assumption is supported in the literature (Etches, Frank, Di Ruggiero, & Manuel, 2006; Fernandez, MacKinnon, & Silver, 2010, Martens, et al., 2010), it was not possible to associate the relationship between access to care and increased rates of ILI in this thesis.

ILI are communicable diseases and require human interaction to spread. A greater number of viruses would be expected in areas with more people, thus increasing incidence of illness (Stamboulian, Bonvehi, Nacinovich, & Cox, 2000). In areas with a greater population, such as the WRHA, a greater number of viruses would be expected given the quantity of virus and ease of spread. The results of this analysis are in line with what is expected.

It is also worth noting that in many Health Districts and Neighbourhood Clusters, rates are higher in the Late Season map than in any other season group, as seen in Figures

17 and 18. This is potentially the result of a late season epidemic in one or more of the study years, or due to seasonal variability. Due to issues with small numbers, case counts for each geographic location by age category for each season were not available, however, the epidemic curves for the 2004-05 and 2008-09 seasons (see Appendix A) showing an increased number of ILI cases reported by sentinel physicians, could suggest an epidemic year.

The spread of ILI diagnoses is shown in Figures 19 and 20. No obvious pattern is observed in the Health Districts. The Neighbourhood Cluster with the highest initial rate that arguably begins the transmission (or has increased levels of persons seeking health care) in the WRHA is Point Douglas. This finding is in keeping with the notion of the social gradient of health that states that individuals who are socially disadvantaged, or have lower socio-economic status, are more likely to have poorer health outcomes (Keating & Hertzman, 1999; Martens, Frohlic, Carriere, Derksen, & Brownwell, 2002) and seek care more readily (Martens, et al., 2010). As a similar pattern of spread was not apparent outside of the WRHA, the initial results from the data visualisation objective do not support that a relationship exists between ILI rates and premature mortality in the Health Districts.

The visualisation of the data showed there were some clusters of cases throughout the province, both at the Health District and Neighbourhood Cluster levels. Figure 21 shows the age standardized rate for the ILI season for the combined study years. This map highlights the Point Douglas Neighbourhood Cluster and the Blue Water Health District as areas of the province that have higher rates of cases in comparison to other

areas. Although these clusters are in the higher rate categories, these results, on their own, do not prove that these areas are more likely to cluster than the others.

Objective 2 – Data Exploration

The second objective of this thesis confirmed that significant spatial clusters of ILI exist in Manitoba. Areas with low or high likelihoods to cluster can be seen in Figure 22. The identification of clusters of cases is a common objective in any epidemiological study (Young, 2005). Typically clusters are identified in outbreak investigations (Onozuka & Hagiahara, 2008; Kuldorff, Heffernan, Hartman, Assunção, & Mostashari, 2005; Fraser, Riley, Anderson, & Ferguson, 2004) as a tool to better understand the risk of the outbreak. In this thesis, clusters were identified to reveal geographic areas (Neighbourhood Clusters and Health Districts) at greater risk of ILI diagnoses.

The previously identified clusters in the areas of Point Douglas in the WRHA and the Blue Water Health District are in fact true clusters. The high likelihood areas are more diffuse than shown by data visualization (particularly as seen in Figure 21), which indicated a smaller at risk area. Neighbourhood Clusters with a higher PMR (Figure 4) have a higher likelihood to cluster. It should, be noted that many areas with a lower PMR are also shown to have a higher likelihood to cluster. This does not necessarily minimize a relationship between PMR and likelihood to cluster, but rather identifies that other factors may exist, such as those modeled in the third objective (including age, vaccination rate and co-morbidity status).

Areas identified as most likely to cluster have characteristics that are elevating their risk relative to other at-risk areas. Almost everyone is exposed to ILI through coughs and sneezes, but the results of objectives 1 and 2 show that not everyone gets sick

enough to seek care. It is therefore important to explore the differences in ILI diagnosis within a diverse population, such as that of Manitoba. In order to help focus public health strategies for disease prevention and treatment, population health focuses on people, place and time as they relate to the spread of infection and disease. The results of this analysis and the comparison to PMR rates in the study area show that risk of ILI diagnosis in Manitoba is not exclusively dependent on the social gradient of health. These results are potentially being altered by the inclusion of repeat cases which are highlighting certain areas which may not actually have higher amounts of true influenza. Identifying and subsequently having a better understanding of locations that are most likely to have true clusters of ILI cases in Manitoba based on this data will help address the factor of place for public health strategic planning.

Objective 3 – Data Modeling

The third and final objective of this thesis was to formally model the degree to which ILI incidence varies by age, gender, household density, immunization status, co-morbidities and socio-economic status (as determined by income and education level). It was hypothesized that the model would show significantly higher ILI rates in populations with low socio-economic status, in populations living in crowded housing conditions, among the very young and very old who are not immunized as well as individuals who have significant co-morbidities.

As was demonstrated through both simple and multiple regression models (Table 11 and 12) in Chapter 5, in many instances, this hypothesis was not confirmed and results were not always consistent with similar studies (Crighton, Elliott, Moineddin, Kanaroglou, & Upshur, 2007; Crighton, Moineddin, Kanaroglou, & Upshur, 2007; Dao,

et al., 2010; Irwin D. , et al., 2001; Schanzer, Langley, & Tam, 2008). It should however be noted that the Crighton et al studies, as well as the Dao et al study used laboratory confirmed cases of influenza and as such do not have the limitations of having included repeat cases of ILI. The inclusion of repeat cases of ILI in this study should be kept in mind as the regression results are interpreted.

The simple regression results represent how each variable affects ILI diagnosis individually, without the influence of any other factors. The multiple regression results are representative of ILI diagnosis when all the included variables (based on the literature) are taken into account and adjusted for in the model.

There is therefore an inherent bias with multiple regression analysis as it assumes that the correct variables were chosen for the model. Although multiple regression analysis has the advantage that each variable is adjusted for in the model, it can also be limiting as the results change with the inclusion or exclusion of variables. It also limits the inclusion of similar variables, for example income and unemployment, due to concerns of interaction. As these advantages and limitations do not exist with simple regression analysis, it is valuable to use both methodologies as was done in this thesis.

A key element of public health practice is to minimize burden of illness in at-risk populations. Perhaps the most important tool to reduce ILI rates, and subsequent severity, is a comprehensive and effective influenza vaccination program that targets the right people at the right time. Vaccines are most effective prior to infection, thus one of the keys to an effective program is timing. If the model (using the combined study years) is an accurate representation of the average influenza season, the results of the season

variable in the simple regression support the timing of the vaccine program in Manitoba (Communicable Disease Control Branch, 2008).

The at-risk population for ILI in Manitoba, and those most encouraged to get vaccinated, has been reported to be those under the age of two and over the age of 65, and those who are immune-compromised (Manitoba Communicable Disease Control Unit, 2006). The results of this analysis are consistent with similar studies and support this assertion (Schanzer, Langley, & Tam, 2008; Irwin D. , et al., 2001). Both simple and multiple regression analyses conducted showed that those in the Severe co-morbidity score and the 0-2 age group had the highest risk of ILI diagnosis. This confirmation provides further support to the age standardization previously calculated for the data visualisation and exploration objectives; it also supports the existing messaging campaign and vaccine strategy for seasonal influenza, including universal vaccination.

Both regression results showed a decreased risk of ILI where vaccination rates were low with the greatest risk occurring where rates of ILI were high, a result that was not expected. Vaccination is intended to protect against influenza and not ILI which could be affecting the results; they should be interpreted with caution. In addition to the aforementioned caution, vaccination rates may be associated with individuals that seek medical care more frequently, therefore ILI are diagnosed more often. The assumption, based on NACI recommendations and supporting literature (Public Health Agency of Canada, 2009; Schanzer, Langley, & Tam, 2008; Irwin D. , et al., 2001; ICES, 2007), is that ILI vaccination is higher among those with co-morbid conditions or those who are immune-compromised. As vaccination rates in Manitoba are tracked through MIMS, another possible explanation for this unexpected result is that the dataset may not be

complete for all areas of the province, which also potentially affects the results. This could be an issue particularly in northern Manitoba, where jurisdictional boundaries result in some reporting challenges.

The results of the regression models show that Severe co-morbid condition category increased the risk of ILI diagnoses. This confirms the notion that those with co-morbid conditions are at greater risk for illness, but questions the results of their increased rate of immunization against influenza. Adjusting for vaccination rate in the multiple regression model, as well as all the other included variables, showed a greater increased risk for those in the Severe co-morbid condition category, than when modeled as an isolated variable in the simple regression model. It should be noted that people in these categories are less likely to experience the full benefits of immunization and that the annual influenza vaccine is more likely to reduce severe illness in this population, than illness all together.

In addition to modeling the more commonly accepted risk factors for ILI, this research sought to identify if other factors (determinants of health) should be included in determining the at-risk population for ILI. Although increasingly, research is finding a link between the determinants of health and illness (Fernandez, MacKinnon, & Silver, 2010; Martens, et al., 2010; The Public Health Disparities Geocoding Project Monograph, 2004) with a large emphasis on the gradient of health model (and socio-economic status), this thesis does not fully support these linkages when ILI is the outcome.

The typical measures of socio-economic status include living conditions, income and education. In the simple regression analysis for ILI, the household density variable

result raises some questions about the importance of socio-economic status. At all levels of geographies, the Low and Moderate household density categories had an increased risk of ILI diagnoses when compared to the High category. The Moderate category was statistically significant in all areas. As ILI spread from person to person, it would seem more intuitive for those living in High density homes to be at increased risk of ILI diagnosis. It is, however, not known how large these homes but rather only how many inhabitants live there at the time of the census. It is also possible that not every member of the same household would seek medical care for an ILI, thus reducing the number of diagnoses in homes with higher densities. Finally, it is possible that those living in High density homes are exposed to more illnesses, and as a result, developed a more robust immune system. This exposure acts as a protective mechanism to more common illnesses such as ILI.

The multiple regression analysis had differing results from the simple regression analysis. The Low density category had the lowest risk (and statistically significant in comparison to the High category) at the Health District level and the High category had the greatest risk at the Neighbourhood Cluster level (but with no statistically significant categories). These results, which take into account the other variables, are more in line with what one would expect for a communicable disease such as ILI. In the Health Districts where the population is more diffuse, household density appears to be more important (as determined by statistical significance) than in the Neighbourhood Clusters where a disease could more easily spread outside the home.

The results of the income quintile variable were different for the Health Districts compared to the Neighbourhood Clusters. The Health District results, for both the simple

and multiple regressions, were insignificant for all the quintiles. At the Neighbourhood Cluster level, in both analyses, the results of the income quintile variable showed a significant increased risk among the lowest two quintiles, as would be expected when considering the social gradient of health, however only the Neighbourhood Cluster analyses yielded the expected results, a concrete association between SES and ILI was not observed in this study.

Income is associated with employment and education, modeled in the simple regression. The findings for the unemployment and education variables were unexpected. The regression found that areas with Low and Moderate unemployment rates were at greater risk, as were those who were more educated. These findings call into question the hypothesis that the determinants of health would serve as good predictors of ILI in Manitoba. It is, however, possible that those in the Low and Moderate unemployment categories experience higher rates of exposure to ILI while at the workplace and as such were at greater risk of diagnosis.

