# Epidemiological Characteristics and Ecological Investigation of the 2009 Influenza Pandemic

by

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## ABSTRACT

Influenza pandemic occurs when a novel influenza virus subtype for which humans do not have sufficient immunity emerges and spreads quickly from person-to-person worldwide. Influenza pandemics result in serious consequences on human health and economy. In April 2009, the World Health Organization (WHO) announced the emergence of a novel swine-origin influenza virus, A(H1N1)pdm09. This was the first influenza pandemic since 1968. The virus embraced a novel combination of gene segments that had not been reported in the past. By April 2010, 428 related deaths were reported in Canada, including 72 from Alberta. The objective of thesis was to investigate the epidemiologic characteristics of influenza A(H1N1)pdm09 using the data from the Provincial Laboratory for Public Health (ProvLab) and linking it with relevant databases from other sources including those from Statistics Canada and Alberta Health. In Alberta, influenza A(H1N1)pdm09 resulted in 6,327 laboratory-confirmed cases. Of these, 48% were males and 83.6% occurred in summer. The highest and lowest rates were reported in the Central and South Zones of Alberta, respectively. Females were at 12% increased risk compared to males. Individuals with asthma were at 6% increased risk of A(H1N1)pdm09 than others without asthma. Individuals aged between 15 and 34 years had 4-fold increased risk compared to those aged 65 years and older. A switch in the vulnerability to A(H1N1)pdm09 occurred in females between 15 to 64 years of age to have

higher risk than males. Associations between influenza A(H1N1)pdm09 virus and other factors (geography, age, sex, and asthma) were found significant in an ecological analysis which is consistent with findings from other studies. Consideration of these factors can result in a more effective public health preparedness and responses to future influenza pandemics.

## PREFACE

This thesis is an original work by Abdel-Halim Hafez Elamy. The research project, of which this thesis is a part, received research ethics approval from the Health Research Ethics Board (HREB), University of Alberta (Pro00016132_REN4) and operational approval from the Northern Alberta Clinical Trials and Research Center (NACTRC), Alberta Health Services ("A Computational Epidemiology Approach for Characterizing and Modeling the Spread of Pandemic Infectious Diseases" ).

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*[Disclaimer: The research analysis and results of this thesis are based on the data obtained from the Provincial Laboratory for Public Health (ProvLab) of Alberta, Government of Alberta, and Statistics Canada and the opinions expressed herein do not represent the views of these organizations.]*

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| **A(H1N1)pdm09** | Influenza A(H1N1) |
| **AGN** | Acute Glomerulonephritis |
| **AKI** | Acute Kidney Injury |
| **BAL** | Broncho-Alveolar Lavage |
| **BMI** | Body-Mass Index |
| **CCHS** | Canadian Community Health Survey |
| **CDC** | Centres for Disease Control |
| **CF** | Cystic Fibrosis |

| | |
|---|---|
| **COPD** | Chronic Obstructive Pulmonary Disease |
| **DIC** | Disseminated Intravascular Coagulation |
| **FSA** | Forward Sortation Area |
| **GENMOD** | Generalized Linear Model Procedure |
| **HA** | Hemagglutinin |
| **hMPV** | Human metapneumo virus |
| **HREB** | Health Research Ethics Board |
| **HR1** | Chinook Regional Health Authority |
| **HR2** | Palliser Health Region |
| **HR3** | Calgary Health Region |
| **HR4** | David Thompson Regional Health Authority |
| **HR5** | East Central Health |
| **HR6** | Capital Health |
| **HR7** | Aspen Regional Health Authority |
| **HR8** | Peace Country Health |
| **HR9** | Northern Lights Health Region |
| **HUS** | Hemolytic Uremic Syndrome |
| **ICU** | Intensive Care Unit |
| **M/F** | Male-Female ratio |
| **NA** | Neuraminidase |
| **NACTRC** | Northern Alberta Clinical Trials and Research Centre |
| **OR** | Odds Ratio |
| **ProvLab** | Provincial Laboratory for Public Health of Alberta |
| **RR** | Relative Risk |
| **RSV** | Respiratory Syncytial Virus |
| **$R_0$** | Basic Reproductive Number |
| **SARS** | Severe acute respiratory syndrome |
| **ATN** | Acute Tubulointerstitial Nephritis |
| **WHO** | World Health Organization |

## LIST OF SYMBOLS

| | |
|---|---|
| $\mu$ | Population mean |
| $\chi^2$ | Chi square test statistic |
| ***CI*** | Confidence interval |
| ***df*** | Degrees of freedom |
| ***DV*** | Deviance |
| $E[Y_i]$ | Estimated value of mean |
| ***sd*** | Sample standard deviation |
| ***SE*** | Standard error |
| ***Var*** | Variance |

CHAPTER ONE

# INTRODUCTION

Infections caused by Influenza viruses (mainly influenza A and B) are major causes of morbidity and mortality that can affect people of all ages and population groups. Influenza viruses primarily attack the upper respiratory tract – the nose, ears, throat and sometimes the lungs [1]. Influenza viruses circulate everywhere in the world and transmit easily from person to person by aerosols of respiratory secretions caused by sneezing, coughing, and talking. The attack rates of influenza are higher among young children [2]. In addition, morbidity and mortality have shown to be higher among young children and the elderly. Moreover, influenza infection is associated with more severe illness and complications in individuals with underlying pulmonary conditions, as well as to individuals who are immune-compromised [3,4].

In spite of the biological causes and differences, influenza pandemics are distinguished from seasonal influenza epidemics by their wider geographical coverage, excess severity, and rapid increase in the infection and mortality rate [5,6].

Influenza virus has eight gene segments that encode proteins, out of which two segments– the hemagglutinin (HA) and neuraminidase (NA)– are important mediators of immunogenicity and pathogenicity [7]. Influenza virus changes its HA and NA protein structures through a process known as "genetic drift" by mutation of nucleic acid sequence that produces modified strains against which humans have less defensive antibodies.

Influenza viruses can be classified into three main types: A, B and C. Type C influenza viruses can affect humans and animals but occur much less

frequently than types A and B and rarely cause illness in humans. Type B influenza viruses infect humans almost exclusively and have not been associated with any pandemics in the past. Only influenza A and B viruses are included in seasonal influenza vaccination plans [8].

Type A influenza virus, which can infect both humans and non-humans (e.g., pigs, birds, horses, ferrets, seals and other animals) uncommonly acquires the so called "antigenic shift", a process through which a totally different set of antigens is produced by reassortment of genetic segments when 2 influenza viruses infected the same cells and result in a new virus of interspecies origin. Such virus can infect a large proportion of the population, resulting in pandemics. These viruses are composed of combinations of 16 different HA subtypes and 9 different NA subtype. They are associated with the most severe illnesses and deaths in humans, such as the 1918 pandemic (known as Spanish Flu pandemic), which were originated by a strain of H1N1 influenza virus [9-12,13]. Nowadays, influenza viruses A(H1N1) and A(H3N2) subtypes are the most common subtypes of influenza-A circulating among humans.

Influenza symptoms include abrupt onset of high fever, dry cough, headache, muscle and joint pain, sore throat, runny nose, and feeling of fatigue. The incubation period of influenza (i.e., the time from infection to illness) varies between one to four days, with an average duration of two days [9]. Most people recover from mild symptoms within a week, but influenza infection can be associated with severe illness or death, especially in people at high risk.

Complications from influenza include primary influenza viral pneumonia, bacterial pneumonia, exacerbation of chronic pulmonary conditions, sinusitis, otitis media (infection or inflammation of the middle ear), febrile seizures, encephalitis, myositis (inflammation of your skeletal muscles) and death [13 14]. Outbreaks of influenza are often associated with excess morbidity and mortality, and characterized by higher than normal rates of pneumonia and influenza-related hospitalizations and deaths [13-15].

**History of influenza pandemics**

The World Health Organization (WHO) defines a pandemic influenza virus as a new influenza virus that spreads easily from person to person around the world and infects people of all ages [16]. The last century witnessed three worldwide pandemic influenza outbreaks that occurred in 1918, 1957, and 1968. The latter two pandemics occurred in the era of modern virology. However, the three pandemics differed from each other with respect to disease severity, epidemiology and etiologic agents, with major changes or shifts in the HA antigen [17].

The 1918-1919 pandemic was the most devastating flu pandemic recorded in human history, during which about one third of the world population was infected, resulting in more than 50 million deaths worldwide [18] over the course of three waves that occurred throughout 1918 and 1919 [12]. In the United States alone, about 675,000 people (out of 105 million population in 1918) were killed from the disease [19]. For unknown reasons, mortality rates were highest among adults aged 20 to 50 years old [20].

The 1957-1958 Asian flu pandemic emerged in China in February 1957 due to a new influenza virus A of the H2N2 subtype. The virus subsequently spread to more than 20 countries by June 1957 [21,22], resulting in about two million deaths worldwide. The largest proportion of the deaths was reported among younger adults aged less than 65 years [23].

The 1968-1969 Hong Kong flu pandemic was first detected in Hong Kong, caused by an influenza virus A of the H3N2 subtype. In comparison with other pandemics, the Hong Kong flu resulted in less severity and low mortality rate [17]. It resulted in about one million deaths worldwide, of which about 34,000 were from the US. Most deaths occurred among elderly people aged 65 years and older.

**The 2009 influenza A(H1N1)pdm09**

In April 2009, the WHO announced the emergence of a novel influenza A virus of the subtype H1N1 had not circulated previously in humans [16]. The observed virus composed of genes from swine, avian, and human influenza A viruses, but it is believed that it has emerged from a reassortment event involving a swine virus over the last couple of decades [24]. Influenza A(H1N1)pdm09 virus can infect humans, pigs, horses, seals and birds. Pigs are usually accountable for carrying and transmitting the virus because they can serve as hosts for productive infections of both avian and human [25].

Influenza A(H1N1)pdm09 virus initially emerged in Mexico before it moved to the United States; in a few weeks, it spread from person to person around the world, resulting in the first influenza pandemic of the 21$^{st}$ century.

On June 11, 2009, the WHO declared that the influenza A(H1N1)pdm09 outbreak had met the criteria to be considered as a pandemic. Accordingly, WHO raised the pandemic alert to the highest level, which indicated that a global pandemic was underway [12]. By the end of 2009, more than 200 countries and overseas territories or communities had reported hundreds and thousands of influenza A(H1N1)pdm09 cases and over 11,500 deaths [16,24]. In June 2010, deaths increased to 18,172 [26,27]. In August 2010, the pandemic was officially declared over [27].

In Canada, the first confirmed case of influenza A(H1N1)pdm09 was reported on April 23, 2009 in Quebec. Two months later, the virus has spread to all provinces and territories. By April 2010, 428 pandemic-related deaths were reported out of 33,509 laboratory-confirmed cases of influenza A(H1N1)pdm09 among Canadians [28]. In the early days of the 2009 pandemic, it was expected that each person in Canada would require 2 doses of vaccine. For securing the health of Canadians, the government spent $1.5 billion on its response to the 2009 pandemic, which includes about $400 millions spent on vaccine [29]. Only

41% of residents aged 12 years and older were vaccinated and the surplus of vaccine was donated to the WHO and Mexico [30-32].

In Alberta, 72 deaths linked to either a confirmed or probable influenza A(H1N1)pdm09 were reported between April 1, 2009 and September 30, 2010. Of these, 64 deaths were attributed directly to infections with influenza A(H1N1)pdm09 [33,34] resulting in a crude mortality rate of 1.77 deaths per 100,000 population [34].

The 2009 influenza virus was identified as H1N1, having the same H and N types of the strain that killed millions of people between 1918 and 1919. However, there is an important genetic difference between the two virus strains. *Padlan* [35] indicates that a significant structural change has occurred to the receptor-binding site of the hemagglutinin (HA), which is responsible for binding and entry of the virus into the target cells. In comparison to the 1918 H1N1 pandemic, the 2009 pandemic was much milder than expected. *Padlan* claims that this may be attributable to the "existence of effective immunity in the host due to previous exposure to or vaccination against other (H1N1) strains, the lessened ability of the 2009 (H1N1) virus to bind to target cells or to replicate in them, and a diminished secretion of molecules that could cause further complications like pneumonia, etc."

In August 2010, the WHO announced the commencement of a post-pandemic stage of influenza A(H1N1)pdm09 [36]. The virus continued to circulate as a seasonal virus strain in most countries, including Canada [36,37]. The activity of A(H1N1)pdm09 continued to increase in Canada since late-November 2013, consistent with the usual timing of the seasonal influenza epidemic. Up to the present time of winter 2014, influenza A(H1N1)pdm09 has emerged as a predominant virus [37]. Between August 2013 and March 2014, a total number of 10,253 laboratory-confirmed cases of influenza were reported in Canada [40,41]. Of these, 3,393 cases (33.1%) occurred in Alberta.

Several terminologies have been used in the literature to refer to the 2009 pandemic influenza. This can potentially create confusion among researchers and the general public when differentiating the virus from the old influenza A(H1N1) viruses circulated in humans before the 2009 H1N1 pandemic. To help minimizing this confusion, the nomenclature A(H1N1)pdm09, which was standardized by WHO in September 2011 [38], has been used in this thesis.

**Research objectives**

Many researchers have studied the epidemiology of influenza pandemics in different populations [9-12, 29, 39] However, a study that handles individual-level of confirmed laboratory data spanning multiple geographic regions with ecological differences and comorbidity with other respiratory viruses and risk factors has not been conducted in the Province of Alberta. The purpose of this thesis is to explore the epidemiological characteristics of influenza A(H1N1)pdm09.

The methodology used in this thesis is based on linking the influenza A(H1N1)pdm09 data obtained from the Provincial Laboratory of Alberta for the period between April 2009 and January 2010 with other databases from various sources; for instance, census data, Canadian community health survey (CCHS) data, and Alberta population data. The details on the linked data are given in Chapter 3. This linkage was made to determine the variation in influenza A(H1N1)pdm09 rates between the health regions of Alberta and the association of influenza A(H1N1)pdm09 rates with the demographic and socioeconomic characteristics and comorbidities in the Province of Alberta.

The research objectives of this thesis are:

(1) to describe the general epidemiologic features of influenza A(H1N1)pdm09 during the 2009 pandemic

(2) to demonstrate the distribution of influenza A(H1N1)pdm09 over the health regions and zones of Alberta during the 2009 pandemic

(3) to compare the distributions and patterns of the common respiratory viruses before and during the 2009 pandemic

(4) to carry out an ecological study that investigates the impact of environment, demography, and health risk factors on the incidence of influenza A(H1N1)pdm09

**Thesis Structure**

This chapter is followed by a literature review of studies related to the 2009 influenza pandemic (Chapter 2). In Chapter 3, a description of the methods and materials used in this thesis are presented; this chapter is followed by the results obtained from descriptive and statistical analysis (Chapter 4). Finally, a summary of the thesis contributions, discussion, and conclusions are given in Chapter 5.

# CHAPTER TWO

# LITERATURE REVIEW

## 2.1 Background

### 2.1.1 Seasonal influenza

Seasonal influenza is a respiratory infection of the airways and lungs, caused by influenza viruses and spread easily from person to person causing annual epidemics that peak in winter in Canada. Annual influenza epidemics can affect people in all age groups. Most people can recover from the illness within a week to ten days, but some are at greater risk of severe complications that can lead to death. The highest risk of complications occurs among children younger than two years old, elderly age 65 or older [42], and people with certain medical conditions– such as weakened immune systems [42-45], and diseases of the heart [43,46], lung [42, 43], kidney [42, 43,141], or liver [42, 43,250]. Most deaths related to seasonal influenza (about 90%) occur among people aged 65 years and older [47]. Worldwide, the annual seasonal influenza epidemics cause about three to five million of severe illnesses, and about 250,000 to 500,000 deaths [48]. In the USA, these epidemics cause illness in about 5–20% of the population, leading to approximately 300,000 influenza-related hospital admissions and 36,000 influenza-related deaths every year [47,49,50]. In Canada, between 10 and 20% of the population becomes infected with seasonal influenza every year. Approximately 20,000 influenza-related hospital admissions and 4,000 deaths occur among Canadians every year [51].