When comparing Figure 4 with those showing the various calculated rates (Figures 13 to 22), either with the data visualisation or exploration methods, the results are not quite what one would expect. Furthermore, when incorporating the results from the data modeling, these unexpected results are confirmed in many cases and additional questions are raised. It is possible that some of these inconsistencies are a function of the inclusion of repeat cases as determined by the definition of ILI. The results of this thesis are consistent with the notion that ILI and the flu do not discriminate in terms of diagnosed infection. The results cannot, however, make a similar statement with regards to the determinants of health and severity of illness caused by ILI.

With a common illness such as influenza and consequently ILI, it is possible the diagnosis of the illness is not affected or influenced by the factors highlighted by the determinants of health, as is the case with various chronic diseases. This thesis is not alone in showing that not all health outcomes have a linear relationship with the determinants of health. Some chronic diseases are more prevalent in more affluent populations whose risk factors for illness are distinct from those presented by the determinants of health. Rates of inflammatory bowel disease and multiple sclerosis are lowest in the populations with the lowest socio-economic status (Green, Elliott, Beaudoin, & Bernstein, 2006; Beaugerie, Seksik, Nion-Larmurier, Gendre, & Cosnes, 2006). In Manitoba, the majority of cases of type 2 diabetes occur in non-First Nation middle class people (Green, 2005). Obesity rates are highest amongst Caucasian males in the upper classes (Public Health Agency of Canada, 2013; Ward, Tarasuk, & Mendelson, 2007).

It is possible that with ILI, which is highly contagious, there is no discrimination as suggested by the gradient of health theory in terms of who becomes ill; it is also possible that the case definition used in this thesis are skewing the results towards areas where care is more readily available. As shown by the Level of Geography variable, the risk of ILI diagnosis is between 1.7 and 2.1 (simple and multiple regression analysis) times as likely in the highly populated Neighbourhood Clusters in comparison to the sparsely populated Health Districts. The result implies that a key determinant for seasonal influenza is simply having a host population that gets infected and in turn infects others – where there are people (as with the Neighbourhood Clusters) there is more virus.

Although the thesis findings supported the characteristics of the at-risk population as determined by the NACI, it is important to keep in mind this population is encouraged to get vaccinated to reduce adverse events from ILI, not because they are the only ones at risk. To that end, research focused on common communicable diseases such as ILI should perhaps focus more on methods about how ILI is transmitted and characteristics of those who get severely ill, rather than focusing on overall population characteristics and rates of diagnoses.

Epidemiology focuses on the triad of person, place and time as it relates to illness. The hypotheses and objective of this thesis focused on each element as they relate to ILI. The expected results were observed with regards to when ILI diagnosis would occur, however the results were not conclusive as to where and who would be at greatest risk. It was hypothesized that the host (person) and the environment (place in time) would be important contributing factors for the diagnosis of ILI in Manitoba. Given the inconsistent results of the data modeling (possibly due to some of the limitations in methodology), the hypothesis was not realized. It could therefore be discerned that the more important element in this triad would be the agent of ILI. As the presence of a common illness such as ILI is not easily modifiable, public health efforts would be best expended on strategies to reduce severity and spread of illness. At this time, the Manitoba Health strategy concerning ILI achieves both these recommendations.

Study Limitations and Assumptions

There are some limitations and assumptions inherent to this research that are important to acknowledge. As the study was highly dependent on administrative data, there is always a risk the data has been incorrectly entered into the database or something

was incorrectly coded at the physician or hospital level. Administrative data only records those seeking care and as such access to care is necessary to be counted. Furthermore, administrative data should not be considered complete, however there are, many reputable studies and reports that use administrative data as their main source (Fransoo R. , et al., 2011; Martens, et al., 2010; Crighton, Moineddin, Kanaroglou, & Upshur, 2007) despite this limitation.

The ultimate objectives of this thesis assume the inclusion criteria provide the correct representation of the population of Manitobans with ILI, and that five years of data collection is sufficient to draw conclusions. It was also assumed that the five years chosen were representative of typical influenza seasons in Manitoba. Using the broadened definition of ILI means that in some instances cases, that were not truly influenza cases, were included. This decision was made with the belief that having false positive cases was preferable to missing true cases in order to study a larger population. There is an inherent limitation when using ILI as a proxy for influenza due to the inclusion of false cases, many of which can be for the same patient.

Deciding which cases to include as ILI was more complicated than simply identifying the ICD codes. An analysis of those that met the case definition (based on ICD codes) was performed to explore the temporal element of each case. As per the definition of influenza, the illness lasts approximately three to five days (Health Canada, 2009) and a clinical case of influenza results in immunity to the offending strain, making it unlikely that a repeat infection occurs in the same season unless alternate strains are present. For this reason ILI cases identified by this research were analyzed to see how often repeat cases appeared, both in a seven-day period as well as within one influenza

season. Although repeat cases within a seven-day period were excluded, those occurring in a single season were not. The inclusion of multiple ILI diagnoses per person in a given season is also a potential limitiation that may have skewed the data, not only by inflating the overall sample size but also by potentially increasing the rates in areas with ahigher number of repeat patients. This added to the likelihood that false cases were counted, but again, that is preferable to deciding which to include and to exclude.

Although literature that addressed the issue of repeat ILI cases was not found, a patient could have potentially been included in the study only once in a season, even if they had multiple ILI diagnoses. The argument made to support the decision to not include any repeat cases would be that as the flu typically only lasts for three to five days (Health Canada, 2009) (and presumably ILI would be comparable), and is likely to only affect a person once in a season. Comparisons with other cases could have been used to determine which case(s) should have been included based on peak numbers and the greatest likelihood to be a true case of influenza. Undergoing this analysis would have broadened the scope of this research and was deemed unnecessary. The ultimate decision to include multiple cases in a season, is representative of a methodological limitation, and it is likely too many cases were included. The decision to include multiple cases per season is supported by the methodology of other studies focusing on ILI using similar (if not identical) case definitions (Menec, Black, MacWilliam, & Aoki, 2003; Tilston, Eames, Paolotti, Ealden, & Edmunds, 2010; Yiannakoulias, Russell, Svenson, & Schoplocher, 2004).

The research sought to determine if, and to what, extent a relationship exists between the determinants of health and ILI. The results were inconclusive and in many

ways inconsistent with the existing literature (Heaman, Green, Newburn-Cook, Elliott, & Helewa, 2007; Keating & Hertzman, 1999; Martens, et al., 2010; Marmot & Wilkinson, 1999). This inconsistency could be the result of the broad and common use of the ILI diagnosis which includes repeat cases. Although the definition could not be made more specific without ultimately using only laboratory confirmed cases (which could present issues of small cell sizes given the population size of Manitoba), it would be possible to focus on only severe cases (i.e., those requiring hospitalization) of ILI in its largest urban centre (i.e. Winnipeg) or potentially conducting a similar study using only pH1N1 cases.

Chapter 7 - Conclusions

This study had three spatially motivated objectives specific to influenza-like-illness diagnoses in the province of Manitoba. The intention was to use tools of spatial epidemiology to provide an understanding of ILI patterns that may otherwise not be apparent, and to test a series of variables as potential contributors to ILI diagnosis. Spatial epidemiology is not commonly used in Manitoba at this time; the results of this thesis are intended to present a different perspective to ILI surveillance. Using ILI as a proxy for influenza ensured that there were sufficient cases to complete the analysis, however it also introduced some limitations with the inclusion of repeat cases.

The first element of spatial epidemiology used was descriptive and presented as data visualisation. This addressed the first objective of the study to visually describe the temporal and spatial variations of ILI cases in Manitoba. Age standardized maps were created to show these variations. Variation was shown at the Health District level for all areas outside of the Winnipeg Regional Health Authority and Neighbourhood Clusters were used inside the Winnipeg Regional Health Authority. This analysis did not yield any unexpected results and was comparable to the epidemiology of ILI as presented by Manitoba Health (Communicable Disease Control Unit, 2006; Communicable Disease Control Unit, 2007; Communicable Disease Control Branch, 2008; Communicable Disease Control Branch, 2009; Manitoba Health - Communicable Disease Control Branch).

The temporal variation was shown by dividing the combined influenza seasons into four time periods: Early, Early-Mid, Mid, and Late Seasons. The pattern of temporal spread among the Health Districts and the province as a whole was minimal however, a

pattern was apparent in the WRHA, a finding supported by the understanding that ILI rates are highest where the population is greatest (Stamboulian, Bonvehi, Nacinovich, & Cox, 2000). Spatial variation, as visually shown in maps, was evident throughout the Neighbourhood Clusters and Health Districts with fairly variable rates throughout, although there were no obvious patterns. This lack of spatial variation can be attributed to the biology of ILI and its indiscriminate infectiousness (Health Canada, 2009). Both analyses showed some geographic areas with increased numbers of cases representing potential statistical clusters.

The second objective used data exploration to test the data for areas with high and low likelihood to cluster, as identified in the first objective. Using the Spatial Scan Statistic® it was determined that within the Health Districts there is an area along the eastside of the province that is highly likely to cluster. Many Health Districts were also shown to have a low likelihood to cluster. In contrast, all but two Neighbourhood Clusters within the WRHA were highly likely to cluster. The WRHA is densely populated, in contrast to the Health Districts, which could explain where the likelihood of clusters was most common.

The final objective used data modeling to investigate the characteristics of those diagnosed with ILI in Manitoba, both at an individual and ecological level. Negative Binomial Regression was used to determine which variables (including age, density and average income quintile) contributed to an increased likelihood of diagnosis. These results were surprising as the hypothesis that the determinants of health would be a significant predictor of illness was not always confirmed.

The analysis of these research objectives were expected to provide information to enhance the understanding of ILI and potentially better focus the provincial surveillance program. One of the key outcomes of this research was the assertion that ILI is a population health issue that does not discriminate. This understanding is in line with the current influenza vaccination program that is being offered universally.

As indicated by the data exploration objective, there were areas of the province that were identified as having a high likelihood to cluster. It would be valuable to use that knowledge to ensure that sufficient and adequate services are available in those areas. These services could include increased messaging about how ILI is transmitted and encourage that those who are ill stay at home to reduce transmission and subsequent illness.

The results of this thesis were subject to some significant limitations largely in part to the use of ILI as a proxy for influenza. One of the concerns was the misuse of the ILI definition and its often over use by physicians. To strengthen research that requires the use of ILI, it may beneficial to remind physicians of the definition during the influenza season to maximize the number of true cases identified. The broadened definition is used to ensure that case numbers are large enough. Another potential way to address this issue would be to encourage physicians to test more readily for influenza during the known season so that there are more lab confirmed cases.

To further gain a better understanding of ILI in Manitoba, the analysis could be re-run using only lab confirmed cases. In order to have sufficient cases larger geographies could be used or potentially more years of data combined. It is also possible that sufficient numbers of lab confirmed cases would be available if the thesis focused on

the Neighbourhood Clusters in the city of Winnipeg. Use of the ILI definition is valuable despite its limitations. A better understanding of ILI could also be achieved if each year were to be examined individually or if only the hospitalized cases were examined.

Non-spatial analysis to see if the regression results hold true for the most likely areas to cluster would also provide a different perspective of the data. The same methodology could also be run using a population that does not include repeat cases within a season. A more elaborate study design could select only one ILI diagnosis for each person per season, based on a timeline of confirmed influenza cases, in an attempt to reflect a more accurate incidence of influenza. A similar study using confirmed pH1N1 influenza cases is also recommended. As pandemic H1N1 influenza is a novel virus, it is possible that the determinants of health would play a more important role in infection rates due to greater susceptibility, as identified by the social gradient of health. Subsequent research studies focusing on the tools and methods of spatial epidemiology could include other communicable diseases, such as those that are sexually transmitted or for chronic illnesses such as cancer.

This thesis aimed to showcase the tools and potential of spatial epidemiology using ILI. Mapping rates of ILI is not common practice in Manitoba at this time. Provincial surveillance occurs through the CDC unit at Manitoba Health, and is presented using epidemic graphs and other epidemiological statistics such as incidence and prevalence. Although the third objective did not yield the anticipated result, the objectives of data visualisation and exploration demonstrated that ILI in Manitoba follows the expected timeline and that it is distributed throughout the province, with some areas having a high likelihood to cluster.

These methods of presenting data, particularly for communicable diseases such as ILI, offer a perspective that enhances understanding and offers a more complete evaluation of the problem. However, the use of ILI to display the various techniques of spatial epidemiology presented some challenges (primarily the inclusion of repeat cases and concerns with small population numbers), and as such may not have been the ideal illness or disease to showcase the potential of spatial epidemiology. Although there are tools to compensate for these issues, a more ideal focus would be an illness with a large enough confirmed population, without using an ambiguous definition.

In conclusion, this study used tools of spatial epidemiology to present ILI case data for the province of Manitoba in a different manner than it is currently presented. Although the analyses did not yield many differing results than were already known, the methodology is valuable and transferable. This thesis should be used as an example of the potential of spatial epidemiology and used as a template for future similar studies, whether focused on ILI or another health outcome.

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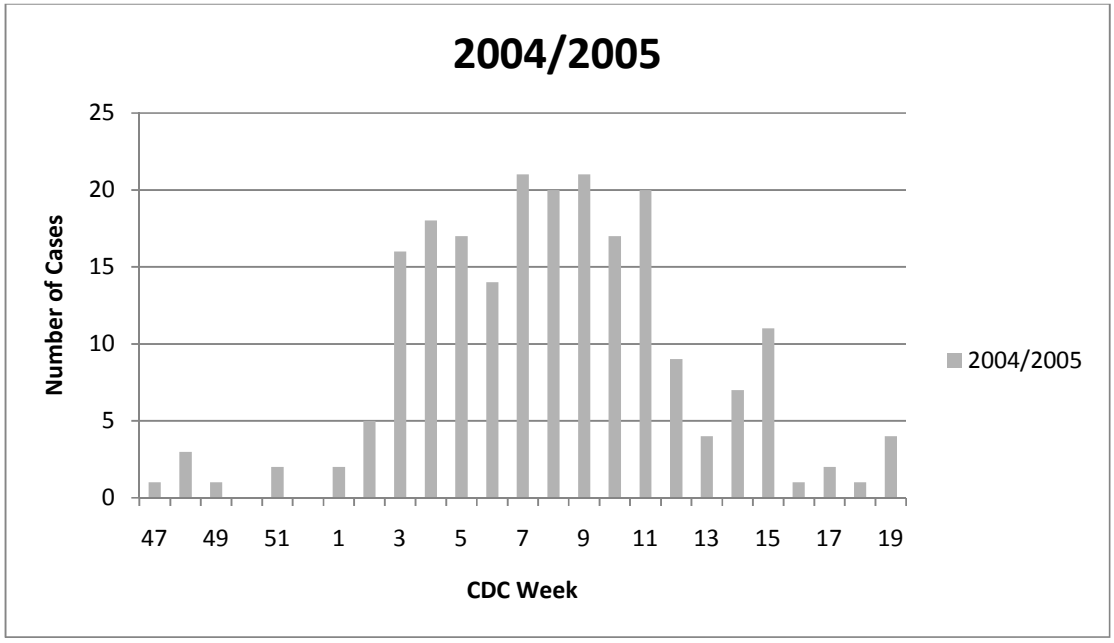
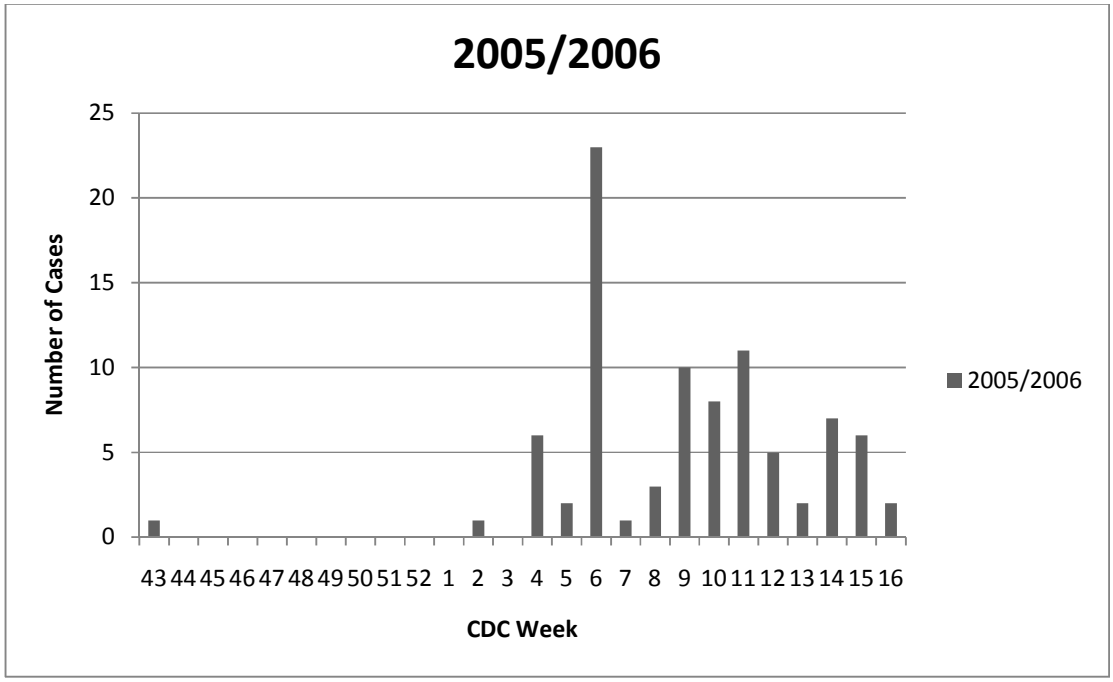
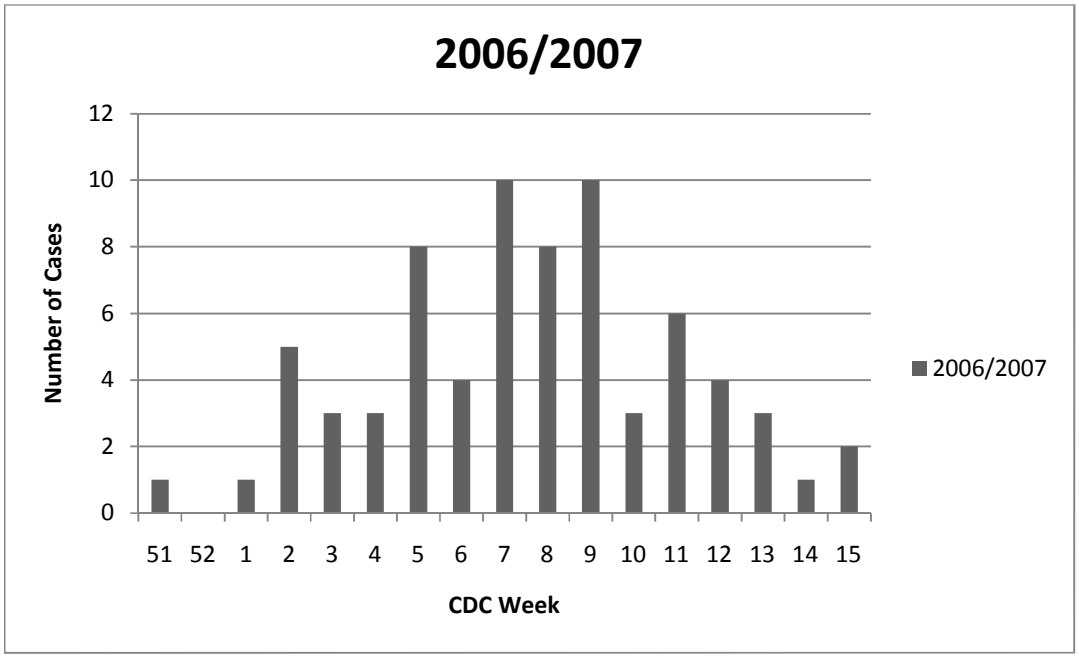
Appendices

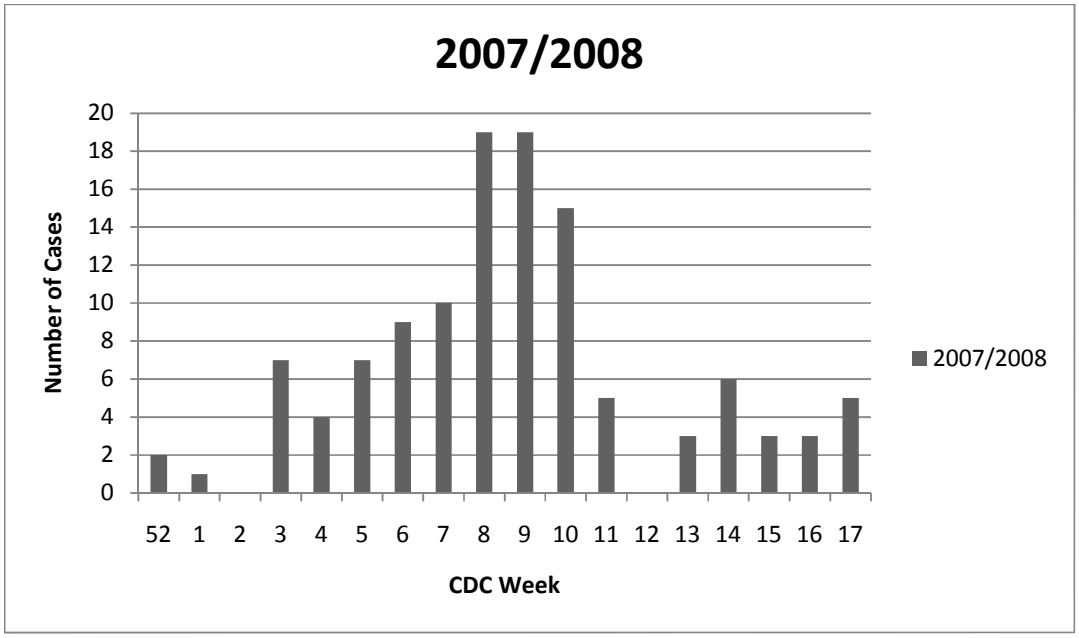
Appendix A – Epidemic Curves

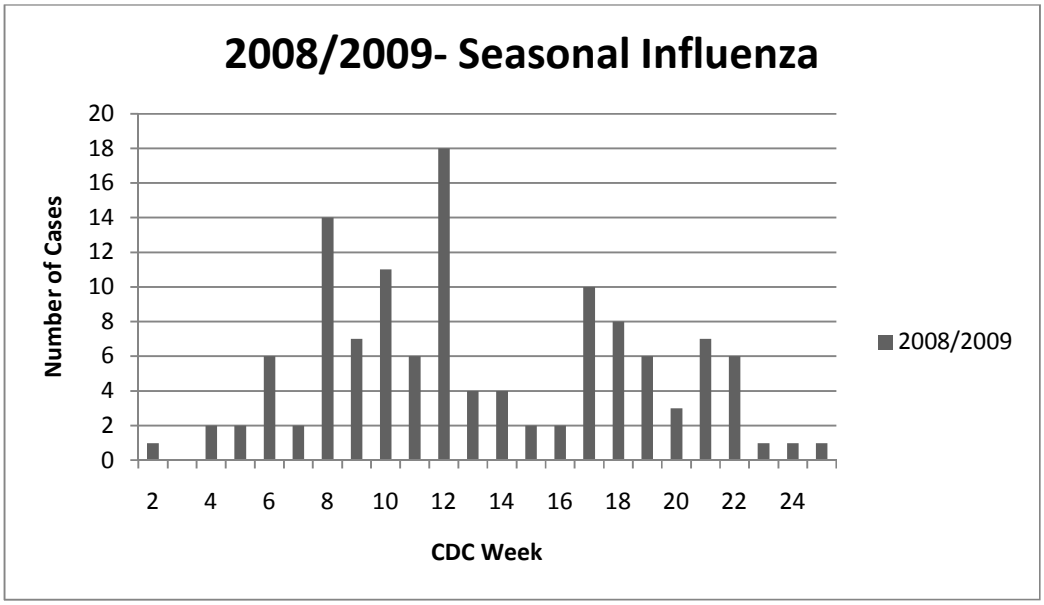
Epidemic Curves for Laboratory Confirmed Influenza Cases from Manitoba Health Data