### 2.1.2 Influenza pandemics

An influenza pandemic occurs when a virus that has not previously circulated – and to which most people do not have immunity – emerges and transmits among humans. However, there are many debates on the WHO's definition and declaration of influenza pandemic, which provide interesting

premises for epidemiological studies to better define the disease burden and consequences [53] .

Influenza pandemics have been observed for several hundred years throughout history. Three global pandemics were observed and documented in the last century – 1918 A(H1N1) Spanish flu, 1957 A(H2N2) Asian flu, and 1968 A(H3N2) Hong Kong flu [52,54]. Viruses of these influenza pandemics arose either entirely or partially from non-human reservoirs [55]. All three pandemics varied in their morbidity, mortality, and dynamical patterns. The 1918 influenza pandemic was the most devastating epidemic with multiple outbreaks in many geographic regions worldwide and over 50 million deaths, including about 50,000 Canadians [56-58] and 675,000 Americans. In contrast to seasonal influenza, influenza pandemics occur rarely, circulate and cause large outbreaks at any time of year.

Influenza A(H1N1)pdm09 virus first emerged in Mexico in April 2009 and rapidly spread to the United States and Canada, and subsequently worldwide, resulting in large numbers of laboratory-confirmed cases and deaths. As a consequence, the World Health Organization (WHO) declared a pandemic alert phase 6 on June 11, 2009, warning that the first influenza pandemic of the 21st century had begun [59-61].

Influenza A(H1N1)pdm09 is a novel combination of viral genes that are closely related to swine-lineage influenza [52,55,62]. The virus embraces six genes from triple-reassortant North American swine virus lineages and two genes from Eurasian swine virus lineages [55].

## 2.2 Spread of Influenza A(H1N1)pdm09 pandemic

As of February 21, 2010, more than 213 countries and overseas territories or communities have reported thousands of laboratory confirmed cases of pandemic influenza A(H1N1)pdm09, along with more than 18,500 deaths [63].

The actual numbers of influenza A(H1N1)pdm09 incidence and mortality cases remain unknown for many reasons. The virological surveillance of influenza A(H1N1)pdm09 in most countries was restricted to patients attending hospitals. Moreover, the majority of influenza A(H1N1)pdm09 cases were diagnosed clinically and were not laboratory-confirmed [64]. Nevertheless, the total number of cases of influenza A(H1N1)pdm09 worldwide can be estimated in the range of tens of millions of cases [64].

## 2.3 Transmission of influenza A(H1N1)pdm09

There are ongoing debates on the mode of transmission of seasonal and pandemic influenza. Theoretically influenza A(H1N1)pdm09 can be transmitted in 3 ways: (1) droplet spray exposure (when infectious droplets are projected onto mucous membranes), (2) airborne exposure (via inhalation of infectious airborne particles), and (3) contact exposure (when a contaminated hand is exposed to facial membranes). The intensity of infection resulting from each of these modes is unknown, but most probably depends on site temperature and humidity [65].

## 2.4 Characteristics of influenza A(H1N1)pdm09 virus

A number of measures are typically used to characterize influenza A(H1N1)pdm09 pandemic and to describe its transmissibility among humans. The following are some important measures that have been found widely reported in the scientific literature.

### 2.4.1 Reproductive Number

A commonly used measure that characterizes pandemic and assesses the strength of infection in a susceptible population is the basic reproductive number, $R_0$. This measure represents the average number of new infected cases caused by a particular infectious individual over the lifetime of that infected

individual. $R_0$ values of less than 1 implies that the infection will fail to carry on transmission within the population, while $R_0$ values that are greater than 1 imply that the infection will keep on spreading, in the absence of control measures [66]. Observing the basic reproductive number ($R_0$) can be of great importance to policy makers in order to propose the appropriate public health interventions during outbreak. The $R_0$ for influenza A(H1N1)pdm09 were estimated in the range between 1.3 and 1.8 and were relatively consistent [67]. A Canadian study of 3,152 laboratory-confirmed cases from Ontario reported a $R_0$ of 1.31 (95% CI: 1.25–1.38) [68]. Yang et al. [69] conducted another study on the basis of reported case clusters in the United States and found the $R_0$ to range from 1.3 to 1.7. Balcan et al. [70] conducted a study that employed a global structured meta-population model integrating mobility and transportation data worldwide on 3,362 sub-populations from 220 countries. In this study, $R_0$ was 1.75 (95% CI: 1.64–1.88) for influenza A(H1N1)pdm09.

$R_0$ also depends on the various characteristics and activities of the population. Some studies claim that school-based outbreaks are responsible for high levels of infection among children [64, 71]. For instance, within a school in the USA the intensity of infection during the influenza A(H1N1)pdm09 outbreak was very high with $R_0$ values between 1.8 and 3.2, indicating that, a child can spread the virus to 2.5 children on average [64]. The worst values of $R_0$ were estimated in the range of 1.8 to 2.4 during the global 1918–1919 influenza A (H1N1) pandemic and the virus was considered highly transmissible and aggressive [72-74].

### 2.4.2 Incubation period

The incubation period of an infectious disease is defined as the time interval from infection with a microorganism to symptom onset [75]. This period is widely reported because of its importance in infectious disease surveillance and control where the time of symptom onset is used as a unique indicator of the

time of infection [76]. In clinical practice, the incubation period is useful for determining the causes and sources of infection, as well as for developing strategies for management of exposed individuals and treatment plans. For example, the incubation period distribution permits the determination of the length of quarantine required for a potentially exposed individual during an outbreak of a newly emerged infectious disease [66]. Understanding the incubation period distribution can also enable statistical estimation of the time of exposure during a point source outbreak [77] as well as testing of hypothesis for investigating whether an outbreak has ended [78]. The mean incubation period of influenza A(H1N1)pdm09 was estimated to be approximately four days, with an average duration of symptoms of seven days [67,68].

### 2.4.3 Serial interval

The serial interval is defined as the time between the onset of a primary case to the onset of the secondary case caused by the primary case [79]. The serial interval is mainly used as a control measure in building transmission networks for contact tracing. This type of information is useful to assess the number of secondary transmissions over the course of an epidemic [80] in addition to evaluating the individual variations in transmission of infection [81]. The serial interval for influenza A(H1N1)pdm09 was approximately identified in the range between 3 and 4.5 days [67].

### 2.4.4 Mortality

A good indicator of the severity of pandemics is the mortality (number and rate of deaths). The WHO has acknowledged that the official laboratory-confirmed reports underestimated the actual number of influenza deaths. This was related to the specimens not being collected from people who died from influenza. In addition, influenza virus might not be detectable at the time of death [63]. A study [82] that adopted an improved modeling approach reported

a global estimate of deaths between 151,700 and 575,400 that is about 20 times higher than the number of laboratory-confirmed deaths reported to WHO during the first 16 months of the influenza A(H1N1)pdm09 outbreak. The largest proportion of related deaths (more than 50% of all influenza A(H1N1)pdm09 deaths, worldwide) occurred in countries in Southeast Asia and Africa, where access to treatment and vaccination was limited, besides improper nutrition and poor quality of health care services [83-90]. Many challenges including the lack of influenza A(H1N1)pdm09 data in many countries, the variations in the level and timing of influenza virus circulation across countries, had to be overcome for the authors to generate these global estimates. The Centers for Disease Control (CDC) estimated over 12,400 A(H1N1)pdm09 influenza-related deaths as occurred from April 2009 to April 2010 in the United States alone [52,91] versus 428 deaths that were reported in Canada [28].

## 2.5 Risk groups and risk factors of influenza A(H1N1)pdm09

The influenza A(H1N1)pdm09 virus showed severe infections and fatal consequences in patients with comorbidities such as asthma, in obese and pregnant patients, as well as some young and healthy who have little or no immunity, and some who succumbed to an overwhelming immune response [58, 92,93]. Many underlying conditions that are associated with complications from seasonal influenza also are risk factors for complications from A(H1N1)pdm09 virus infections [94]. Nevertheless, about one quarter to one half of patients with influenza A(H1N1)pdm09 virus infection who were hospitalized or died had no reported coexisting medical conditions [94-99].

### 2.5.1 Age

An important feature of the A(H1N1)pdm09 virus is that it disproportionately affects children and young adults as compared to the older age groups [100]. The majority of illnesses caused by the virus were acute and self-limited, with the highest attack rates reported among children and young

adults [64,101]. One of the early studies in the USA showed that, although the age of influenza A(H1N1)pdm09 patients in the study ranged from three months to 81 years, 60% of the patients were 18 years of age or younger [64,102]. In most countries, including Canada, the USA, Chile, Japan and the UK, influenza A(H1N1)pdm09 caused greater disease burden on young individuals, with an estimated median age between 12 and 17 years [43]. Van Kerkhove et al. [44] conducted a retrospective study that utilized information on approximately 70,000 laboratory-confirmed influenza A(H1N1)pdm09 hospitalized patients, 9,700 patients admitted to intensive care units (ICUs), and 2,500 deaths reported between April 1, 2009 and January 1, 2010 from 19 countries or administrative regions (Canada, the United States, Mexico, the United Kingdom, France, Germany, Australia, China, Hong Kong SAR, Japan, Argentina, the Netherlands, New Zealand, Singapore, South Africa, Spain, Thailand, Chile, and Madagascar). The study aimed to compare and characterize the distribution of risk factors among influenza A(H1N1)pdm09 patients based on 3 levels of severity: hospitalizations, ICU admissions, and deaths. The authors concluded that the median age of patients increased with severity of disease. The highest risk of hospitalization was among young children under five years old and in children of ages 5 to 14 years with a relative risk (RR) of 3.3 and 3.2, respectively, compared to the general population. On the other hand, the highest risk of death was found among patients in the age groups 50–64 years and ≥ 65 years (RR = 1.5 and 1.6, respectively, compared to the general population). The authors have also found that the ratio of influenza A(H1N1)pdm09 deaths to hospitalizations increased with age and was the highest among elderly people who aged 65 years and older [103]. Compared with patients aged 10–19 years, Campbell et al. [112] found that those aged 20–64 years were significantly more likely to be admitted to ICU, and those aged 45 years or more were significantly more likely to die, even after adjustment for sex and underlying medical conditions.

The age distribution versus A(H1N1)pdm09 infection suggests partial immunity to the virus in the older population [43]. This hypothesis was supported by subsequent studies, which concluded that one-third of the elderly population over 60 years of age had cross-reacting antibodies to influenza A(H1N1)pdm09 that was identified by means of hemagglutination-inhibition test and neutralization tests [104,105].

### 2.5.2 Sex

The cellular differences between males and females (i.e., a female cell has two X chromosomes, while male cells have one X and one Y chromosomes) on the infectious disease process are not entirely understood. Nevertheless, it is known that the X chromosome governs many of the immune system responses [107]. The biological differences between male and female can influence the infectious disease process and can thus result in differences between males and females in terms of incidence rate, duration, disease severity and case fatality rates following the pandemic of an infectious disease. Moreover, the impact of sex and gender on infection is associated with age since both the cultural and biological factors can change considerably with age [107-109]. Worldwide, the incidence rates, disease burden, morbidity and mortality following exposure to influenza A(H1N1)pdm09 were different among males and females [107].

The assessment of male-female differences in reported incidences of influenza A(H1N1)pdm09 can be confounded by some factors. For instance, many studies do not disaggregate data by both sex and age. This may consequently contribute to masking sex differences among the age groups that are most likely to be exposed (e.g., children and young adults). Moreover, the profound differences in health seeking behaviors or healthcare access between males and females can mislead the incidence rates computed [110]. A survey conducted by WHO in 59 countries during the period between 2002 and 2004 revealed that adult women are more likely to seek healthcare in both higher and lower income countries [110]. In many countries, women represent more than

50% of the healthcare workforce. For instance, nurses, daycare workers, and young children teachers are mostly female [111], which can potentially lead to a gender-specific occupational risk of influenza infection [107]. Above all, pregnancy itself, which was identified as a risk factor for severe illness of influenza pandemic, occurs in women. Campbell et al. [112] conducted a study on all patients admitted to Canadian hospitals with laboratory-confirmed influenza A(H1N1)pdm09 reported to the Public Health Agency of Canada from April to September 2009. They concluded that the risk of admission to ICU was greater among females than among males.

### 2.5.3 Pregnancy

Pregnancy causes changes in hormone levels and immune functions, in addition to cardiopulmonary stresses and difficulty in treatment from respiratory diseases [113]. Along with these potentially disease-modifying pregnancy-associated factors, the presence of other comorbidities or risk factors can result in higher rates of severe illness, hospitalization, and adverse neonatal outcomes. These complications have been observed in pregnant women for both pandemic and seasonal influenza infections when compared to the general population or to age-matched non-pregnant women [114,115].

Although it is not easy to quantify precisely the degree of risk associated with pregnancy, pregnant women can be approximately four to five times more likely to develop severe disease, when compared to non-pregnant women [116-118].

Compared to non-pregnant women, pregnant women, especially those in the second or third trimester and women who are less than two weeks post-partum, have shown to have higher mortality rates [114,119] and severe illnesses [94,96,97,100,120] after influenza A(H1N1)pdm09 infection. Although pregnant women represent about 2% of the population, among patients with influenza A(H1N1)pdm09 virus infection, they accounted for 7 to 10% of hospitalized cases [94,96,100,121], 6 to 9% of ICU cases [94,97,98], and 6 to 10% of deaths [94,96,122].

Mosby et al. [123] conducted a systematic literature review that included a total number of 120 studies to investigate practices regarding influenza A(H1N1)pdm09 in pregnant women. They concluded that pregnancy was associated with increased risk of A(H1N1)pdm09 related hospitalizations and admissions to intensive care unit as well as death. Furthermore, WHO has also stated that both mother and baby experience increased risk when infected with either pandemic or seasonal influenza during pregnancy, and pregnant women should be vaccinated [124].

### 2.5.4 Ethnicity

The rates of severe influenza A(H1N1)pdm09 virus infection in disadvantaged groups, including Canadian, American, and Australian Aboriginals, were five to seven times higher than the rates in the non-Aboriginal groups. Crowding, alcoholism, smoking, presence of coexisting medical conditions, poor access to health care services and possibly unidentified genetic factors may be accountable for the increased risk of pandemic among these groups. [98,125]

### 2.5.5 Obesity

Worldwide, there were more than 1.4 billion overweight adults, more than 500 million obese adults, and 40 million overweight children (<5 years old) in 2011 [126]. Many studies indicated that obese adults have a greater risk of morbidity and mortality from infection with influenza A(H1N1)pdm09 virus [120, 127-131]. Moreover, the Centers for Disease Control and Prevention recognized obesity as an independent risk factor for influenza A(H1N1)pdm09 complications [132]. Furthermore, among patients with severe influenza A(H1N1)pdm09 virus infection, obese individuals with body-mass index (BMI) ≥35 and individuals with severe obesity (BMI≥40) were reported at five to 15 times higher rates than the rate in the general population [94,96-98,133].

Mertz et al. [134] conducted a large systematic review with meta-analysis to evaluate the risk factors for severe outcomes in patients with seasonal and pandemic influenza from a total number of 234 studies. Of these, 59 studies on obesity as a risk factor showed that obesity has increased the risk of death to about three times. Moreover, obesity was significantly associated with the need for admission to hospital and intensive care, as well as the need for ventilator support.

Kwong et al. [128] conducted a cohort study over 12 influenza seasons between 1996 and 2008 on 82,545 respondents aged 18–64 years from Ontario, Canada. The study aimed to examine the association between self-reported body mass index (BMI) and hospitalization for selected respiratory diseases, including influenza. The authors found that obesity (BMI ≥30) was independently associated with an increased risk of respiratory hospitalizations during seasonal influenza epidemics. In addition, the association between severe obesity (BMI ≥35) and respiratory hospitalizations was significantly higher in obese individuals than those without previously recognized risk factors. Other studies have revealed a high prevalence of obesity among individuals with complications of influenza A(H1N1)pdm09 infection [135-139].