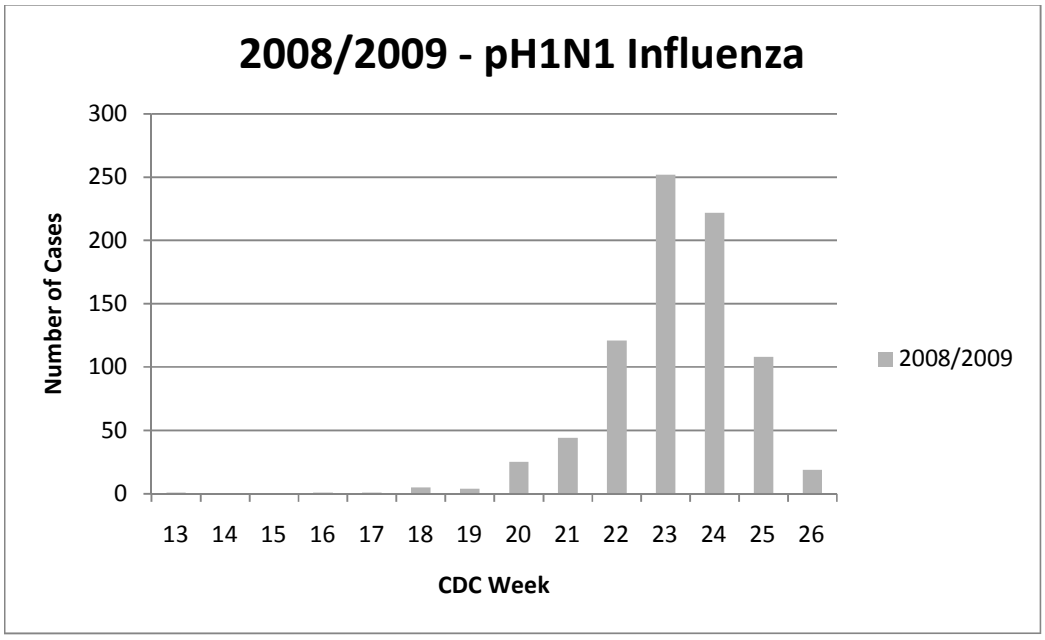




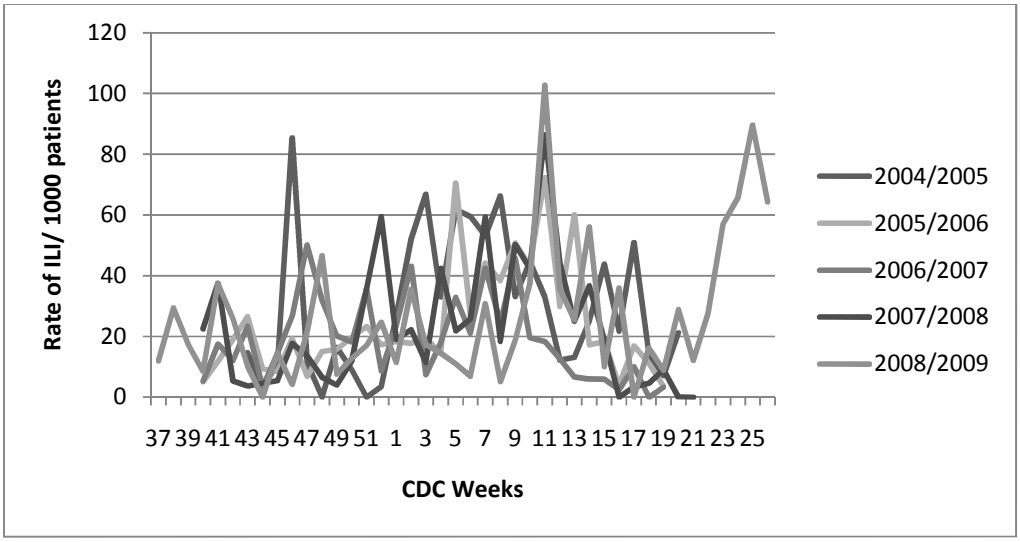

2006/2007
Number of Cases
0
2
4
6
8
10
12
51 52 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
CDC Week
2006/2007


2007/2008
Number of Cases
0
2
4
6
8
10
12
14
16
18
20
52 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
CDC Week
2007/2008

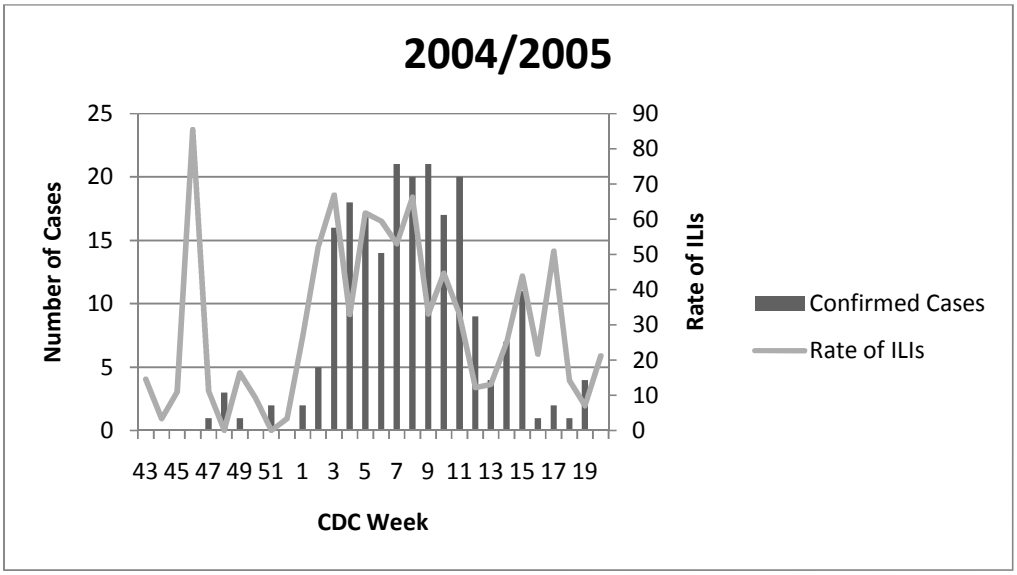

2008/2009- Seasonal Influenza
Number of Cases
0
2
4
6
8
10
12
14
16
18
20
2
4
6
8
10
12
14
16
18
20
22
24
CDC Week
2008/2009

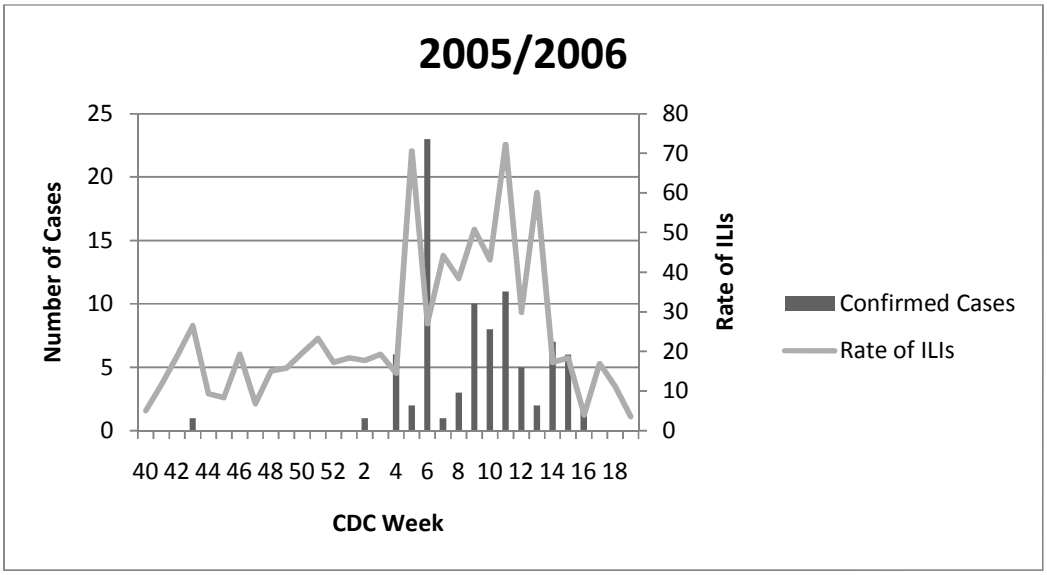

2008/2009 - pH1N1 Influenza
Number of Cases
0
50
100
150
200
250
300
13
14
15
16
17
18
19
20
21
22
23
24
25
26
CDC Week
2008/2009

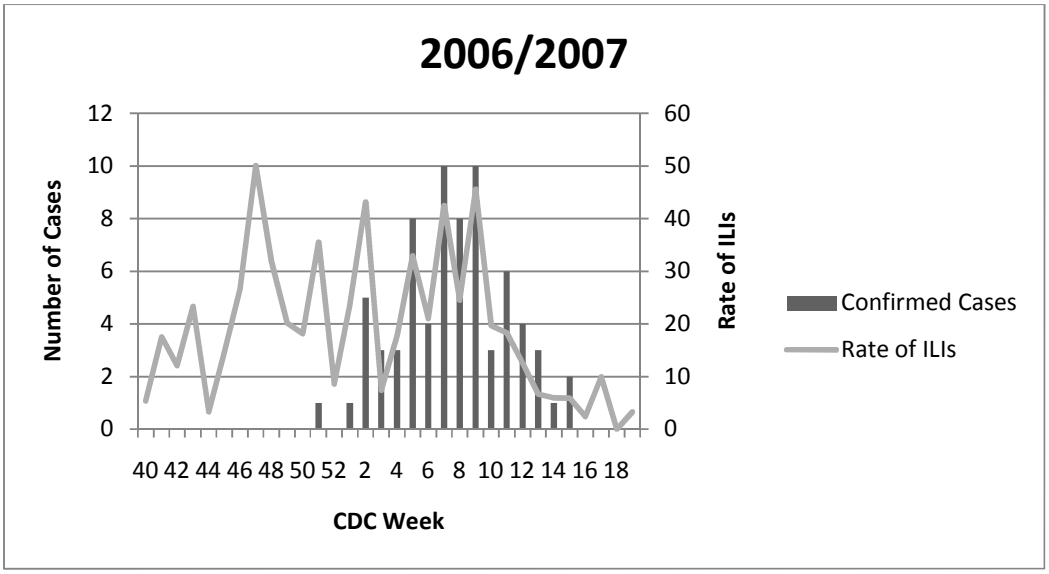
Epidemic Curve of ILI Rates for Study Seasons

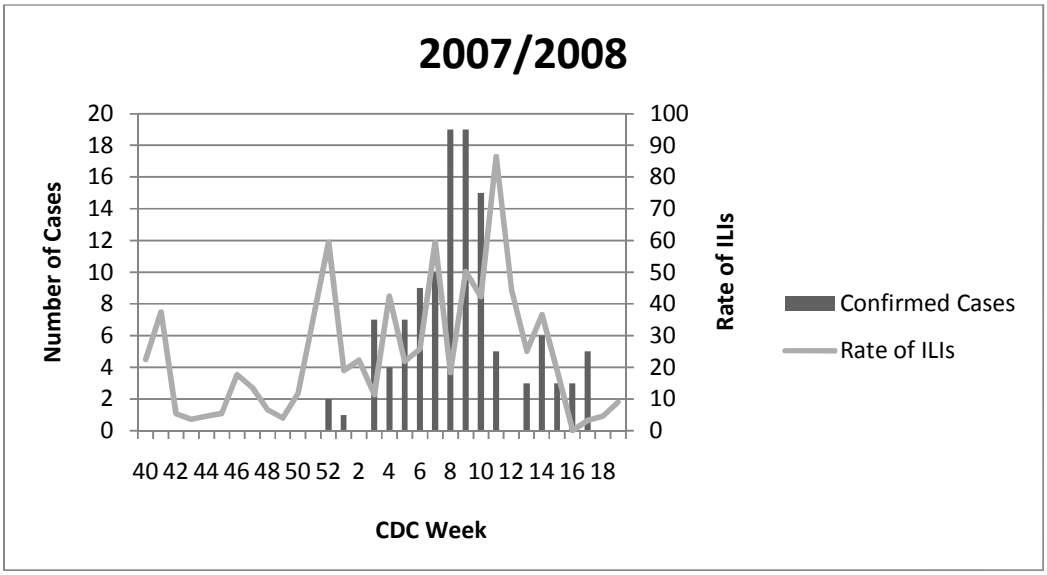


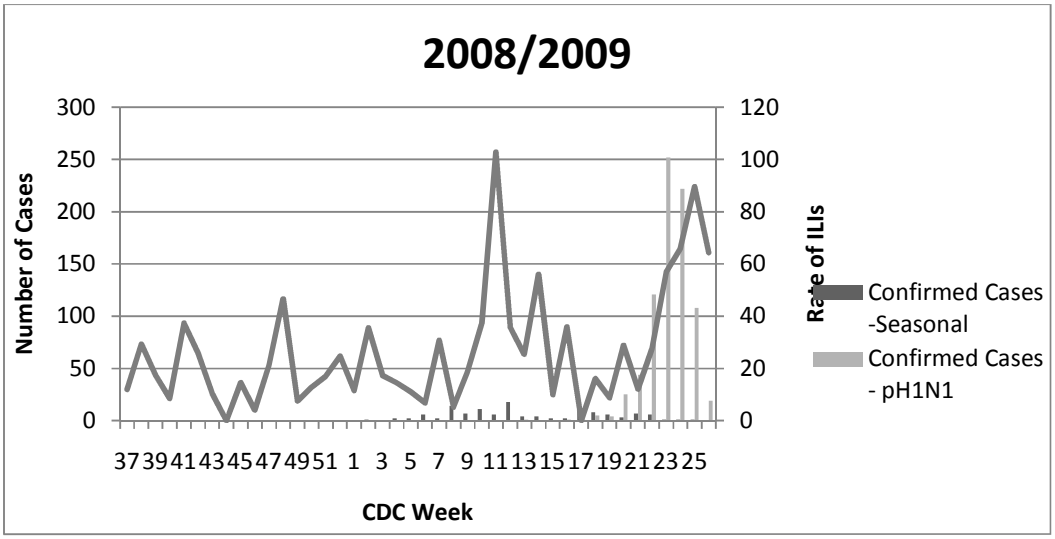
Epidemic Curves Comparing Confirmed Influenza Cases and ILI



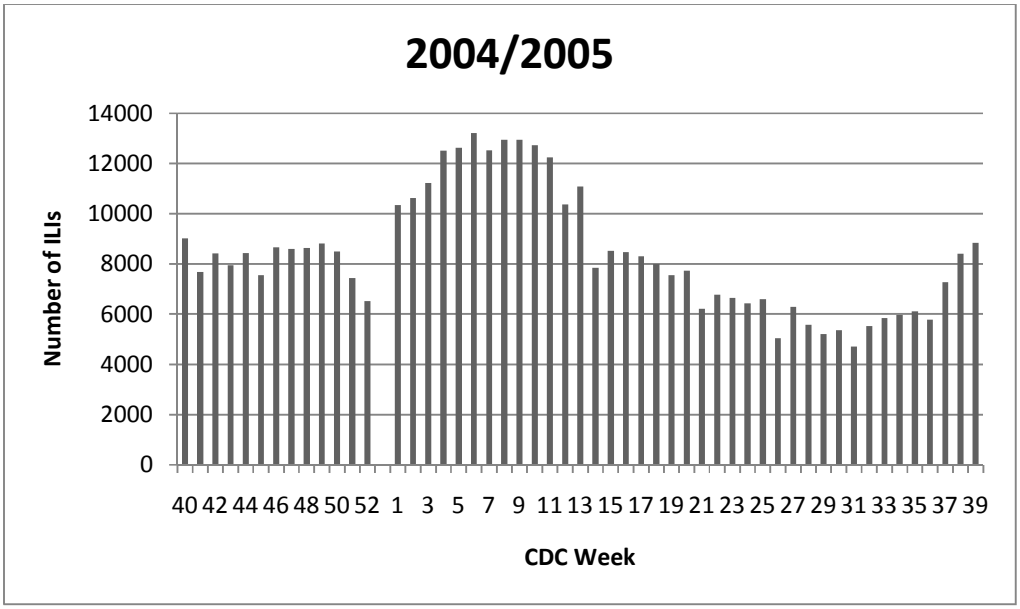

2005/2006
Number of Cases
Rate of ILIs
25
20
15
10
5
0
80
70
60
50
40
30
20
10
0
40 42 44 46 48 50 52 2 4 6 8 10 12 14 16 18
CDC Week
Confirmed Cases
Rate of ILIs

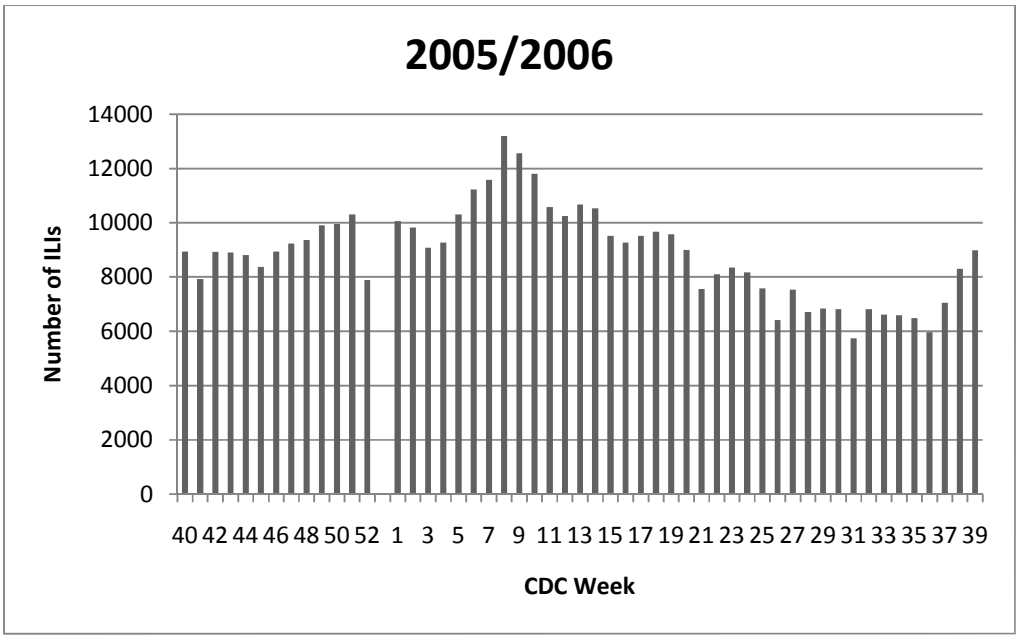

2006/2007
Number of Cases
Rate of ILIs
12
10
8
6
4
2
0
60
50
40
30
20
10
0
40 42 44 46 48 50 52 2 4 6 8 10 12 14 16 18
CDC Week
Confirmed Cases
Rate of ILIs

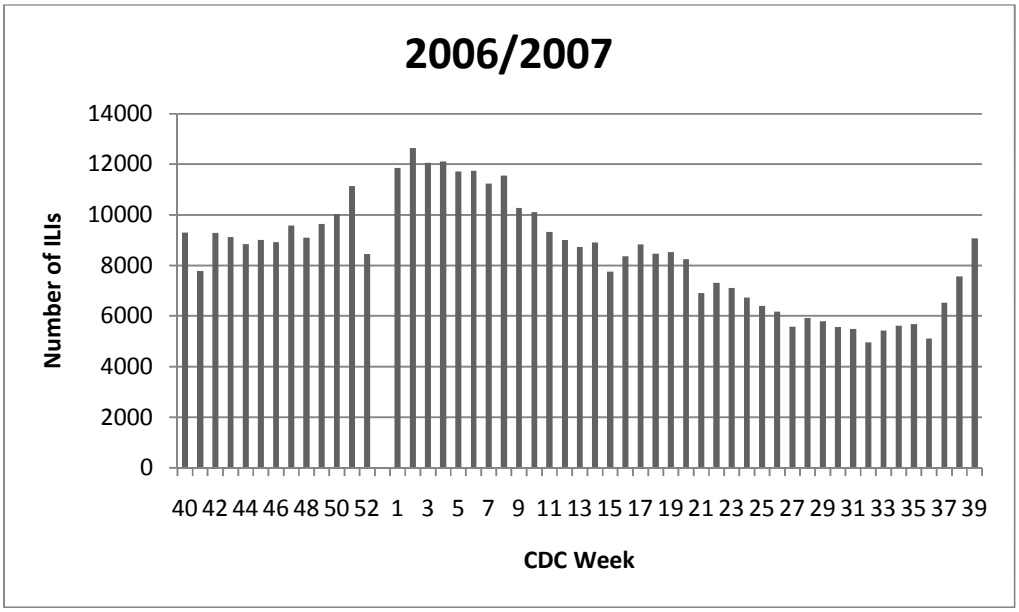

2007/2008
Number of Cases
Rate of ILIs
CDC Week
Confirmed Cases
Rate of ILIs
0 2 4 6 8 10 12 14 16 18 20
0 10 20 30 40 50 60 70 80 90 100
40 42 44 46 48 50 52 2 4 6 8 10 12 14 16 18