### 2.5.6 Other risk factors

Diabetes, cardiovascular diseases, and abnormal immunologic status can also be accountable for increase in morbidity and mortality of influenza A(H1N1)pdm09 virus infections [112]. In the study conducted by Van Kerkhove et al. [44], the authors concluded that the proportion of influenza A(H1N1)pdm09 patients with one or more reported chronic conditions, including asthma, increased by 31.1% among hospitalized cases, 52.3% among ICU-admitted cases, and 61.8% in fatal influenza A(H1N1)pdm09 cases. Campbell et al [112] also concluded that lung disease, including asthma, was the most common underlying medical condition associated with increased risk of death from influenza A(H1N1)pdm09. Hanslik et al. [140] conducted a study on

patients diagnosed with influenza A(H1N1)2009 in France during the 2009 pandemic. They aimed to estimate the magnitude of several risk factors by comparing their prevalence among hospitalized severe cases to that in the general population. In addition to the significance of age, pregnancy and obesity as risk factors, the authors determined that heart failure and diabetes were risk factors for admission into intensive care unit (OR= 3.3, 95% CI: 2.6-4.1 and 2.8, 95% CI: 2.3-3.4, respectively). They also found that heart failure, obesity, and diabetes were significantly associated with death (OR=6.9, 95% CI: 4.9-9.8 and 3.5, 95% CI: 2.5-5.1, respectively).

Some uncommon risk factors have also been reported in the literature. For instance, renal complications of influenza A(H1N1)pdm09 can lead to deterioration of the patient's condition, including acute kidney injury (AKI) in critically ill patients, rhabdomyolysis, hemolytic uremic syndrome (HUS), acute glomerulonephritis (AGN), disseminated intravascular coagulation (DIC), Good pasture's syndrome, and acute tubulointerstitial nephritis (TIN) [141].

In summary, influenza pandemics are unpredictable but persistent events. Nonetheless, influenza pandemics cause negative impact and serious consequences to human health and economy. Influenza A(H1N1)pdm09 pandemic was the first one since the 1968 pandemic. The virus incorporated a unique combination of gene segments that had not been reported previously. The virus had a distinctive feature to have a higher disease burden among children aged 14 years old and younger. However, its severity and mortality was much higher among elderly people aged 65 years and older. The risk of severe outcome of influenza A(H1N1)pdm09 was significantly associated with the presence of one or more underlying medical condition or risk factor, including age, sex, obesity, pregnancy, asthma, immune disorders, Aboriginal status, and other chronic illnesses.

# CHAPTER THREE

# METHODS

## 3.1 Databases used in the thesis

This research was conducted based on information obtained from different sources as described in the sections below.

### 3.1.1 Laboratory data

This database contained the laboratory results of respiratory specimens submitted to the Provincial Laboratory for Public Health (ProvLab) of Alberta. The data were obtained based on the Operational Approval #11376 from the Health Research Ethics Board (HREB) of the Northern Alberta Clinical Trials and Research Center (NACTRC) attached in Appendix I. The data obtained were guided by the Health Information Act, and no identifying health information was provided. The ProvLab provides respiratory virus testing for the province of Alberta and the Northern Territories. The methods used to detect respiratory virus has changed overtime with different respiratory viruses being targeted [142,143]; Figure 3.1 illustrates these changes.

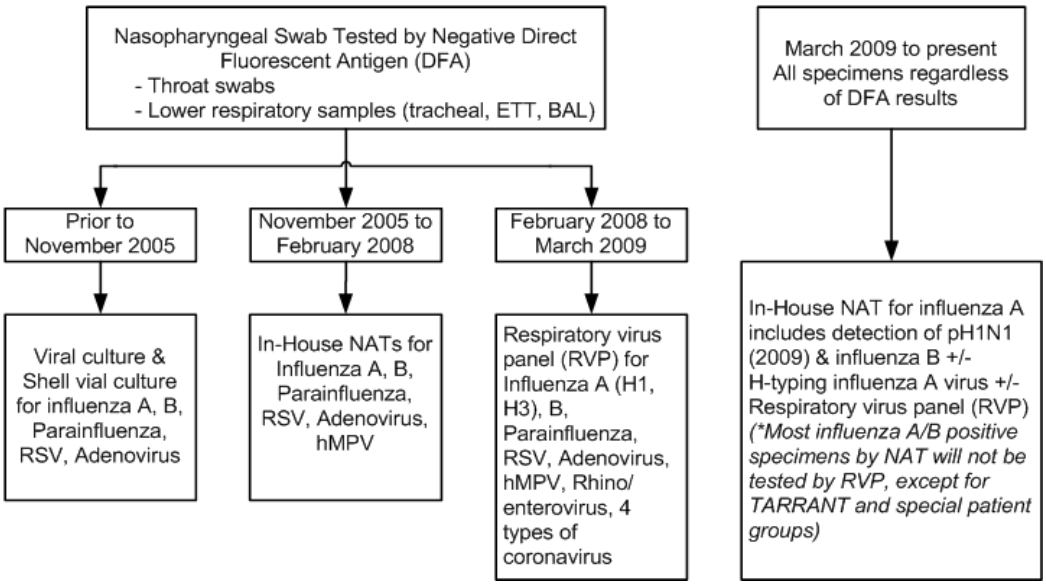


Figure 3.1: Changes in testing methods used in laboratory

The laboratory data included comprehensive information and results of specimens collected from Alberta residents between April 1, 2004 and January 31, 2010 that were tested for the following respiratory viruses: influenza virus A, influenza virus B, human metapneumovirus (hMPV), parainfluenza virus, respiratory syncytial virus (RSV), adenovirus, 4 types of coronavirus (229E, HKU1, NL63, and OC43), and rhino/enterovirus not differentiated.

The laboratory data also included demographic information of these patients (i.e., age, sex, city of residence, forward sortation area, and health region), date of specimen collection, date of receipt of specimen, type and source of specimen, and test results. In addition, anonymized data on the laboratory-confirmed influenza A(H1N1)pdm09 patients who were identified during the 2009 outbreak were included. The laboratory data contained 124,858 records of specimen information for 91,310 patients.

Rather than using specimens as a unit of analysis, patient-based information was used for analyzing and interpreting the laboratory data. This information was generated only for specimens with the most recent laboratory confirmed positive results. For instance, if a patient was tested positive for RSV in 2006 and in 2009, information on the 2009 specimen only will be included. On the other hand, specimens that were confirmed negative or were not tested for whatever reason have been excluded from the analysis. The term ‘case’ was used to refer to a ‘patient’. This has been made so as to adhere to the terms used in the relevant literature [144-147].

In total, 91,310 cases were identified in the laboratory data for individuals who submitted 124,858 specimens. Of these, 6,972 (7.6%) cases were non-Alberta individuals and excluded from the analysis. After excluding the non-Alberta individuals, 84,338 cases with 115,535 specimens were included in the analysis. Of these cases, 82.3% had one specimen only, 11.3% had two specimens, 3% had three specimens, and 3.4% had four or more specimens (Figure 3.2). As shown in Figure 3.3, the majority of specimens tested for

respiratory viruses were for children under 15 years old (46.5%), followed by adults aged 35-64 years (24%).

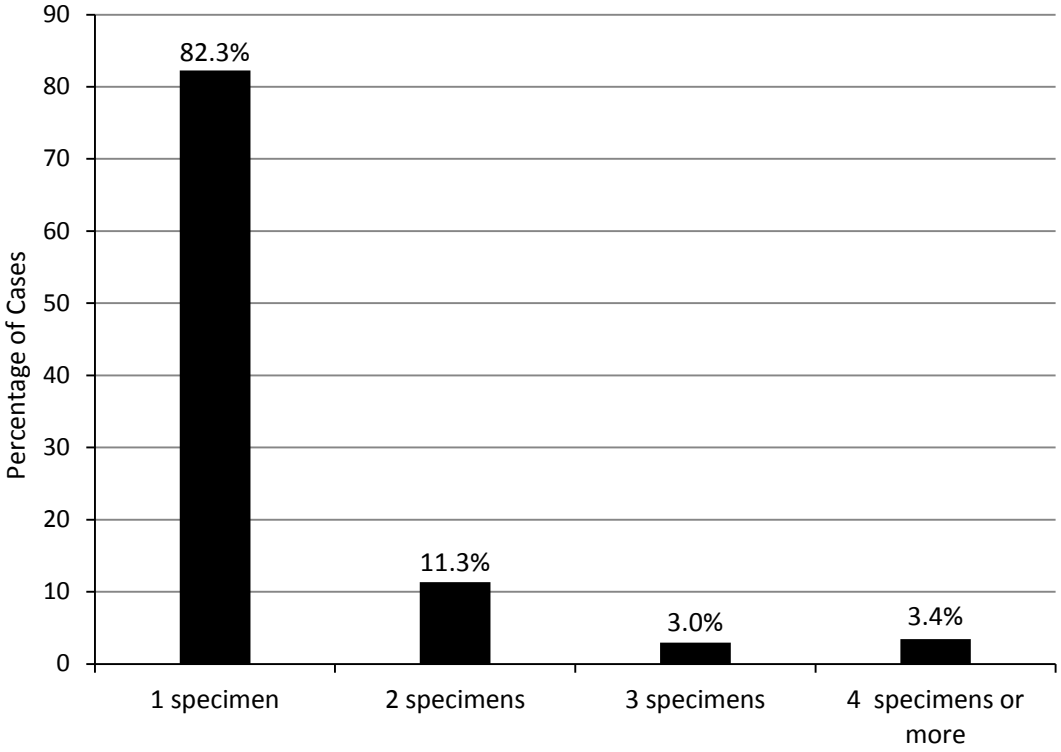


Figure 3.2: Percentage of cases with different number of specimens submitted to the laboratory from April 1, 2004 to January 31, 2010

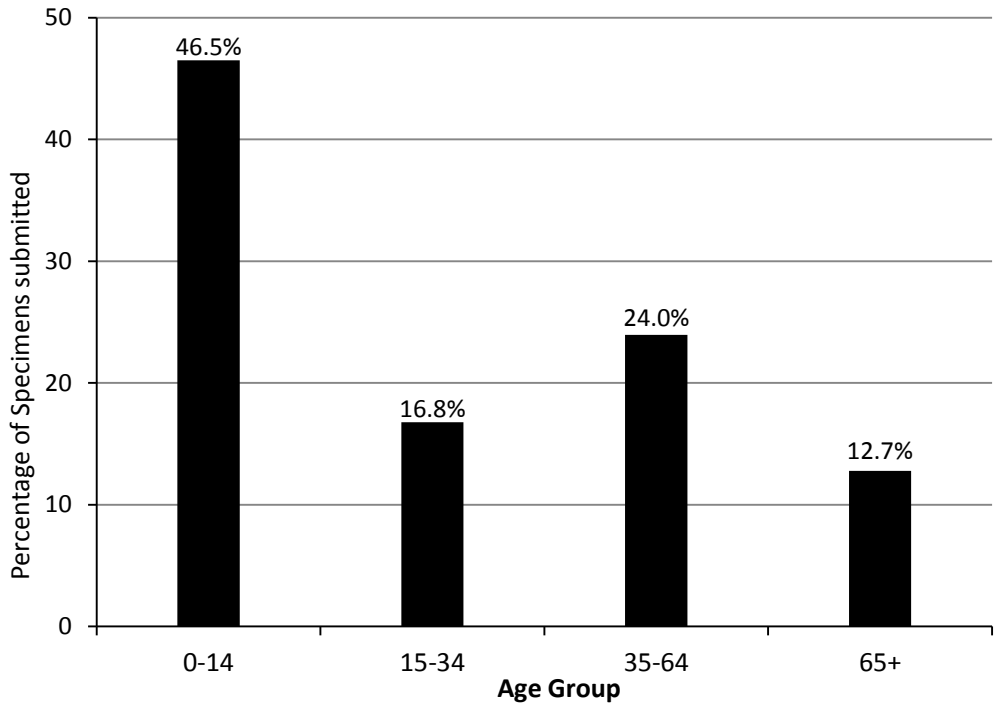


Figure 3.3: Proportions of specimens submitted to the laboratory by age group from April 1, 2004 to January 31, 2010

***Specimen sources*** - specimens collected from different sources by means of more than 300 descriptive terminologies were grouped into five main categories based on the method of collection. These categories are: aspirates, auger suction, autopsy, broncho-alveolar lavage (BAL), and others (e.g., nasopharyngeal, biopsy, blood, bronch wash, endotracheal, throat, and trachea). Of these categories, aspirates (e.g., auger suction aspirates, endotracheal aspirates, endotracheal tube aspirates, nasopharyngeal aspirates, and tracheal aspirates) were the most common tests applied to 97% of the collected specimens.

***Specimen types***- there were 14 types of specimens (swab, fluid, sputum, tissue, urine, blood, fluid cystic fibrosis (CF), swab cystic fibrosis, sputum cystic fibrosis, feces, brush, isolate, slide, and air). Figure 3.4 shows that swabs and fluid specimens were the most dominant types.

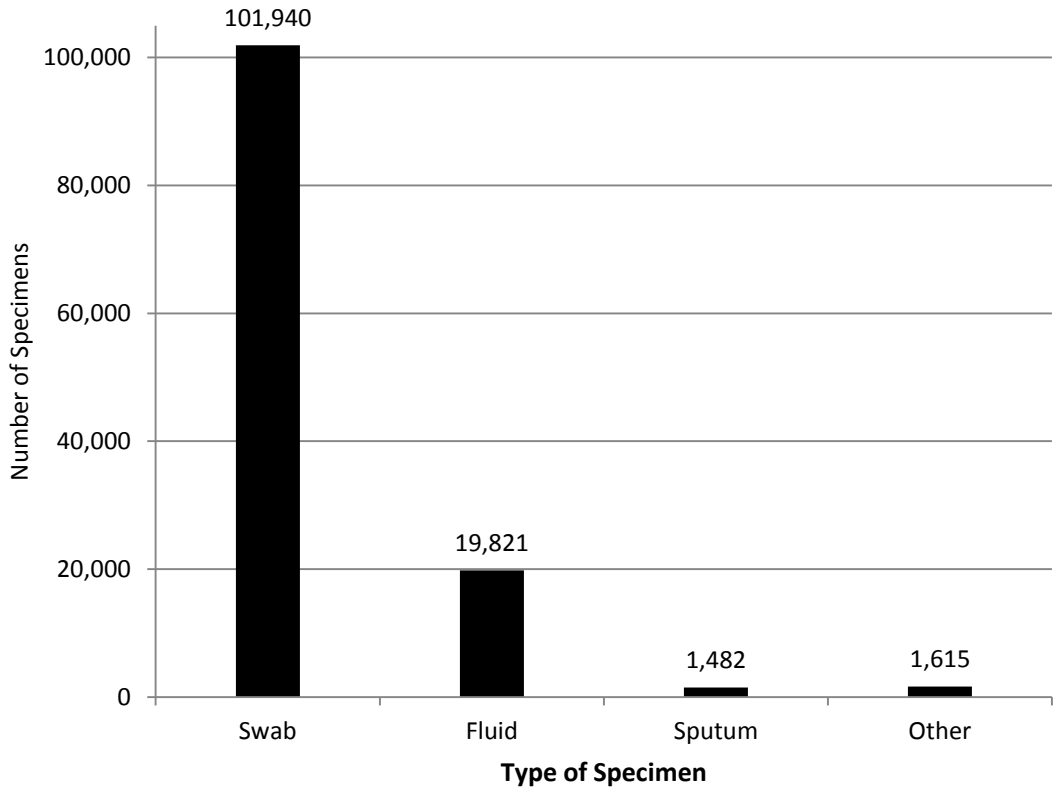


Figure 3.4: Distribution of specimens by type submitted to the laboratory from April 1, 2004 to January 31, 2010

### 3.1.2 Data from the Canadian community health survey

The Canadian community health survey (CCHS) database, Cycle 4.1 [148-150], was collected by Statistics Canada through a national survey on information related to health status, health care utilization and health determinants for the Canadians. The survey gathered information during the period between 2008 and 2009 from a large random sample of 131,061 participants, which represented the population of 12 years of age and over living in all provinces and territories. The survey did not include people living on reserves and other Aboriginal settlements, as well as the full-time members of the Canadian Forces and residents of some remote regions.

Of these 131,061 CCHS participants, 11,925 (9.1%) were from Alberta, which included 5,602 (47%) males and 6,323 (53%) females. The survey questionnaire included more than 1,000 questions grouped into various

categories. These categories included alcohol use, illicit drugs use, smoking, health status and major illnesses (e.g., diabetes, heart diseases, obesity, hypertension, cancer, stroke, mental disorder, and respiratory diseases), access to health care services, injuries, spiritual values, diet and dietary supplement use, physical activity, satisfaction with life, and healthcare system satisfaction. Additional details about the CCHS questionnaire can be found at the website of Statistics Canada [151].

In the CCHS survey data were collected on respondents of 12 years of age and over, except for COPD and obesity. The information on COPD was collected from individuals aged 30 years and over. The information on obesity was collected from individuals aged 18 years and over; pregnant women were excluded. Responses to questions related to specific medical conditions were collected to conditions diagnosed by a health professional. In the analysis reported in the thesis, only responses from individuals aged 15 years and over were considered. The following variables were included and used as health risk factors: asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), mood disorder, history of stroke or cancer, heart disease, hypertension, physical activity, perceived health, flu shot vaccination, alcohol intake, smoking, access to regular medical doctors, and obesity. According to WHO [126], obese individuals have BMI that is greater than or equal to 30, whereas overweight individuals have BMI between 25 and 29.

### 3.1.3 Census database

The community profiles of the 2006 Census of Population collected by Statistics Canada [153] at the community-level, grouped by health regions, are used in this study. The following demographic factors were considered in this study: Aboriginal status, population density per square kilometer, family income, unemployment rate, education, and dwelling age. These data were linked with the influenza A(H1N1)pdm09 laboratory-confirmed data to study the association between influenza A(H1N1)pdm09 incidence and demography over the nine

health regions of Alberta. A health region was used as a primarily geographical unit because zones were not yet created at the time the influenza A(H1N1)pdm09 pandemic was commenced.

### 3.1.4 Alberta population database

Alberta population data grouped by age, sex, and health region for the period between 2004 and 2009 were obtained from Alberta Health, Government of Alberta [154]. This population data were used as dominators for computing rates and estimating statistical parameters presented in this thesis. The CCHS data was linked with both the population data and the laboratory data at the community level in order to carry out an ecological study that investigated the association between the incidence of influenza A(H1N1)pdm09 cases and the health profile of Albertans.

### 3.1.5 Data preparation

A set of validation criteria was applied to ensure consistency and integrity among databases. A number of derived variables were created from the existing variables, such as age group, season of pandemic, and health zone/region. Then, a relational database model was developed to link the tables included in the databases by means of SQL Server 2008®. A unique identifier for each table was created and used to access data in the same table. Computational algorithms were used by means of SQL functions and materialized views to deliver consistent tables that were converted into SAS format. SAS 9.3® was used as a main tool for manipulating and analyzing the data to produce all results and statistics presented in this thesis.

### 3.1.6 Data Linkage

The laboratory data were generated at the patient level; each patient was given a unique anonymous key. These data contained information fields on sex, age group, geographical location (zone and RHA), specimen submitted, and

laboratory results. A set of common fields (sex, age group, and geographical location) were also included in the other databases (i.e., CCHS data, census data, and population data) and used as linking attributes. This set was standardized to match the corresponding definition and boundaries in the laboratory data. All databases were then aggregated, grouped, and ordered by sex, age group, and geographical location. Both the laboratory data and population data included additional common field, year. The laboratory data were linked with the population data based on matching their common fields (year, sex, age group, and geographical location) at the same order. The laboratory data were linked with the CCHS data and the census data by matching their common fields (sex, age group, and geographical location).

## 3.2 Study boundaries

### 3.2.1 Geography

This study was limited by the geographic boundaries of the Province of Alberta, Canada.

### 3.2.2 Age groups

The following four age groups were used in this study: 0-14 years, 15-34 years, 35-64 years, and 65 years and older. The first age group (0-14 years) was eliminated from any analyses that included the CCHS database. This is because the CCHS data included only the individuals of 12 years of age and over.

### 3.2.3 Study period/timeframe

The data obtained from different sources cover the period between April 1, 2004 and January 31, 2010. In Chapter 4, where the epidemiology of respiratory viruses before and during pandemic was studied, the 2004 cases were excluded from the analysis. This modification was made because some respiratory viruses did not have complete data for 2004. Two seasons, summer (months of May, June, July, August, September and October) and winter

(months of January, February, March, April, November and December), were defined for categorizing cases.

In order to study the epidemiology of respiratory viruses before and during pandemic, the study year was defined from April in a year to January of the following year. This definition was used because influenza A(H1N1)pdm09 cases were first detected in April 2009 and last detected in January 2010 during the outbreak. This modification was performed to make the epidemiologic measures comparable. Accordingly, the total number of respiratory-virus cases extracted between 2005 and 2009 was 60,389. This represented 72% of the total number of Alberta cases with 84,338 specimens included from the laboratory data. Figure 3.5 shows the distribution of the 12-month (January to December) and 10-month (April to January) proportions of cases by year over the period between 2005 and 2009. The proportion of cases was lower between 2005 and 2008 in comparison to those in 2009. In 2009, however, the proportion of all respiratory cases increased in response to the emergence of the influenza A(H1N1)pdm09 outbreak.

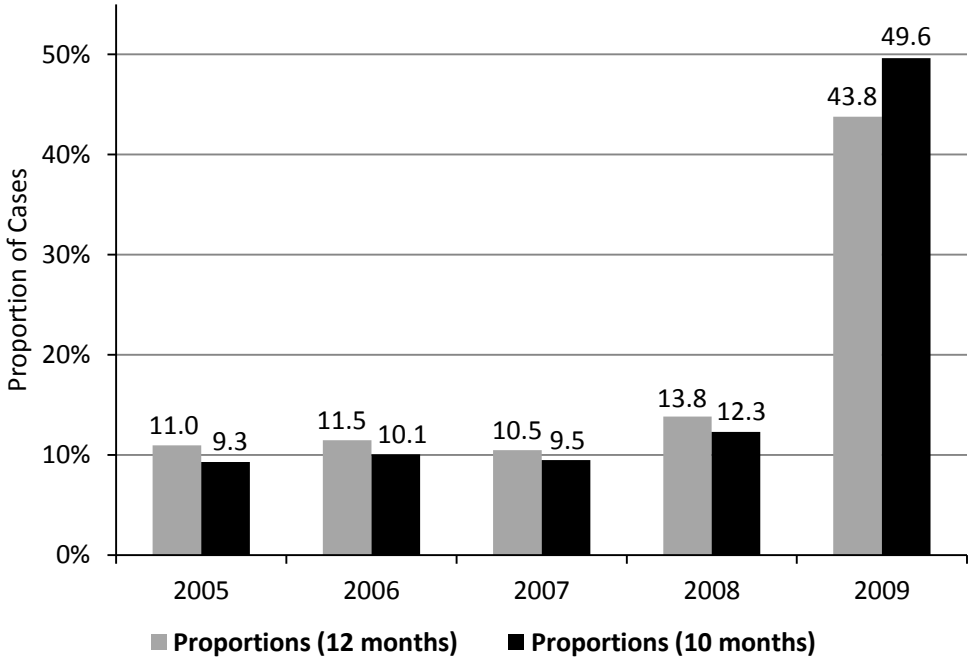


Figure 3.5: Proportions of respiratory-virus cases by year from April 1, 2004 to January 31, 2010

### 3.2.4 Respiratory viruses included

Over the study period between 2005 and 2009, no positive cases of coronavirus and rhino/enterovirus were reported between 2005 and 2007 as testing for these viruses only commenced in March 2008. Thus, these two viruses were excluded from the analysis. The study included six viruses: influenza virus A, influenza virus B, human metapneumovirus (hMPV), parainfluenza virus, respiratory syncytial virus (RSV), and adenovirus. In this study, influenza A(H1N1)pdm09 was the outcome of interest.

## 3.3 Statistical methods for epidemiological analysis

Influenza A(H1N1)pdm09 cases was evaluated using a set of common measures that include the proportions and rates of influenza A(H1N1)pdm09 cases by zone and health region, proportions of influenza A(H1N1)pdm09 cases by season, sex, age, and health region, as well as the overall association between influenza A(H1N1)pdm09 and both sex and age group over the nine health regions of Alberta. This association was studied by means of negative binomial regression models that were applied using the Generalized Linear Model procedure (GENMOD) in SAS [155].

The other respiratory viruses, i.e., all respiratory viruses included in this study except influenza A(H1N1)pdm09 virus, were evaluated by computing their proportions and incidence rates before and during the 2009 pandemic. The rates were also computed by season, sex, age group, and health region. Both laboratory and population databases were joined together to obtain the rates of viruses investigated.

## 3. 4 Statistical methods for ecological analysis

The databases described in Sections 3.1.1–3.1.4 (i.e., laboratory data, CCHS data, Alberta population data, and the census community profile) were all linked together to carry out an ecological study that investigates the impact of a

set of demographic and health risk factors on the occurrence of influenza A(H1N1)pdm09. These factors were described previously in Sections 3.1.2 and 3.1.3. The impact of these factors was investigated based on the incidence of influenza A(H1N1)pdm09 by studying their association by means of correlation and negative binomial regression. The relative risk ratios were determined along with their confidence intervals for each factor analyzed.

### 3. 5 Poisson and negative binomial models

The given data show that the outcome, influenza A(H1N1)pdm09, represents the number of influenza A(H1N1)pdm09 confirmed cases occurred over a certain period of time (i.e., during the 2009 pandemic). Therefore, the data being analyzed are count data and the statistical methods to be used should then be able to handle such data of positive counts. There are two common methods that can be used to statistically analyze this type of count data – Poison regression and negative binomial regression. Poisson models were initially considered in the analysis. However, the obtained values of the deviance were much greater than 1.0, indicating over-dispersion and inadequacy of using Poisson models.

An important assumption in the Poisson model is that the mean and variance of a distribution are equal (i.e., equidispersion, $Var(Y_i) = E[Y_i] = \mu$). , However, the variance is usually much greater than the mean in real life applications; that is, $Var(Y_i) > E[Y_i]$. This property is referred to as 'over-dispersion'. Accordingly, Poisson models may not be well suited to handle some types of count data [156,157]. Fekedulegn et al. [158] claim that "Over-dispersion leads to underestimates of the standard errors (SEs) yielding large values of the chi-square statistics which consequently increases the type I error." Over-dispersion in Poisson regression can be tested using the ratio of the sum of Pearson residuals, represented by the chi-square, over the number of degrees of freedom [159]. This ratio is known as the deviance (*DV*). That is, $DV = \chi^2/df$. A

value of *DV* that is larger than 1.0 indicates over-dispersion, whereas a value that is smaller than 1.0 indicates under-dispersion.

There are several approaches to overcome the above restrictive assumptions of Poisson models, such as Quasi-likelihood regression and negative binomial regression [159-161]; the latter was used in the thesis. The negative binomial distribution is similar to the Poisson distribution, except the variance and mean are not assumed to be equal, so over-dispersion is no longer problematic [162]. Unlike Poisson, the negative binomial distribution has an additional non-negative parameter *k* that describes the dispersion, such that the variance can exceed the mean [163]. Researchers comparing Poisson and negative binomial regression models have concluded that, in most applications, the negative binomial model was more appropriate in fitting count data than in Poisson [156,164]. The range of applications of the negative binomial distribution has been extended recently to include the epidemiology of infectious diseases, as the negative binomial model has shown to be appropriate to apt the 'offspring distribution' for several disease transmission datasets. Severe acute respiratory syndrome (SARS), measles, and smallpox are typical examples of infectious diseases of this category, with distributions that reveal a high degree of over-dispersion [165-167].

In this study, a negative binomial regression model was used to study the association between influenza A(H1N1)pdm09 and sex and age groups over the nine health regions of Alberta. The SAS GENMOD procedure [155] was employed with a *log* link function to build a *log* model that included influenza A(H1N1)pdm09 cases as a response variable versus sex, age group, and health region as explanatory variables (i.e., predictors). It is worth noting that the GENMOD procedure ignores observations with missing values for any variable included in the model. The domain of analysis included the entire laboratory data for sex and age groups defined in Section 3.2.2. Equation 3.1 describes a model that included sex, age group and health region as predictors of the response

variable influenza A(H1N1)pdm09 cases. Equation 3.2 describes the variance of this distribution.

$$log(\text{pH1N1 cases}) = \beta_o + \beta_1 \text{agegroup} + \beta_2 \text{sex} + \beta_3 \text{HR} \quad (3.1)$$

$$Var(\text{pH1N1cases}) = E[p\text{H1N1 cases}]\{1 + k \times E[\text{H1N1cases}]\} \quad (3.2)$$

As $k \rightarrow 0$, $Var(Y_i) \rightarrow \mu$ and the distribution converges to Poisson. On the other hand, the greater the heterogeneity in the Poisson means, the larger the value of $k$, and consequently, the greater the over-dispersion compared with Poisson variability [163].

Statistical procedures based on negative binomial regression, both univariate and multiple, were applied to examine the association between influenza A(H1N1)pdm09 and the health risk factors defined in Section 3.1.2 and described in Table 3.1.

## 3.6 Factors considered in the ecological analysis

**Table 3.1: CCHS health risk factors used [148-152]**

| Variable | Question/Explanation | Categories |
|---|---|---|
| Asthma | Do you have asthma? | Yes, No |
| COPD | Do you have chronic obstructive pulmonary disease? | Yes, No |
| Chronic Bronchitis | Do you have chronic bronchitis? | Yes, No |
| Obesity | this variable was derived from the question of another variable [152] that is based on the BMI classes | Normal, Overweight, Obese |
| Cancer | Have you ever had cancer? | Yes, No |
| Mood Disorder | Do you have a mood disorder such as depression, manic depression, bipolar disorder, mania or dysthymia? | Yes, No |
| Flu Shot | Have you ever had a flu shot? | Yes, No |
| Perceived Health | In general, would you say your health is excellent, very good, good, fair, or poor? By health, it means not only the absence of illness or injury but also physical, mental and social well-being. | Good, Poor |
| Physical Activity | This variable was derived from other variables [152] that depend on monthly frequency of physical activities lasting >15 minutes. The values reflect a one-month average based on data reported for a 3 month period. | Regular, Occasional |
| Smoking | At the present time, do you smoke cigarettes daily, occasionally or not at all? | Daily, Occasional, No Smoking |
| Alcohol Intake | During the past 12 months, have you had a drink of beer, wine, liquor or any other alcoholic beverage? If yes, how often did you drink alcoholic beverages? (The word drink means one bottle or a can of beer or a glass of draft, one glass of wine or a wine cooler, or one drink or cocktail with 1½ ounces of liquor). | Occasional, Regular, No Drinking |

# CHAPTER FOUR

# RESULTS

## 4.1 Characteristics of influenza A(H1N1)pdm09 outbreak

Figure 4.1 shows the pattern of influenza A(H1N1)pdm09 between April 2009 and January 2010 in Alberta. Along with Figure 4.2, two waves of influenza A(H1N1)pdm09 were observed during pandemic, one in June 2009 with 887 (14%) positive cases of influenza A(H1N1)pdm09 and the other in October 2009 with 3,649 (58%) positive cases. Further, around the first wave, 1,512 positive cases (24%) were reported during the summer months of May, June and July versus 4,617 (73%) positive cases that were reported around the second wave between October and November 2009. In relation to all respiratory viruses, 33,827 cases (51%) were reported before pandemic (i.e., between January 2005 and March 2009) versus 32,903 cases (49%) that occurred during pandemic (between April 2009 and January 2010). This uneven pattern occurred due to the elevation of some respiratory viruses during pandemic. Of the 32,903 cases of all respiratory viruses reported during the 2009 pandemic, 6,327 cases (~19%) were influenza A(H1N1)pdm09.