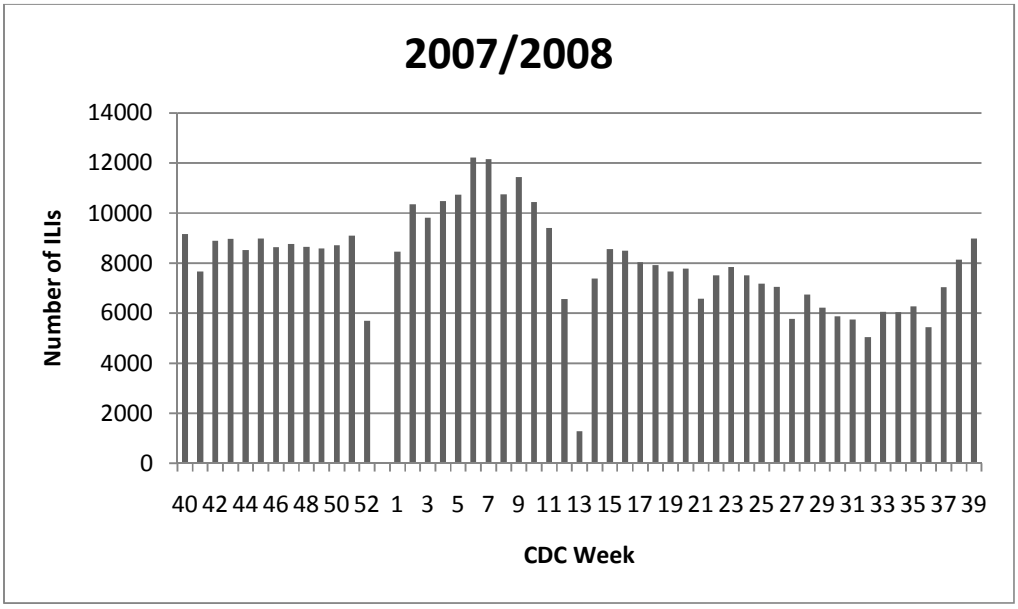

2008/2009
Number of Cases
Rate of ILIs
CDC Week
Confirmed Cases -Seasonal
Confirmed Cases - pH1N1
0 50 100 150 200 250 300
0 20 40 60 80 100 120
37 39 41 43 45 47 49 51 1 3 5 7 9 11 13 15 17 19 21 23 25

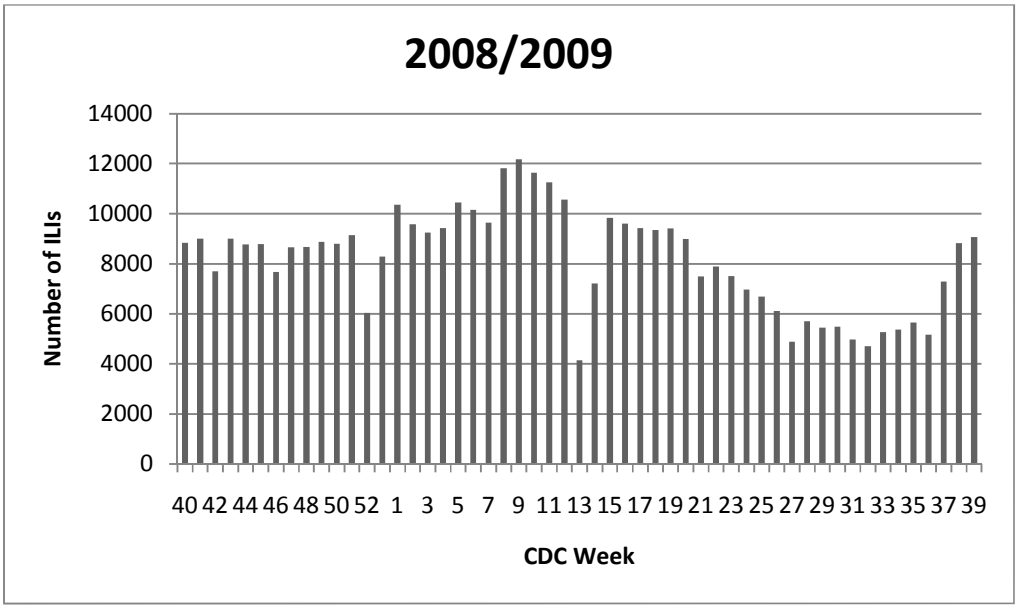
Epidemic Curves of ILI for Study Population






2006/2007
Number of ILIs
14000
12000
10000
8000
6000
4000
2000
0
40 42 44 46 48 50 52 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39
CDC Week


2007/2008
Number of ILIs
14000
12000
10000
8000
6000
4000
2000
0
40 42 44 46 48 50 52 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39
CDC Week


2008/2009
Number of ILIs
14000
12000
10000
8000
6000
4000
2000
0
40 42 44 46 48 50 52 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39
CDC Week

Appendix B – Manitoba Health Influenza Vaccine Eligibility Criterion

2005/2006 Manitoba Health Influenza Vaccine Criteria

Appendix A: Eligibility Criteria Influenza Vaccine

Persons recommended by Manitoba Health to receive vaccine and for whom vaccine is available at no cost:

a) ***People at high risk of influenza-related complications:***

- Adults and children with chronic cardiac or pulmonary disorders severe enough to require regular medical follow-up or hospital care (including bronchopulmonary dysplasia, cystic fibrosis and asthma)
- People of any age who are residents of personal care homes or other chronic care facilities.
- Adults ≥ 65 years of age.
- Adults and children with chronic conditions, such as diabetes mellitus and other metabolic diseases, cancer, immunodeficiency, immunosuppression (due to underlying disease and/or therapy), renal disease, anemia, hemoglobinopathy, inflammatory bowel disease, celiac disease, multiple sclerosis, rheumatoid arthritis, lupus, alcoholism, etc.
- **New this year -** Adults and children who have any condition that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration.
- Healthy children aged 6 – 23 months
- Children and adolescents (age 6 months to 18 years) with conditions treated for long periods with acetylsalicylic acid.
- People at high risk of influenza complications (as outlined above) embarking on travel to destinations where influenza is likely to be circulating.

b) ***People capable of transmitting influenza to those at high risk of influenza-related complications:***

- Healthcare and other service providers in facilities and community settings who are potentially capable of transmitting to those at high risk for influenza complications. This includes:
  - Employees in hospitals, physicians' offices, personal care homes, seniors' recreation centers, home care employees, and first responders (police officers, firefighters, ambulance workers).
  - Household contacts of people ≥ 65 years of age.
  - Health-care workers, volunteers and other personnel in settings where care is provided for those at high risk noted above.
  - Household contacts of people at high risk of influenza complications including family, relatives or friends of persons in chronic care institutions who visit frequently.
- Household contacts (adults and children) of people at high risk of influenza complications. This group includes;
  - Household contacts children < 6 months of age, (who are at high risk of complications from influenza but for whom there is currently no licensed vaccine)
  - Household contacts of children 6 to 23 months whether or not they have been immunized.
  - Pregnant women in their third trimester expected to deliver during influenza season (as they will become household contacts of their newborn)
- Those providing regular child care to children aged 0 to 23 months, whether in or out of the home.

4

2006/2007 Manitoba Health Influenza Vaccine Criteria

Influenza Vaccine Eligibility Criteria

a) People at high risk of complications from influenza:

- Anyone 65 years of age or over
- Healthy children six to 23 months of age
- Residents of personal care homes and other chronic care facilities
- Persons of any age with chronic heart or lung disease
- Anyone with cancer, anemia or a weakened immune system due to disease or medication
- Persons with other chronic conditions such as diabetes, kidney disease, inflammatory bowel disease, celiac disease, rheumatoid arthritis, lupus, alcoholism and multiple sclerosis may also benefit
- Anyone with a condition that reduces ability to breathe or increases risk of choking. Such conditions may include spinal cord injury, seizure disorders, mental disability, nervous system and muscular disorders
- Children on long-term aspirin therapy

b) People capable of spreading influenza to those at high risk should also receive an annual flu shot:

- Household contacts of those at risk, such as small children up to 23 months of age; seniors aged 65 years and older; and individuals with a weakened immune system due to disease or medication
- Anyone providing child care to infants up to 23 months of age, in or out of the home
- Pregnant women in their third trimester if they are expected to deliver during flu season (October-March)
- Health care workers, because they may unknowingly spread the flu to their patients
- Other staff in settings where care is provided for those at high risk, such as personal care home staff and volunteers who work with seniors
- First responders (police officers, firefighters, ambulance workers)

Pneumococcal Polysaccharide Vaccine (23 Valent) Eligibility Criteria

a) Adults ≥ 65 years of age

b) All residents of personal care homes and chronic care facilities

c) Anyone over age two at high risk of complications with:

- chronic heart disease (ex: congestive heart failure and cardiomyopathies)
- chronic lung disease: includes COPD and emphysema (excludes asthma)
- cirrhosis or alcoholism
- chronic renal disease or nephrotic syndrome
- diabetes mellitus
- asplenia or splenic dysfunction (ex: sickle cell disease, lupus, thalassaemia)
- chronic cerebrospinal fluid leak
- immunosuppressive disease or treatment (ex: HIV infection, Hodgkin's disease, lymphoma, multiple myeloma, organ transplantation, immunosuppressive chemotherapy, long-term systemic corticosteroids)
- congenital immune deficiencies: specifically IgG/IgG subclass and IgM deficiencies, Severe Combined Immunodeficiency Disorder (SCID) (Note: people with granulocyte and complement disorders are not at risk)
- persons receiving cochlear implants

Questions?

Contact Jill Chambers, Immunization Program Specialist, CDC Unit, Public Health Branch, call (204) 788-6330 or e-mail: **jchambers@gov.mb.ca**

2007/2008 Manitoba Health Influenza Vaccine Criteria

Influenza Vaccine Eligibility Criteria

a) **People at high risk of complications from influenza:**
   - Anyone 65 years of age or over
   - Healthy children six to 23 months of age
   - Residents of personal care homes and other chronic care facilities
   - Persons of any age with chronic heart or lung disease
   - Anyone with cancer, anemia or a weakened immune system due to disease or medication
   - Persons with other chronic conditions such as diabetes, kidney disease, inflammatory bowel disease, celiac disease, rheumatoid arthritis, lupus, alcoholism and multiple sclerosis may also benefit
   - Anyone with a condition that reduces ability to breathe or increases the risk of choking; such conditions may include spinal cord injury, seizure disorders, mental disability, nervous system and muscular disorders
   - Children on long-term aspirin therapy
   - All pregnant women, regardless of trimester or delivery date (National Advisory Committee on Immunization, July 2007)

b) **People capable of spreading influenza to those at high risk who should receive an annual flu shot:**
   - Health care workers, in facilities and community settings, because they may unknowingly spread the flu to their patients
   - Household contacts of those at risk, such as small children up to 23 months of age; seniors aged 65 years and older; and individuals with a weakened immune system due to disease or medication
   - Anyone providing child care to infants up to 23 months of age, in or out of the home
   - Other staff in settings where care is provided for those at high risk, such as personal care home staff and volunteers who work with seniors
   - First responders (police officers, firefighters, ambulance workers)

Pneumococcal Polysaccharide Vaccine (23 Valent) Eligibility Criteria

a) Adults 65 years of age and older

b) All residents of personal care homes and chronic care facilities

c) Anyone over age two at high risk of complications with:
   - chronic heart disease (ex: congestive heart failure and cardiomyopathies)
   - chronic lung disease
   - cirrhosis or alcoholism
   - chronic renal disease or nephrotic syndrome
   - diabetes mellitus
   - asplenia or splenic dysfunction (ex: sickle cell disease, lupus, thalassaemia)
   - chronic cerebrospinal fluid leak
   - immunosuppressive disease or treatment (ex: HIV infection, Hodgkin's disease, lymphoma, multiple myeloma, organ transplantation, immunosuppressive chemotherapy, long-term systemic corticosteroids)
   - congenital immune deficiencies, specifically IgG/IgG subclass and IgM deficiencies, Severe Combined Immunodeficiency Disorder (SCID) (Note: people with granulocyte and complement disorders are not at risk)
   - persons receiving cochlear implants

Questions?