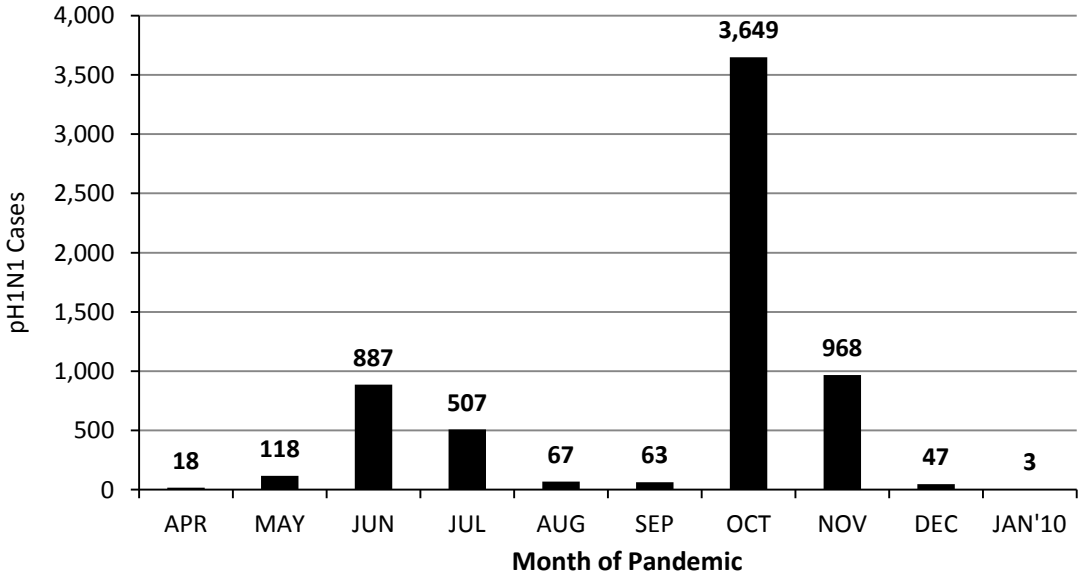


Figure 4.1: Laboratory-confirmed cases of influenza A(H1N1)pdm09 during the pandemic months in the Province of Alberta from April 25, 2009 to January 29, 2010

Figure 4.2 shows the frequencies of the influenza A(H1N1)pdm09 laboratory confirmed cases in Alberta during the 2009 pandemic. As shown, the first confirmed case of influenza A(H1N1)pdm09 was reported on April 25, 2009, while the last confirmed case was reported on January 29, 2010. Accordingly, the entire outbreak occurred between April 25, 2009 and January 29, 2010 in Alberta. Moreover, the total number of influenza A(H1N1)pdm09 confirmed cases in Alberta was 6,327 cases that occurred over 231 days out of 280 days of the entire duration of the outbreak. This is because 49 days had no influenza A(H1N1)pdm09 cases reported by the laboratory. Of the 6,327 influenza A(H1N1)pdm09 confirmed cases in Alberta, 3,277 cases (51.8%) were females, and 2,950 cases (46.6%) were males. Information on sex was missing for 100 cases (1.6%).

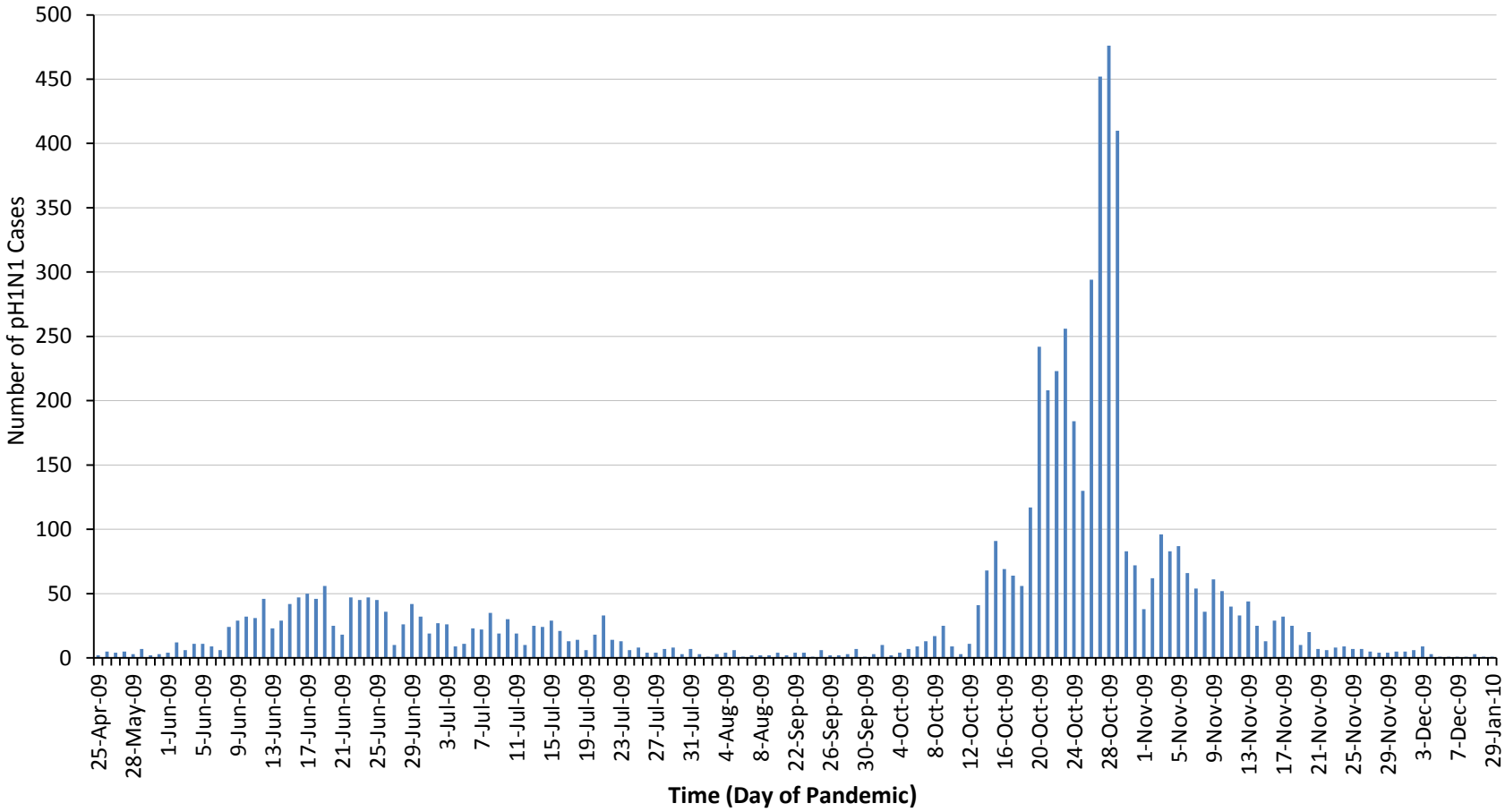


Figure 4.2: Frequency distribution for two pandemic periods: May 25 – August 9, 2009 and September 23 – December 8, 2009 (Note: first and last days included)

Figure 4.3 shows that 2,372 cases (37.5%) were younger than 15 years old, 2,163 cases (34.2%) aged 15 to 34 years old, 1,631 cases (25.8%) aged 35 to 64 years old, and 161 cases (2.5%) were older than 64 years.

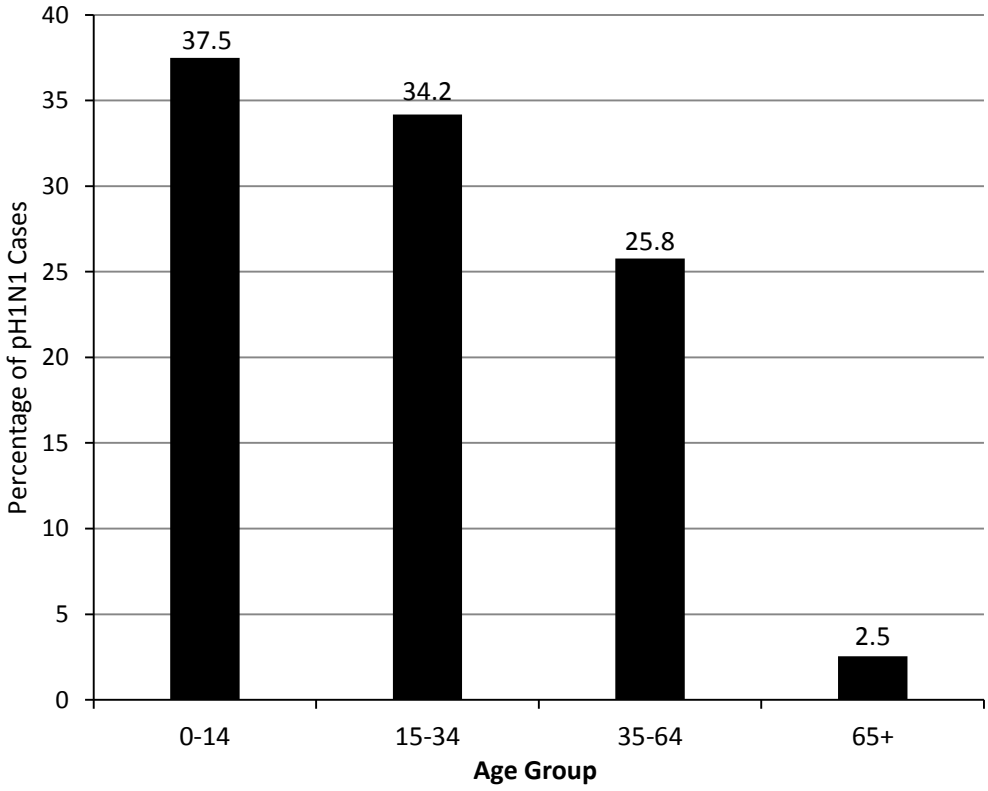


Figure 4.3: Distribution of influenza A(H1N1)pdm09 cases by age group in the Province of Alberta from April 25, 2009 to January 29, 2010

Figures 4.4(a) and 4.4(b) show the proportions and rates of influenza A(H1N1)pdm09 cases by sex and age group. In children younger than 15 years old, the proportion and rate of influenza A(H1N1)pdm09 cases were greater in boys than in girls. However, this pattern was reversed in adults with the proportion of influenza A(H1N1)pdm09 cases being greater in women than in men, with slight increase in the rate in males aged 65 and older.

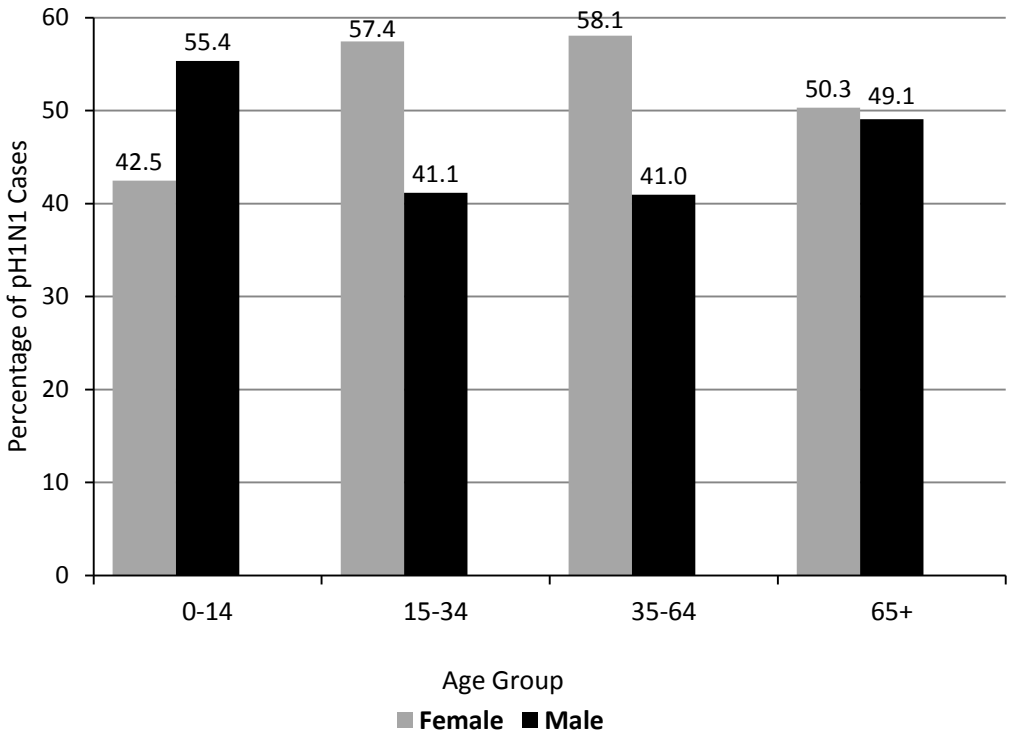


Figure 4.4 (a): Proportions of influenza A(H1N1)pdm09 cases by sex and age group in the Province of Alberta from April 25, 2009 to January 29, 2010

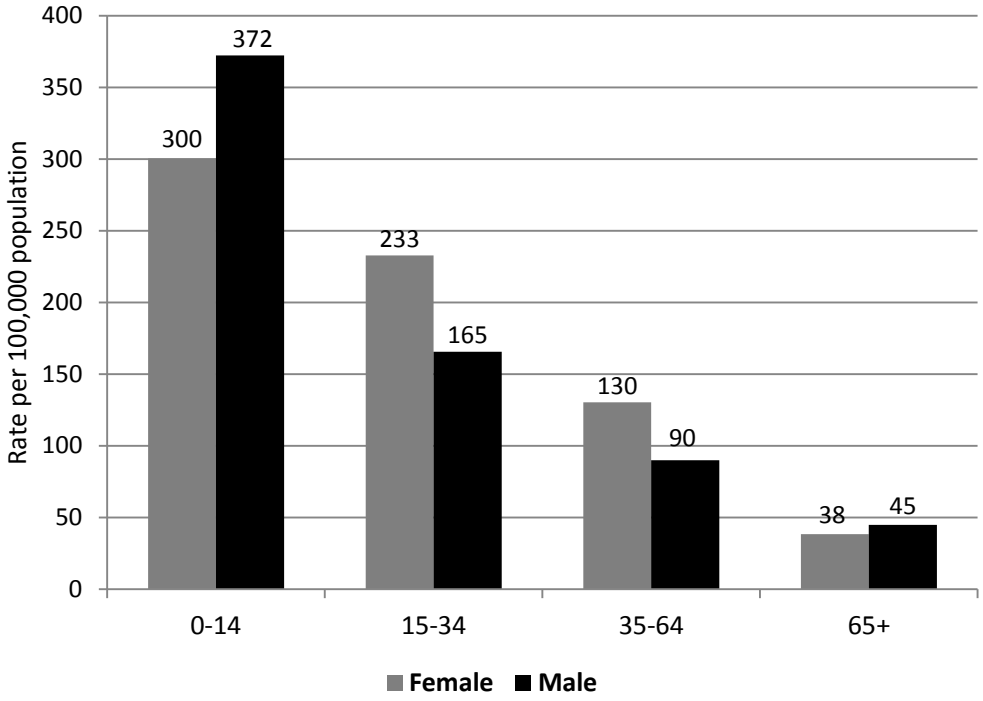


Figure 4.4 (b): Population rates of influenza A(H1N1)pdm09 cases by sex and age group in the Province of Alberta from April 25, 2009 to January 29, 2010

## 4.2 Rates of influenza A(H1N1)pdm09 during outbreak

The highest rate of influenza A(H1N1)pdm09, 187 per 100,000 population (95% CI: 161–214) was reported in the Central Zone of Alberta. This was above the average rate of the entire province, 175 per 100,000 cases (95% CI: 149–201). Figure 4.5 shows the pattern and distribution of rates of influenza A(H1N1)pdm09 over zones. Figure 4.6 shows the pattern and distribution of rates by health region. David Thompson had the highest rate, 203 per 100,000 (95% CI: 175 – 231) of cases with pH1N1. This was above the average proportion of the whole province, 175 per 100,000 cases (95% CI: 149 – 201).