Contact the CDC Unit, Public Health Branch at (204) 788-6737 or by e-mail: Gloria.Watkins@gov.mb.ca

2008/2009 Manitoba Health Influenza Vaccine Criteria

Influenza Vaccine Eligibility Criteria (for provision of vaccine at no charge)

a) People at high risk of complications from influenza:
   - Anyone 65 years of age or over
   - Healthy children 6 to 23 months of age
   - Residents of personal care homes and other chronic care facilities
   - Persons of any age with chronic heart or lung disease
   - Anyone with cancer, anemia or a weakened immune system due to disease or medication
   - Persons with other chronic conditions such as diabetes, kidney disease, inflammatory bowel disease, celiac disease, rheumatoid arthritis, lupus, alcoholism and multiple sclerosis may also benefit
   - Anyone with a condition that reduces ability to breathe or increases risk of choking. Such conditions may include spinal cord injury, seizure disorders, cognitive dysfunction (mental disability), nervous system and muscular disorders
   - Children on long-term aspirin therapy
   - All pregnant women, regardless of trimester or delivery date

b) People capable of spreading influenza to those at high risk of influenza complications:
   - Health care workers, in facilities and community settings, because they may unknowingly spread the flu to their patients
   - Household contacts of those at risk, such as small children up to 23 months of age; seniors aged 65 years and older; and individuals with a weakened immune system due to disease or treatment
   - Anyone providing child care to infants up to 23 months of age, in or out of the home
   - Other staff in settings where care is provided for those at high risk, such as personal care home staff, volunteers who work with seniors and child care workers
   - First responders (police officers, firefighters, ambulance workers)
   - Household contacts of pregnant women

Pneumococcal Polysaccharide Vaccine (23 Valent) Eligibility Criteria (for provision of vaccine at no charge):

a) Adults ≥ 65 years of age

b) All residents of personal care homes and chronic care facilities

c) Anyone over age two at high risk of complications with:
   - chronic heart disease (ex: congestive heart failure and cardiomyopathies)
   - chronic lung disease
   - cirrhosis or alcoholism
   - chronic renal disease or nephrotic syndrome
   - diabetes mellitus
   - asplenia or splenic dysfunction (ex: sickle cell disease, lupus, thalassaemia)
   - chronic cerebrospinal fluid leak
   - immunosuppressive disease or treatment (ex: HIV infection, Hodgkin's disease, lymphoma, multiple myeloma, organ transplantation, immunosuppressive chemotherapy, long-term systemic corticosteroids)
   - congenital immune deficiencies: specifically IgG/IgG subclass and IgM deficiencies, Severe Combined Immunodeficiency Disorder (SCID) (Note: people with granulocyte and complement disorders are not at risk)
   - persons receiving cochlear implants

Questions?

Call the CDC Branch, Public Health Division, Manitoba Health and Healthy Living at (204) 788-6737 or e-mail: Gloria.Watkins@gov.mb.ca

Appendix C – Copy of Manitoba Centre for Health Policy Data Usage Agreement

An Agreement Respecting Access to Manitoba Health Information at the Manitoba Centre for Health Policy (University of Manitoba) for Research Being Conducted by University Researchers Within The Secure Data Environment of MCHP.

THIS AGREEMENT dated as of the 12 day of July, 2010 (the "Effective Date").

BETWEEN:

THE GOVERNMENT OF MANITOBA,
represented by the Minister of Health

(hereinafter referred to as "Manitoba")

- and -

THE UNIVERSITY OF MANITOBA,
MANITOBA CENTRE FOR HEALTH POLICY

(hereinafter referred to as the "University")

WHEREAS:

A. This constitutes an agreement of the conditions under which anonymized electronic data from Manitoba will be disclosed to the University in accordance with the provisions stated in *The Personal Health Information Act* (Manitoba), *The Freedom of Information and Protection of Privacy Act* (Manitoba) and all other applicable Federal and Provincial legislative acts governing the use of this data;

B. This constitutes a research agreement pursuant to the Information Sharing and Protection of Privacy Agreement between the University and Manitoba which became effective January 1, 2007;

C. Andrea Rush-Sirski, an academic staff member of the University in the Faculty of Medicine (hereinafter referred to as the "Principal Investigator") has certain expertise in Community Health Sciences;

D. The Principal Investigator has requested access to information owned by Manitoba and held by the University in the Manitoba Population Health Research Data Repository housed at the Manitoba Centre for Health Policy. The Principal Investigator needs to access this information to conduct a proposed Research Project;

E. This Agreement shall apply to access for the Principal Investigator or University researcher to conduct research within the Centre;

F. The Principal Investigator has obtained ethical approval for the Research Project from the University's Health Research Ethics Committee or Research Ethics Committee;

G. The Health Information Privacy Committee has approved the Principal Investigator's access to the information for the Research Project described in subsection 2.01 of this Agreement, in accordance with the provisions of section 24 of *The Personal Health Information Act* (the "Act"), subject to the University entering into this Agreement;

MANITOBA AND THE UNIVERSITY AGREE AS FOLLOWS:

SECTION 1.00 – DEFINITIONS AND INTERPRETATION

1.01 In this Agreement:

(a) "Aggregate Level Data" means information not at the level of an individual person. It may include summary statistics or categorical descriptors. Aggregate information does not include identifying information or potentially identifying information;

(b) "Centre" means the Manitoba Centre for Health Policy, a research unit established by the University in the Department of Community Health Sciences at the University of Manitoba;

(c) "Data Repository" means the Population Health Research Data Repository, a comprehensive population-wide health research database of De-identified Individual Level Information developed by the Centre over the last twenty-five (25) years, primarily from De-identified Individual Level Information provided by Manitoba Health;

(d) "De-identified Individual Level Information" means information about an individual that has been modified or from which identifying or potentially identifying information has been removed in a way that minimizes the likelihood that an individual's identity can be determined by any reasonably foreseeable method. Methods of de-identifying information can include scrambling or encrypting identifying or potentially identifying information;

(e) "Health Information Privacy Committee" or "HIPC" means the Health Information Privacy Committee established under section 59(1) of the Act;

(f) "Information" means the project specific individual level data including any information which may inadvertently be identifying or potentially identifying, as detailed in Schedules "A" or "B";

(g) "Personal Health Information" has the meaning given to this term in the Act and includes any information about an individual's health or health care history, provision of health care to the individual or payment for health care provided to the individual which, alone or in combination with other information, could potentially identify an individual;

(h) "Personal Information" has the meaning given to this term in *The Freedom of Information and Protection of Privacy Act*, and includes any information about an

identifiable individual which, alone or in combination with other information, could potentially identify an individual. Personal Information includes Personal Health Information;

(i) "Research Project" means "Using Spatial Epidemiology As A Tool To Better Understand Influenza-Like Illnesses: Lessons For Pandemic Preparedness".

1.02 The requirements and obligations in this Agreement respecting protection of Information by the University apply to all Information received by the University from Manitoba in whatever manner, form or medium and apply whether the Information was provided or received before or after the signing of this Agreement.

SECTION 2.00 - RESEARCH PROJECT

2.01 The University has requested access to Information for the Research Project described in the HIPC submission. The HIPC Submission is attached hereto as Schedule "A" and the Final Approval Letter(s) are attached as Schedule "B".

2.02 The University acknowledges that much of the information in the Data Repository is information about the health of individuals and would, if it were not De-Identified, constitute Personal Health Information. The University acknowledges the sensitivity of Personal Health Information and the necessity for this Agreement and the approval of HIPC in order to conduct the Research Project.

2.03 The University acknowledges that the Research Project described in Schedule "A" complies with all current policies and guidelines of the Centre, including the Centre's Private Sector Guidelines, as applicable.

SECTION 3.00 - ACCESS TO INFORMATION BY THE UNIVERSITY

3.01 The University will give access only to the minimum amount of Information (herein termed "Approved Information") necessary to conduct the Research Project. The Approved Information is limited to only that information which has been described in Schedule "A" and approved by the Health Information Privacy Committee in Schedule "B".

3.02 Subject to the terms and conditions of this Agreement, the University may have access to the Approved Information in the following form and manner:

(a) access the Approved Information through a computer terminal on the premises of the Centre in the Centre's secure data environment; and

(b) access with a user ID and a password provided by the Centre that will permit access to the Approved Information.

3.03 The University agrees and acknowledges that Manitoba owns all title to, and rights and interest in, any Information that the Principal Investigator accesses including copyright, intellectual property and other proprietary rights.

SECTION 4.00 - USE OF INFORMATION BY THE UNIVERSITY

4.01 The University may analyze and manipulate the Approved Information described in subsection 3.01 for the purpose of carrying out the Research Project and may produce Aggregate Level Data that may be printed, placed on a disc or otherwise transmitted outside the Centre's secure data environment.

SECTION 5.00 - OBLIGATIONS OF THE UNIVERSITY RESPECTING USE AND DISCLOSURE OF INFORMATION

5.01 The University represents and warrants that:

(a) the University shall keep the Information secure and in strict confidence;

(b) only Approved Information shall be accessed in accordance with subsections 3.01 and 3.02;

(c) the Approved Information shall be accessed and used only by the Principal Investigator's project specific team within the Centre;

(d) Approved Information will be accessed and used solely for the research purpose as described in subsection 2.01 of this Agreement and for no other purpose; and

(e) the University shall not permit the Information to be accessed or used for any purpose other than the research purpose as described in subsection 2.01 of this Agreement.

5.02 The University shall ensure that no Information will be used, disclosed, published or made available in any manner, form or medium (including, without limitation, in any research results, research paper or publication respecting the research and in any related presentation).

5.03 The University shall not:

(a) make copies or reproductions of the Information, in whole or in part, in any manner, form or medium, except in accordance with the terms and conditions of the Data Sharing Agreement;

(b) use the Information received from Manitoba, or any part of it, to develop, establish, expand, modify or maintain a database or other collection of information in machine-readable form or any other form, except as may be required for the research purpose described in subsection 2.01;

(c) sell or disclose the Information, or any part of the Information, for consideration or exchange the Information for any goods, services or benefit; or

(d) give the Information to any individual, corporation, business, agency, organization or entity for any purpose, including (but not limited to) for solicitation for charitable or other purposes;

and shall not permit any of these activities to take place.

SECTION 6.00 - REPORTS, MONITORING AND ENFORCEMENT

6.01 The University shall, via the Centre, immediately upon becoming aware of any of the following, notify Manitoba in writing of:

(a) any use of, access to or disclosure of the Information which is not authorized by this Agreement; and

(b) any breach of any term or condition of this Agreement;

with full details of the unauthorized use, access or disclosure or of the breach. The University shall immediately take all reasonable steps to prevent the recurrence of any unauthorized use, access or disclosure of the Information, or to remedy the breach, and shall notify Manitoba and the Centre in writing of the steps taken.

6.02 Manitoba and its representatives may carry out such inspections or investigations respecting the use and handling of the Information by the University as Manitoba considers necessary to ensure that the University is complying with the terms and conditions of this Agreement and that the Information is adequately protected. The University shall cooperate fully in any such inspection or investigation. If any inspection or investigation identifies deficiencies in the information practices of the University, the University shall take steps to correct the deficiencies immediately to the satisfaction of Manitoba.

6.03 Where Manitoba is reasonably of the opinion that the University:

(a) has used, permitted access to or disclosed the Information in a manner which is not authorized under this Agreement, or is about to do so;

(b) has not adequately protected the Information from risks such as unauthorized use, access or disclosure; or

(c) has failed to comply with, or is about to fail to comply with, any of its obligations or undertakings under this Agreement;

Manitoba may terminate this Agreement at any time by providing notice in writing, effective immediately or as of the date set out in the notice.

6.04 On termination of this Agreement for any reason, the University shall immediately refrain from any further use of, access to, disclosure of and activities and transactions involving the Information.

6.05 In addition to its rights under subsection 6.03 of this Agreement or any other rights Manitoba may have under this Agreement, or the Information Sharing and Protection of Privacy Agreement, or under any enactment, or otherwise, where Manitoba is of the opinion that the University has used, permitted access to or disclosed the Information in a manner which is not authorized under this Agreement, or is about to do so, Manitoba may report these activities to any one or more of the following for appropriate action:

(a) the Centre;

(b) the University;

(c) the Health Information Privacy Committee;

(d) the institutional research review committee which approved the research;

(e) any professional association or disciplinary or other body with jurisdiction to discipline, supervise or regulate the University; and

(f) the institution from which funds were provided to conduct the research study.

6.06 Nothing in this Agreement shall prevent the following uses of any information, data (including data in tabular form), analyses and research acquired, developed or discovered by the University upon the completion of an approved project:

(a) publication in learned journals or other printed media;

(b) oral presentation or the distribution of printed materials at educational or professional conferences or seminars; or

(c) publication of a thesis by a graduate student;

provided that:

(d) such publication or use shall not disclose any Confidential Information;

(e) such publication or use shall not disclose any Personal Information or Personal Health Information (as these terms are defined in *The Freedom of Information and Protection of Privacy Act*), respecting a third party in a way that could reasonably be expected to identify the third party, without the consent of that third party.

6.07 As used herein "Confidential Information" means any and all information disclosed by Manitoba to the University which is identified in writing as confidential by Manitoba. Confidential Information shall not include information that is:

(a) already known to the University prior to receipt from Manitoba as evidenced by written records; or

(b) generally available to the public or becomes publicly known through no fault of the University; or

(c) received by the University from a third party who had a legal right to disclose without restriction; or

(d) developed by the University independently of and without reference to the Confidential Information as evidenced by written records.

Notwithstanding any other provision of this Agreement, disclosure of Confidential Information shall not be precluded if such disclosure is in response to a valid court order of any governmental agency, court or other quasi-judicial or regulatory body of competent jurisdiction, provided

however that the University, as promptly as reasonably possible, gives notice to Manitoba of the requirement to disclose.

6.08 The University and any employees of the University or persons involved with research shall treat as confidential, and shall not disclose or permit to be disclosed to any person, corporation or organization, any Confidential Information provided by Manitoba under this Agreement without prior consent of Manitoba, whose consent shall not be unreasonably withheld.

6.09 Regarding the use of this project specific Approved Information, the University shall provide to Manitoba:

(a) at least thirty (30) calendar days prior notice of every intended publication in learned journals or thesis presentation;

(b) at least ten (10) calendar days prior notice of every poster or oral presentation where such presentation material will be physically released or distributed, or posted on a website.

6.10 In the case of publications in learned journals or thesis presentations, Manitoba will review same for confidentiality and proper representation of Manitoba and Information and advise the Principal Investigator of any required changes within two (2) weeks of receipt. Manitoba has no right of censorship of the research content including any research findings or recommendations.

6.11 In the case of poster or oral presentations as described in clause 6.09(b), Manitoba will review same for confidentiality and proper representation of Manitoba and Information and advise the Principal Investigator of any required changes within three (3) working days of receipt. Manitoba has no right of censorship of the research content including any research findings or recommendations.

6.12 The University will acknowledge Manitoba in any report or paper that is based upon the Information and it shall be stated in such publication that the results and conclusions are those of the authors and no official endorsement by Manitoba is intended or should be inferred.

SECTION 7.00 - GENERAL

7.01 While this Agreement is in effect, and at all times thereafter, the University shall be solely responsible for and shall save harmless and indemnify Manitoba, and its ministers, officers, employees and agents, from and against all claims, liabilities and demands of any kind with respect to any injury to persons (including, without limitation, death), damage to or loss of property, economic loss or incidental or consequential damages or infringement of rights (including, without limitation, privacy rights) caused by, or arising directly or indirectly from:

(a) the provision of any Information by Manitoba to the University;

(b) the breach of any term or condition of this Agreement by the University or an employee or agent of the University; and

(c) any omission or wrongful or negligent act of the University or of an employee or agent of the University.

7.02 This Agreement is subject to any restrictions or limitation in, or provisions of, any statute, regulation or other legislation enacted or amended by the Province of Manitoba or the Government of Canada and in effect from time to time which may affect any term or provision of this Agreement.

7.03 The obligations and undertakings of the University under this Agreement shall survive the completion or termination of the Research Project.

7.04 The University shall not assign or transfer this Agreement or any of the rights or obligations under this Agreement.

7.05 The University shall not enter into any contract, sub-contract or arrangement with a third party involving use of or access to, or disclosure of, the Information for any purpose.

7.06 This Agreement shall be interpreted, performed and enforced in accordance with the laws of the Province of Manitoba.

7.07 Any notice or other communication given or required under this Agreement shall be in writing and shall be delivered personally or sent by registered mail, postage prepaid, or by way of facsimile transmission, as follows:

To Manitoba:

Manitoba Health, Health Information Management
Room 4036 – 300 Carlton Street
Winnipeg, MB R3B 3M9
Attention: Executive Director

To the University:

Manitoba Centre for Health Policy
4th Floor Brodie Centre
Winnipeg, MB R3E 3P5
Attention: Director

With a copy to:

The University of Manitoba
Room 260 Brodie Centre, 727 McDermot Avenue
Winnipeg, MB R3E 3P5
Attention: Dean, Faculty of Medicine

7.08 Any notice given in accordance with subsection 7.07 of this Agreement shall be deemed to have been received by the addressee:

(a) on the day delivered, if delivered personally;

(b) on the third business day after the date of mailing, if sent by prepaid registered mail; or

(c) on the date of the transmission shown on the sender's confirmation of transmission notice, if sent by facsimile transmission.

If mail service is disrupted by labour controversy, notice shall be delivered personally or by facsimile transmission.

This Agreement has been executed on behalf of Manitoba and by the University on the dates noted below.

SIGNED IN THE PRESENCE OF:

Witness

FOR THE GOVERNMENT OF MANITOBA

Per: Deborah M Dyck
Executive Director, Health Information Management

DATE: JUL 2 0 2010

FOR THE UNIVERSITY OF MANITOBA

Witness

Per:
Dean, Faculty of Medicine

DATE: July 27, 2010

READ AND UNDERSTOOD

PRINCIPAL INVESTIGATOR - SUPERVISOR

Witness

Name: Dr. S. Michelle Driedger

DATE: July 12, 2010

READ AND UNDERSTOOD

PRINCIPAL INVESTIGATOR - STUDENT

Witness

Name: Andrea Rush-Sirski

DATE: July 12, 2010

Appendix D – Health Information Privacy Committee Approval

Manitoba
Health
Health Information Privacy Committee
4043 – 300 Carlton Street
Winnipeg MB R3B 3M9
Phone: (204) 786-7204
FAX: (204) 944-1911

June 11, 2010

Andrea Rush-Sirski
University of Manitoba
Community Health Sciences
S113 – 750 Bannatyne Ave.
Winnipeg, MB R3E 0W3

File No. 2010/2011 – 06

Dear Ms. Rush-Sirski:

Re: Using Spatial Epidemiology as a Tool to Better Understand Influenza-like Illness: Lessons for Pandemic Preparedness

Thank you for submitting the requested documentation and providing clarification for the above project. The Health Information Privacy Committee has now ***approved*** your request for data for this project. Additionally, please note that the Database Support Files housed at the Manitoba Centre for Health Policy (MCHP) are derived from the Manitoba Health (MH) Population Registry and therefore, considered MH data.

Any significant changes to the proposed study design should be reported to the Chair/HIPC for consideration in advance of their implementation. Also, please be reminded that *all manuscripts and presentation materials resulting from this study must be submitted for review at least 30 days prior to being submitted for publication or presentation.*

Please note that a Researcher Agreement will need to be completed before work on this project can commence. This will be initiated by MCHP. If you have any questions or concerns, please do not hesitate to contact Lisa LaBine, Committee Coordinator at 786-7204.

Yours truly,

R. Walker, MD FRCPC
Chair, Health Information Privacy Committee

Please quote the file number on all correspondence

cc. D. Malazdrewicz

Appendix E – Copy of Ethics Approval

P126 - 770 Bannatyne Avenue
Winnipeg, Manitoba
Canada R3E 0W3
Tel: (204) 789-3255
Fax: (204) 789-3414

UNIVERSITY OF MANITOBA | BANNATYNE CAMPUS
Research Ethics Boards

APPROVAL FORM

Principal Investigator: Ms. A. Rush-Sirski
Supervisor: Dr. M. Driedger

Ethics Reference Number: H2010:110
Date of Approval: March 27, 2012
Date of Expiry: March 27, 2013

Protocol Title: Using Spatial Epidemiology as a Tool to Better Understand Influenza-like Illnesses: Lessons for Pandemic Preparedness (H2009:201)

The following is/are approved for use:

- **Annual Approval**

The above was approved by Dr. John Arnett, Ph.D., C. Psych., Chair, Health Research Ethics Board, Bannatyne Campus, University of Manitoba on behalf of the committee per your submission dated March 7, 2012. The Research Ethics Board is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement, and the applicable laws and regulations of Manitoba. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the *Food and Drug Regulations of Canada*.

This approval is valid until the expiry date only. A study status report must be submitted annually and must accompany your request for re-approval. Any significant changes of the protocol and informed consent form should be reported to the Chair for consideration in advance of implementation of such changes. The REB must be notified regarding discontinuation or study closure.

This approval is for the ethics of human use only. For the logistics of performing the study, approval must be sought from the relevant institution, if required.

Sincerely yours,

John Arnett, PhD., C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Ethics Reference Number on all correspondence.
Inquiries should be directed to the REB Secretary **Telephone**: (204) 789-3255 / Fax: (204) 789-3414

www.umanitoba.ca/medicine/ethics