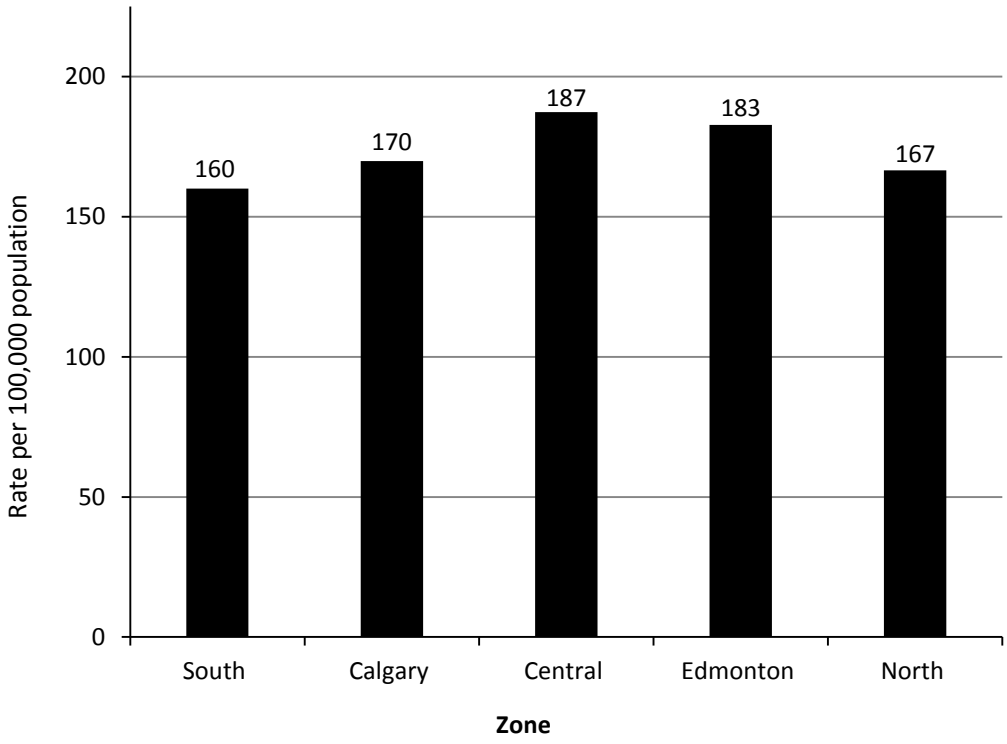


Figure 4.5: Population Rates of influenza A(H1N1)pdm09 cases by zone in the Province of Alberta from April 25, 2009 to January 29, 2010

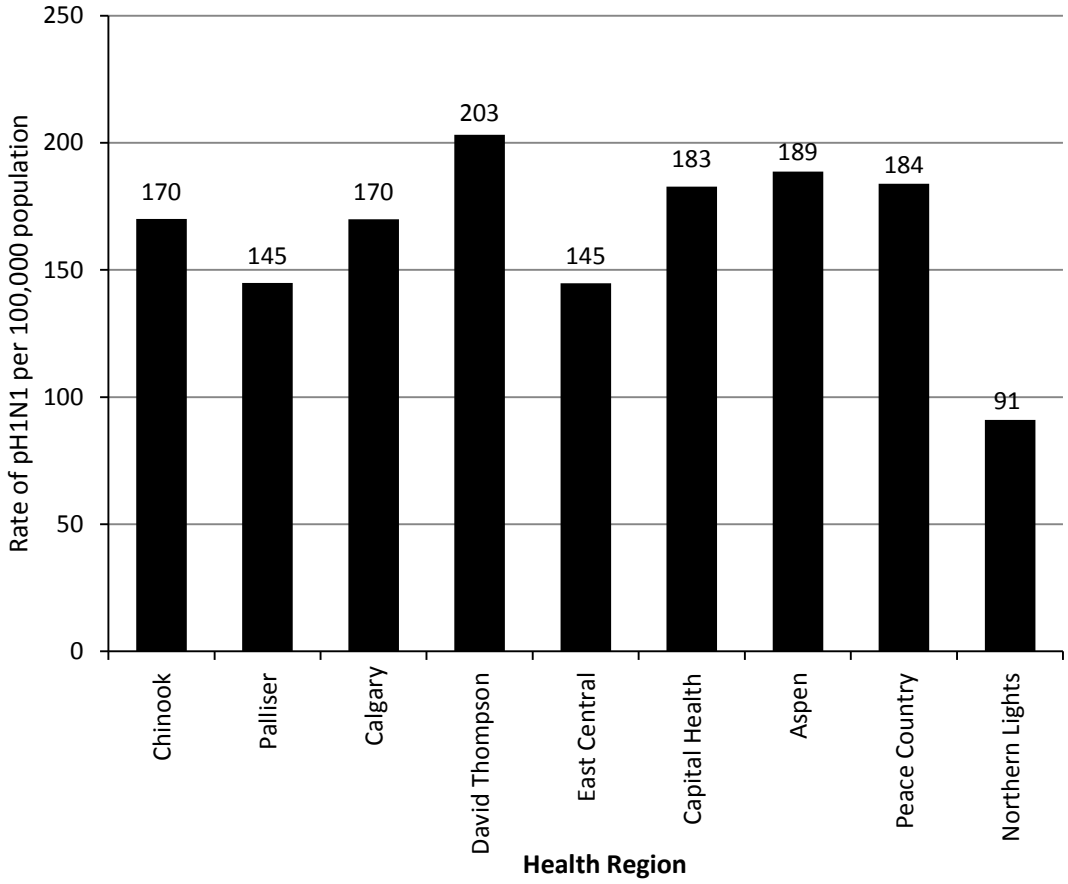


Figure 4.6: Population Rates of influenza A(H1N1)pdm09 cases by health region in the Province of Alberta from April 25, 2009 to January 29, 2010

## 4.3 Comparison of the incidence of respiratory viruses before and during pandemic period

This section describes the distribution and pattern of common respiratory viruses before and during the 2009 influenza A(H1N1)pdm09 pandemic. Several epidemiologic features were identified based on the incidence rates of viruses. Both the laboratory and population data of Alberta were linked together to perform the relevant analysis. The results were illustrated by sex, age group, and season.

### 4.3.1 Influenza virus-A (Flu A)

Before pandemic, both females and males were almost having the same incidence rates (Figure 4.7). During pandemic, however, the rate of influenza virus-A, i.e., influenza A(H1N1)pdm09, was greater in females than in males (191 versus 171, per 100,000 population). Please note that 103 influenza A(H1N1)pdm09 cases (1.6%) had unknown sex.

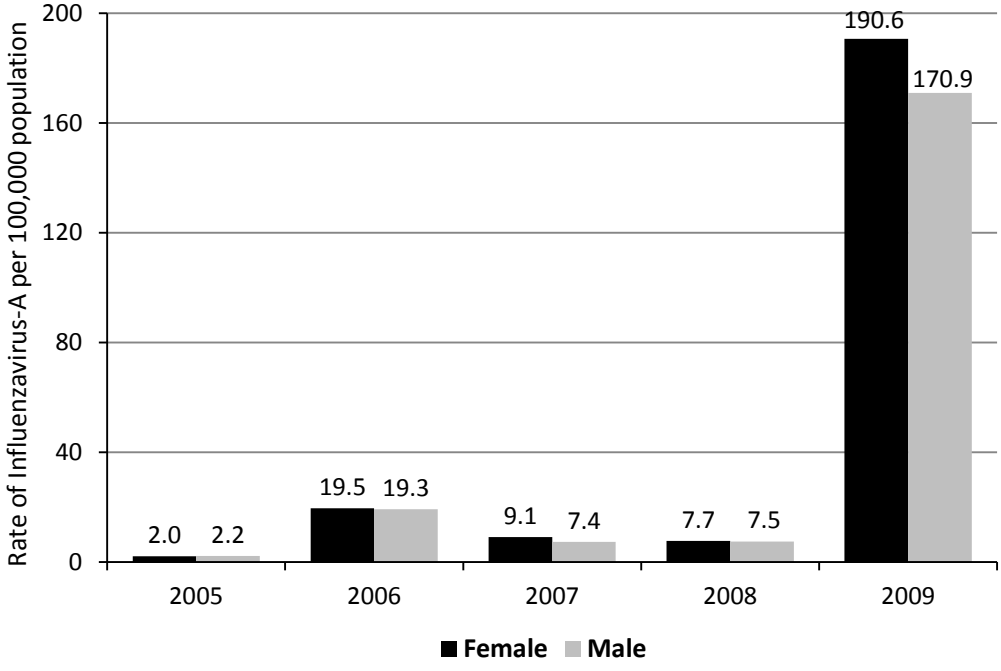


Figure 4.7: Rates of influenza virus-A by sex before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010†

*† a study year starts from April to January of the following year. Thus, the study period between 2005 and 2009 covers cases from April 1, 2005 to January 31, 2010*

The rates of influenza virus-A by age group shown in Figure 4.8 indicate that influenza virus-A was more dominant among young children under 15 years old before and during pandemic.

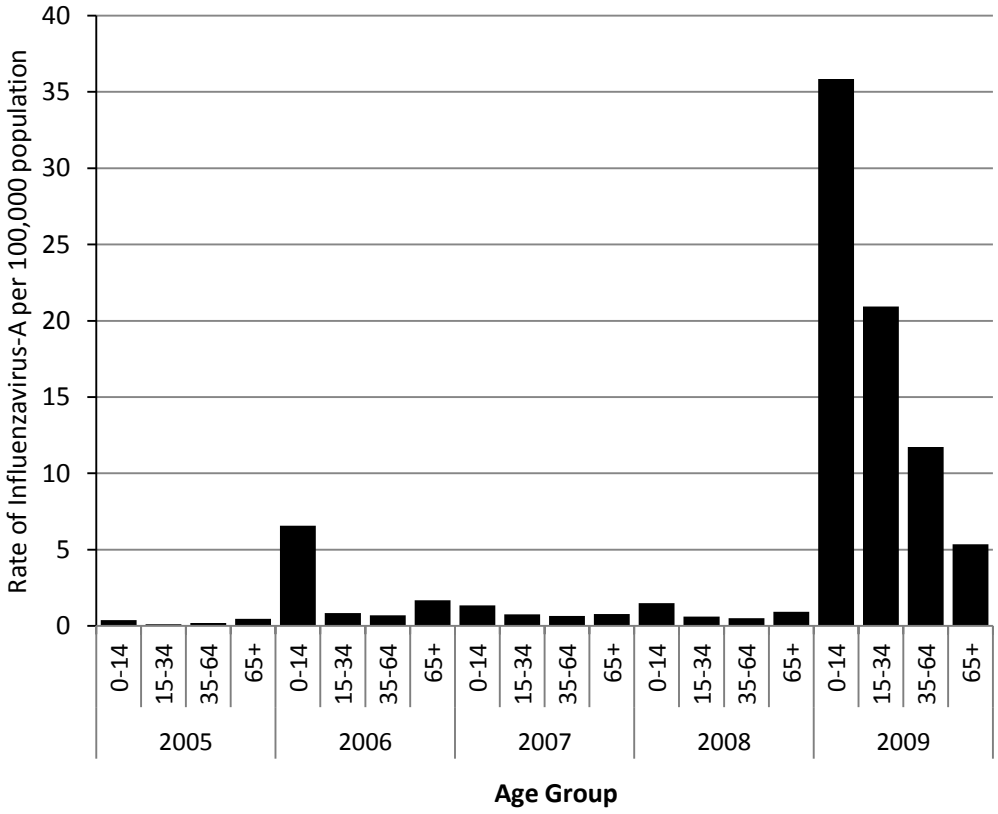


Figure 4.8: Rates of influenza virus-A by age group before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

Figure 4.9 shows the rates of influenza virus-A by season. Before pandemic, the rates in summer were always much lower than the rates in winter. During pandemic, in contrast, the rate in summer was much higher than the rate in winter (~5 folds).

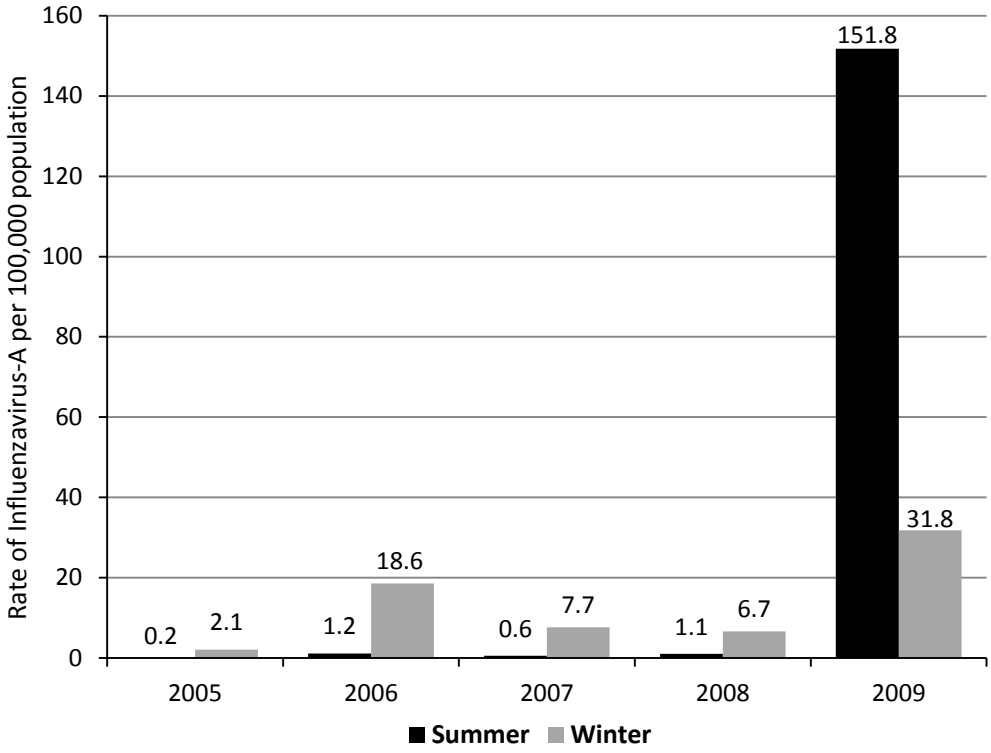


Figure 4.9: Rates of influenza virus-A by season before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

Figure 4.10 shows that the rates of influenza virus-A before and during pandemic. During pandemic, the incidence rate of influenza virus-A (184 per 100,000 population, 95% CI: 157.0 – 210.1) was almost five times the rate of seasonal influenza A during the entire pre-pandemic period between 2005 and 2008.

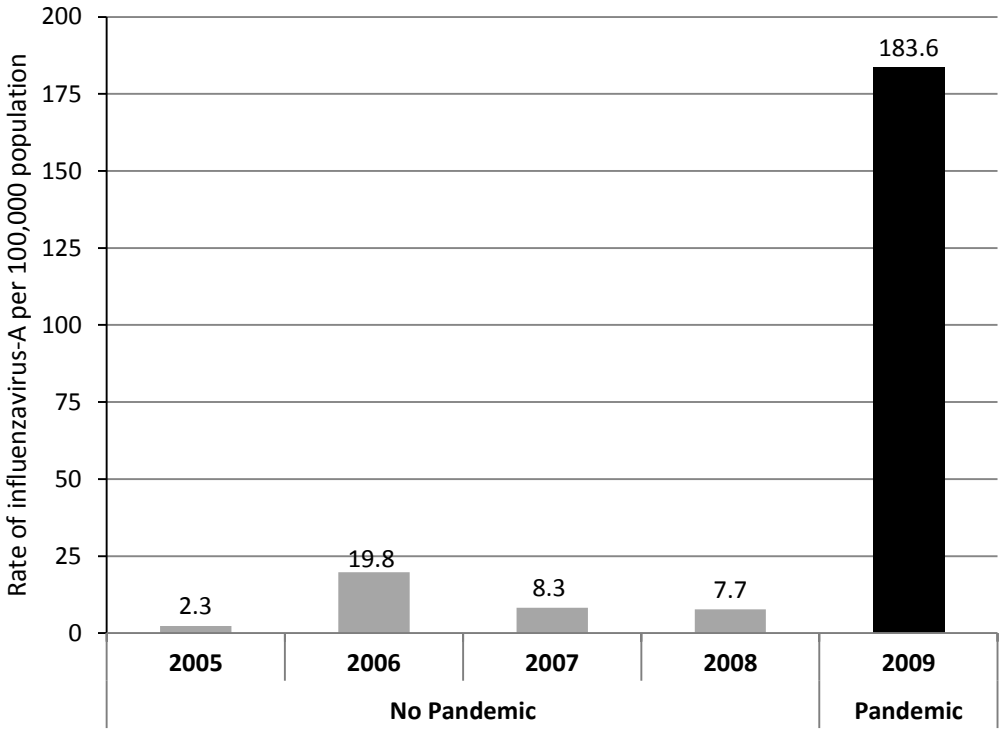


Figure 4.10: Rates of influenza virus-A before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

### 4.3.2 Influenza virus-B

Before pandemic, the incidence rates of influenza virus-B were fluctuating slightly with tendency to increase in females (Figure 4.11). During pandemic, the rates of influenza virus-B were relatively similar between males and females (5.0 per 100,000 population; 95% CI: 0.6–9.3 vs. 4.3 per 100,000 population; 95% CI: 0.2–8.3). Figure 4.12 shows that influenza virus-B was more common in elderly people aged 65 and above before pandemic. It was more common in people aged between 35 to 64 years during pandemic. Figure 4.13 shows that the incidence rates of influenza virus-B cases in winter were greater than the rates in summer before pandemic. However, the rates were equal during the pandemic.

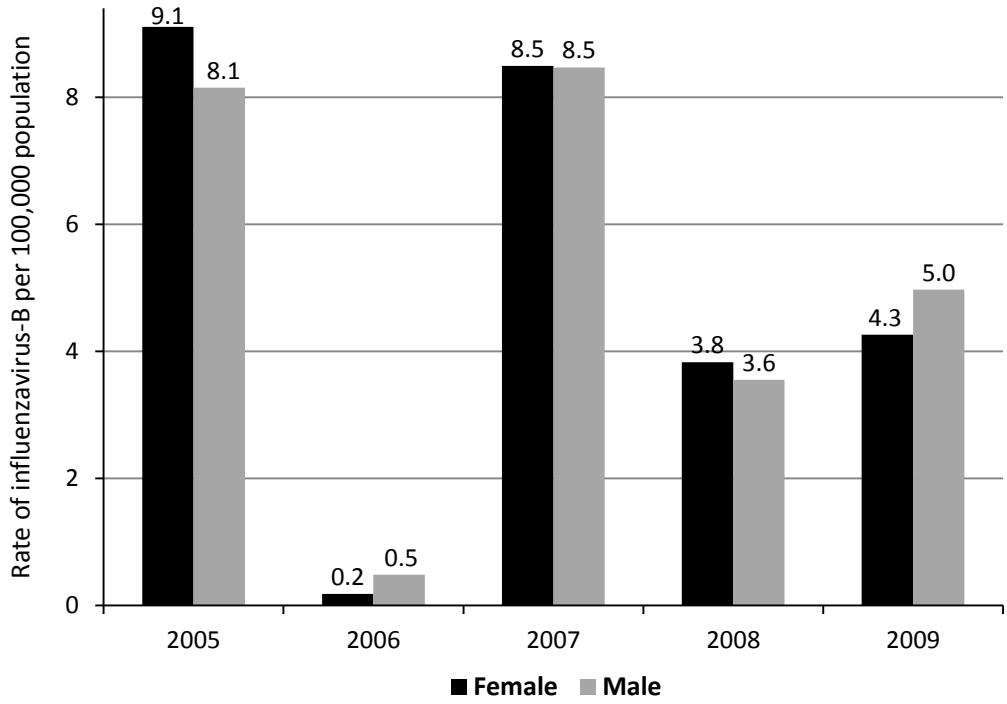


Figure 4.11: Rates of influenza virus-B by sex before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

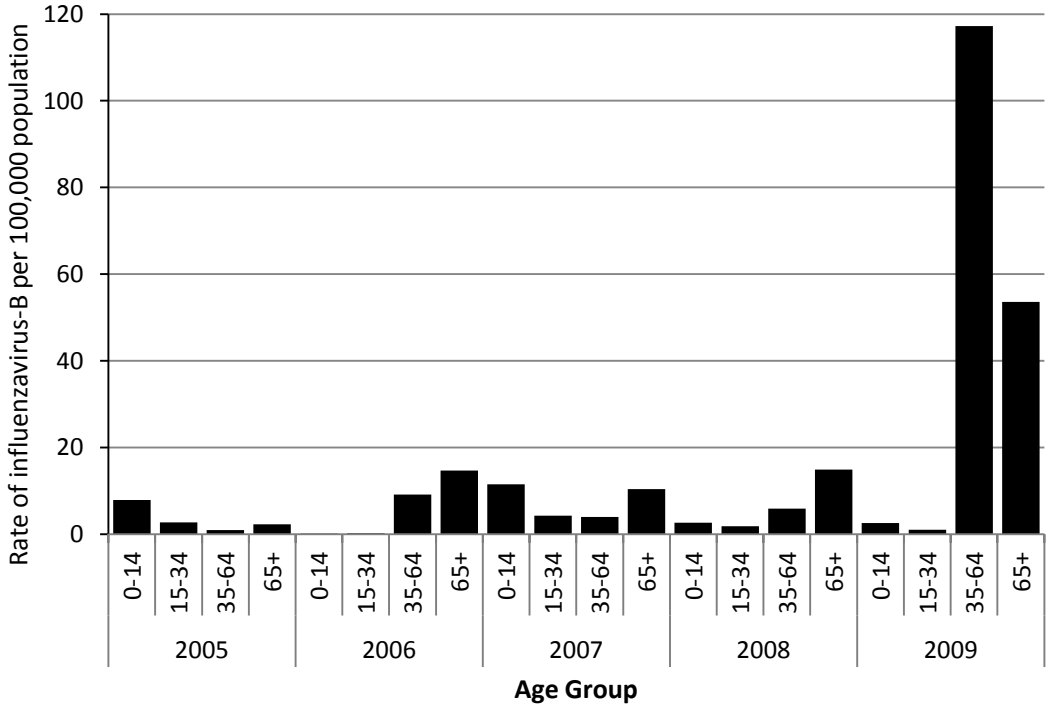


Figure 4.12: Rates of influenza virus-B by age group before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

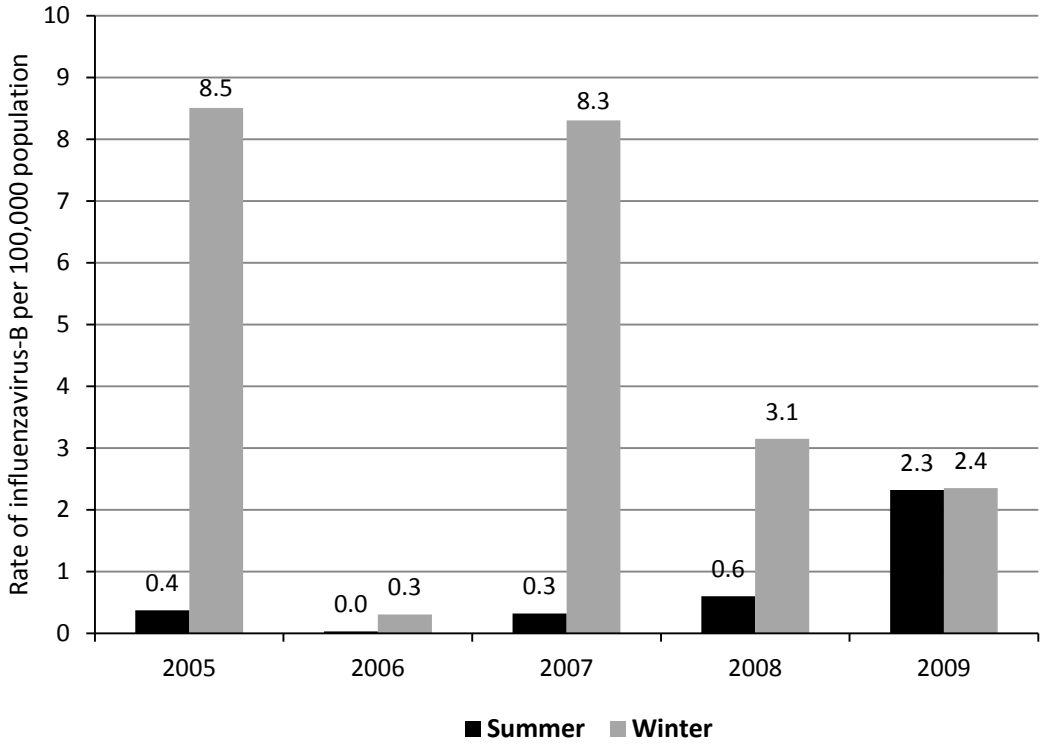


Figure 4.13: Rates of influenza virus-B by season before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

### 4.3.3 Human metapneumovirus (hMPV)

Before and during pandemic, the incidence rates of hMPV were almost the same, with slight increase among females (Figure 4.14). In addition, hMPV was more common in younger and older ages (Figure 4.15).

Figure 4.16 shows that the incidence rates of hMPV in winter were greater than the rates in summer before pandemic. However, the rate during pandemic was slightly greater in summer (6.0 versus 5.4 cases per 100,000 population). Figure 4.17 shows systematic and sharp drop in the incidence rate of hMPV every second year before pandemic. During pandemic, the rate of hMPV continued the same pattern with increases from 2.7 to 11.4 cases per 100,000 population.

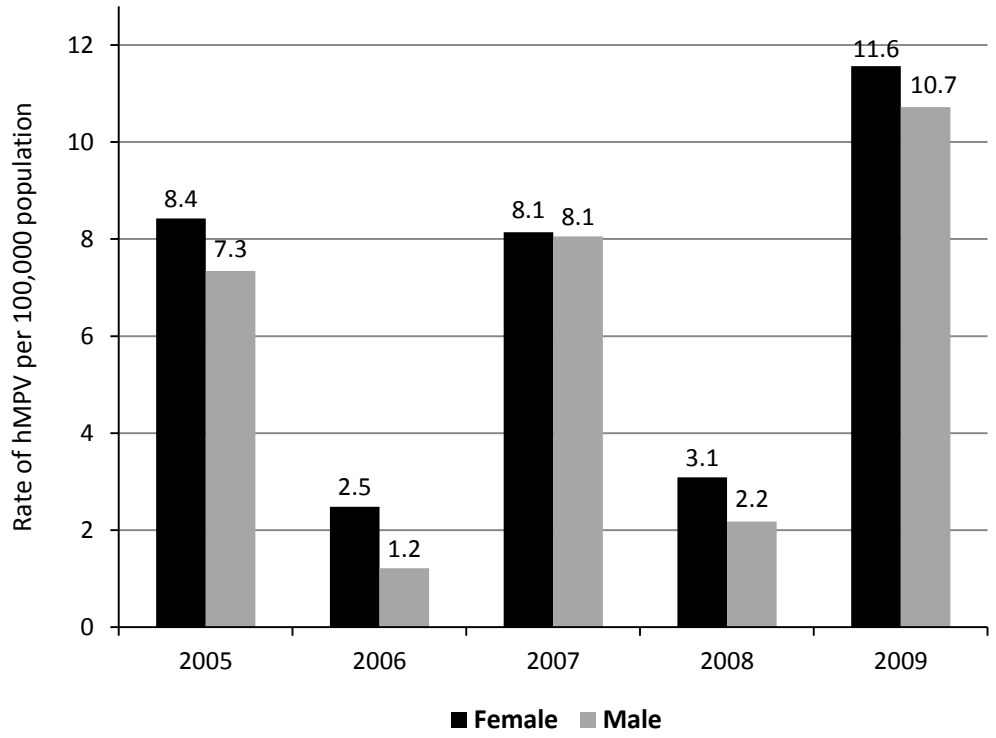


Figure 4.14: Rates of hMPV by sex before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

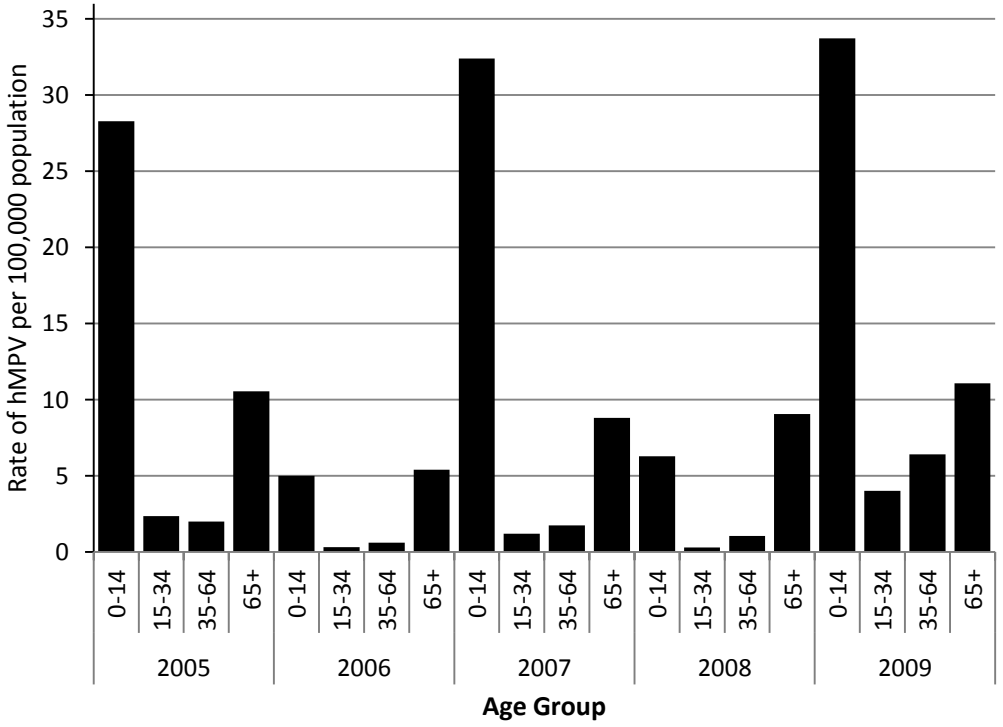


Figure 4.15: Rates of hMPV by age group before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

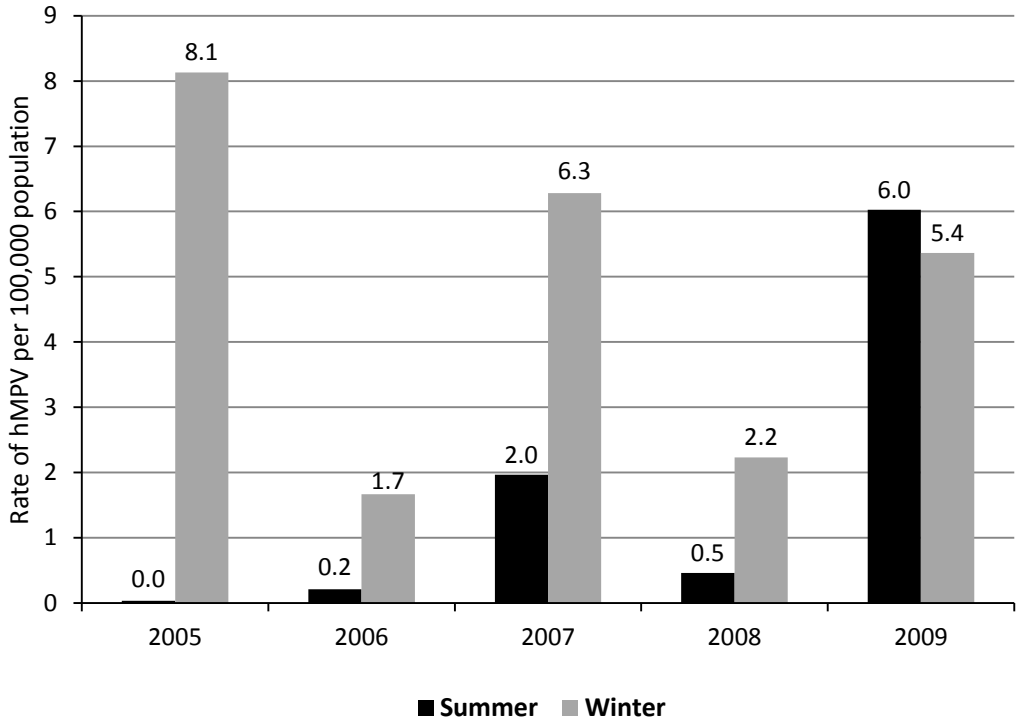


Figure 4.16: Rates of hMPV by season before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

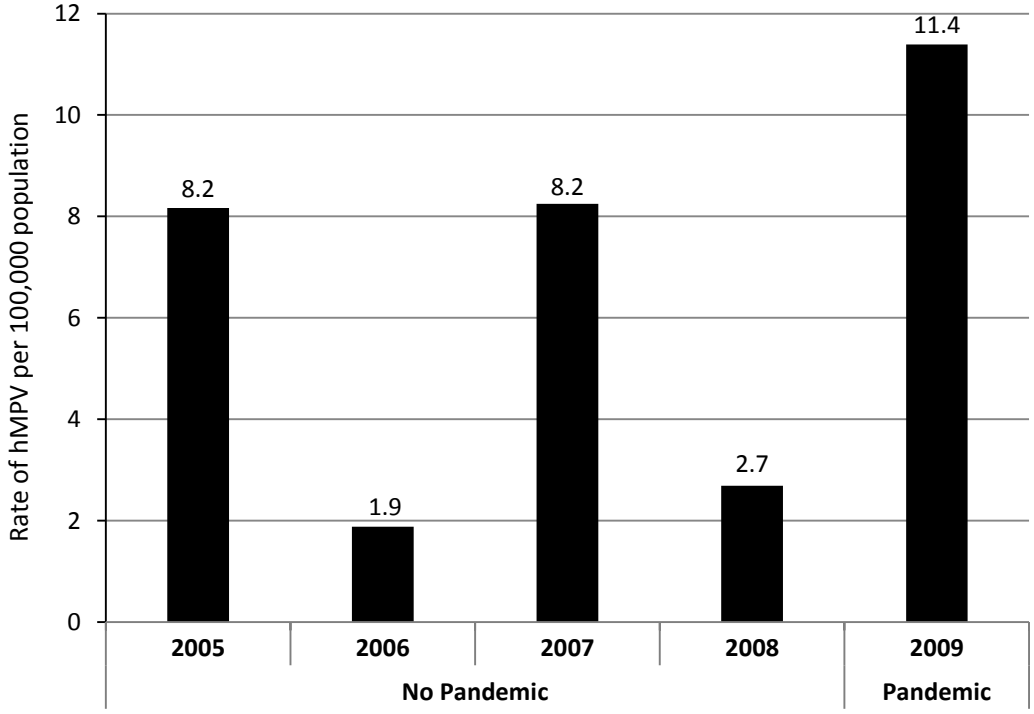


Figure 4.17: Rates of hMPV before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

### 4.3.4 Parainfluenza virus

Before pandemic, the incidence rates of parainfluenza were higher in males than in females (Figure 4.18). During pandemic, however, the rate was higher among females (31.2 cases per 100,000 population; 95% CI: 20.3 42.2 vs. 28.1 cases per 100,000 population; 95% CI: 17.7–38.5). Before and during pandemic, parainfluenza was more common in younger and older ages (Figure 4.19). Figure 4.20 shows that the incidence rates of parainfluenza in winter were almost higher than the rates in summer before pandemic. During pandemic, however, the rate was much higher in summer (19.6 cases per 100,000 population, 95% CI: 10.9 – 28.3) than in winter (10.6 cases per 100,000 population, 95% CI: 4.2 – 16.9). Figure 4.21 shows that the incidence rate of parainfluenza varied between 10.4 to 18.1 cases per 100,000 population before pandemic. Then, the rate increased considerably during pandemic from 10.4 cases per 100,000 population in 2008 to 30.2 cases in 2009.

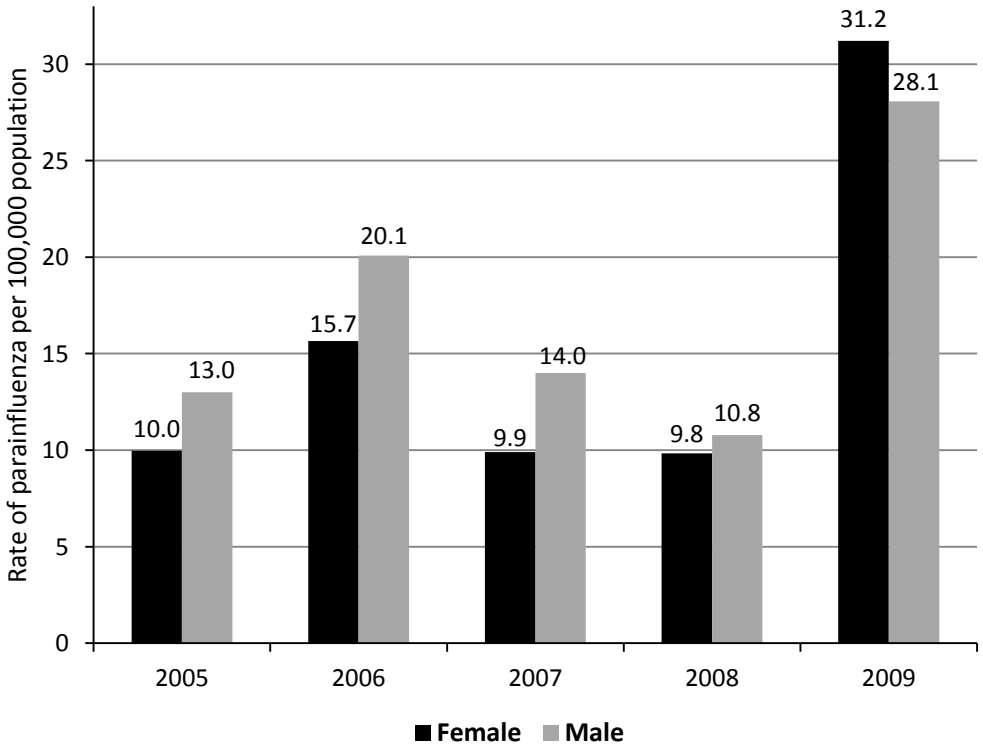


Figure 4.18: Rates of parainfluenza by sex before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

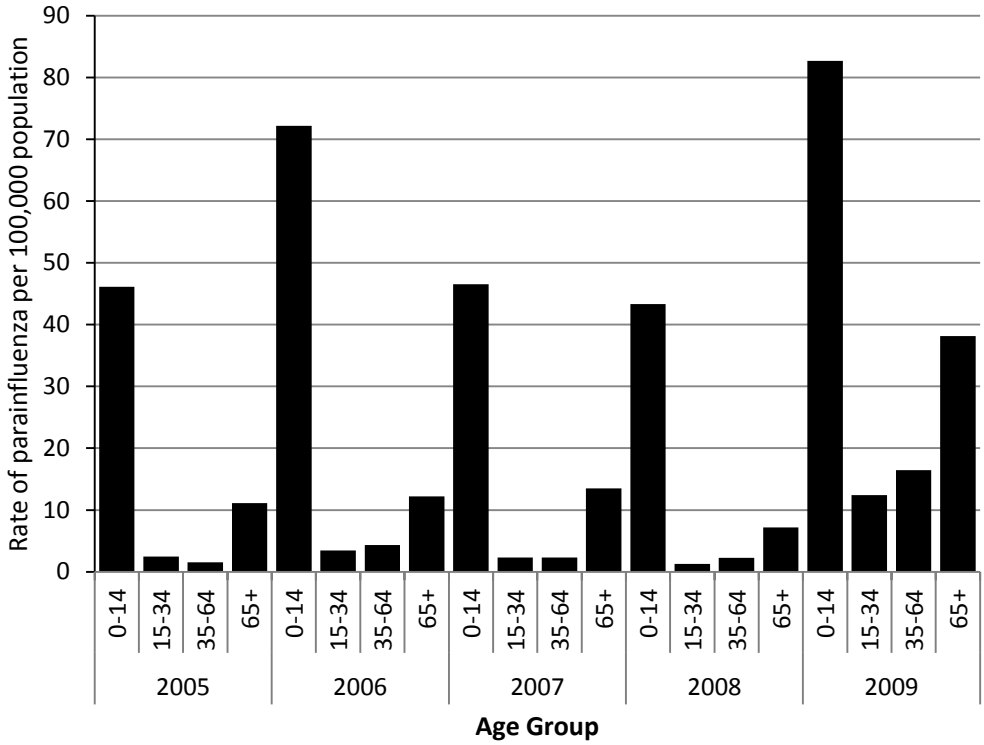


Figure 4.19: Rates of parainfluenza by age group before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

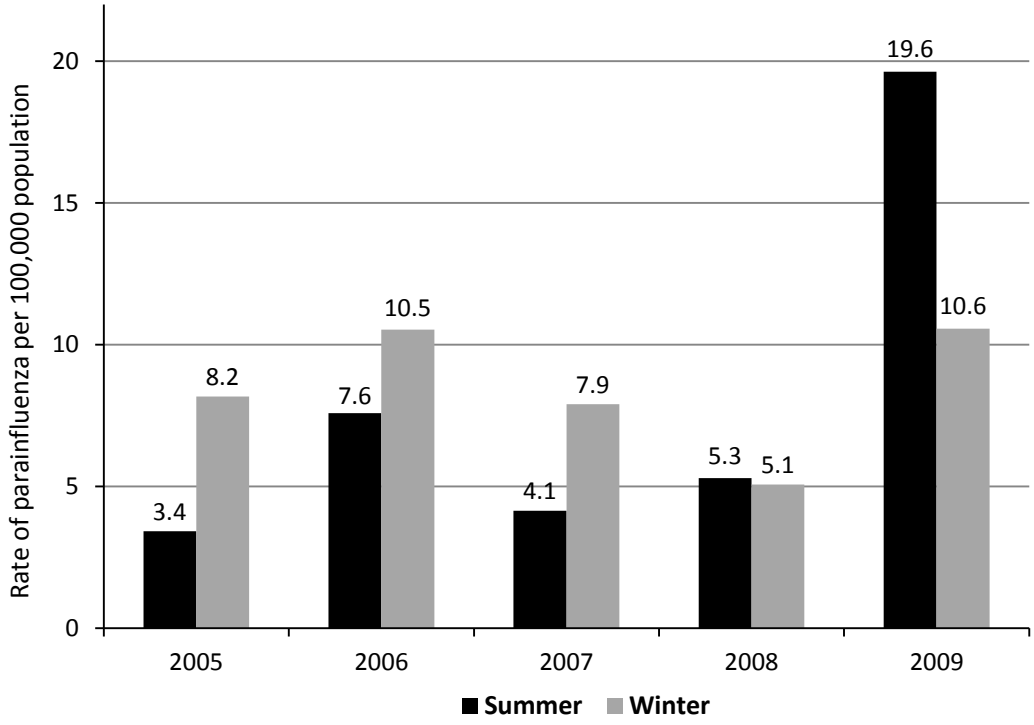


Figure 4.20: Rates of parainfluenza by season before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

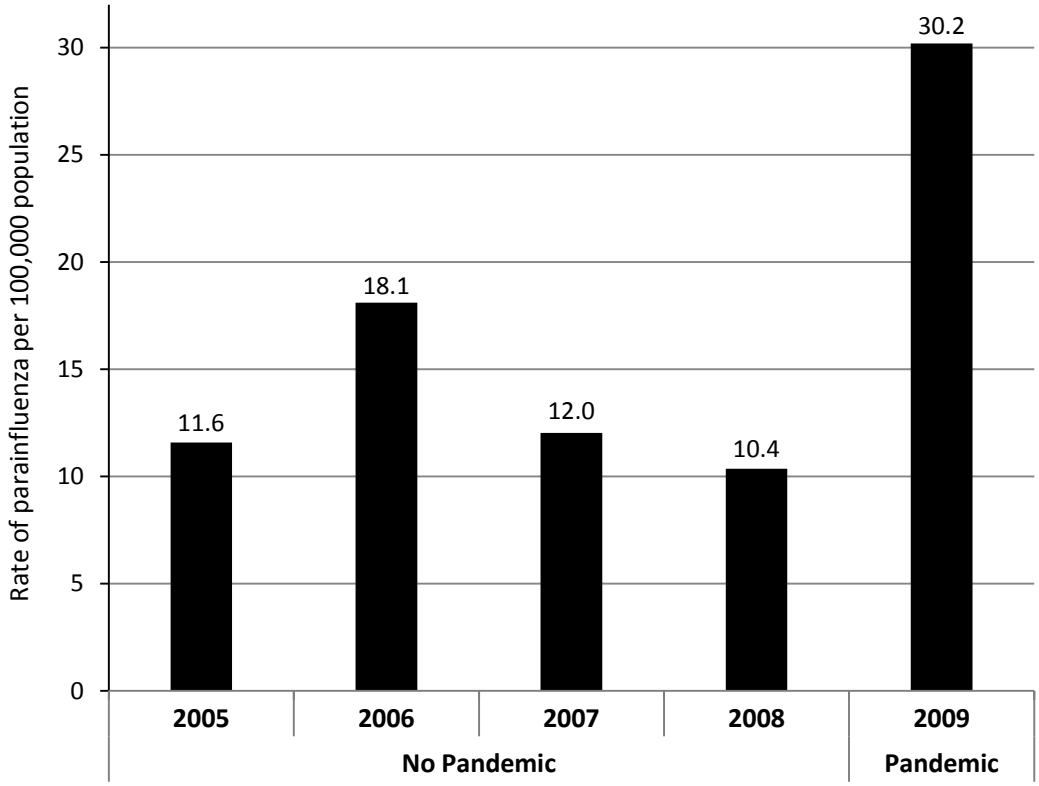


Figure 4.21: Rates of parainfluenza before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

### 4.3.5 Respiratory syncytial virus (RSV)

Before pandemic, the incidence rates of RSV were higher in males than in females (Figure 4.22). During pandemic, however, the rate was slightly higher in females (8.4 cases per 100,000 population; 95% CI: 2.7–14.0 vs. 7.5 cases per 100,000 population; 95% CI: 2.1–12.8).

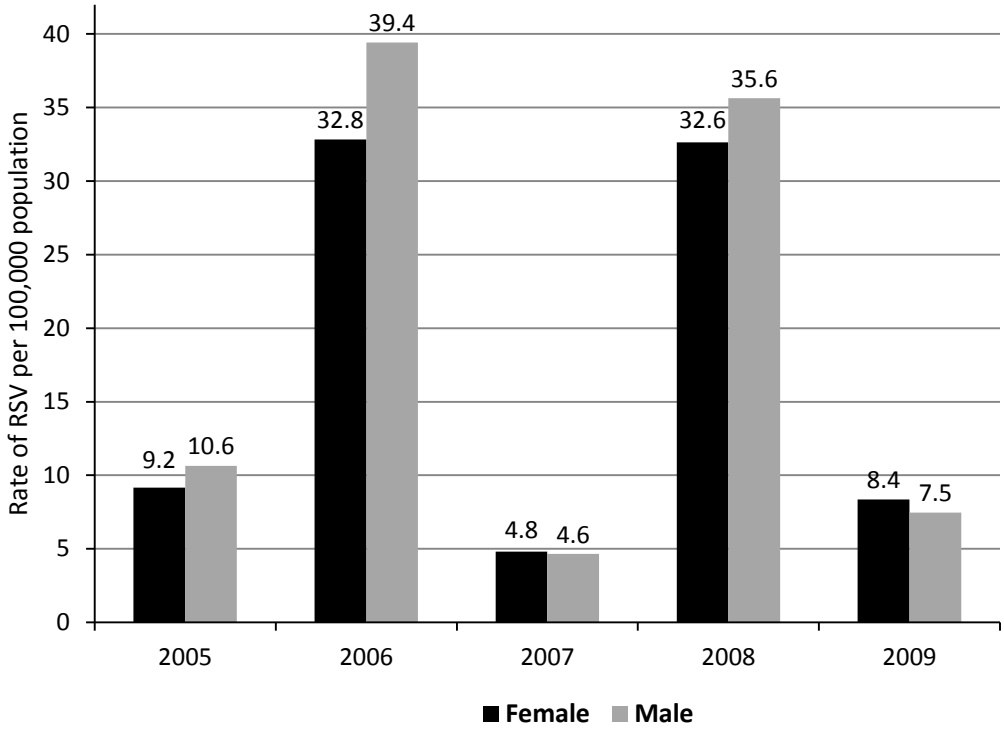


Figure 4.22: Rates of RSV by sex before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

Before and during pandemic, RSV was more dominant in younger children under 15 years of age, in particular, as well as in older ages (Figure 4.23). Two RSV waves have been reported during the winter time of 2006 and 2008 among children younger than 15 years old (Figures 4.23-4.25).

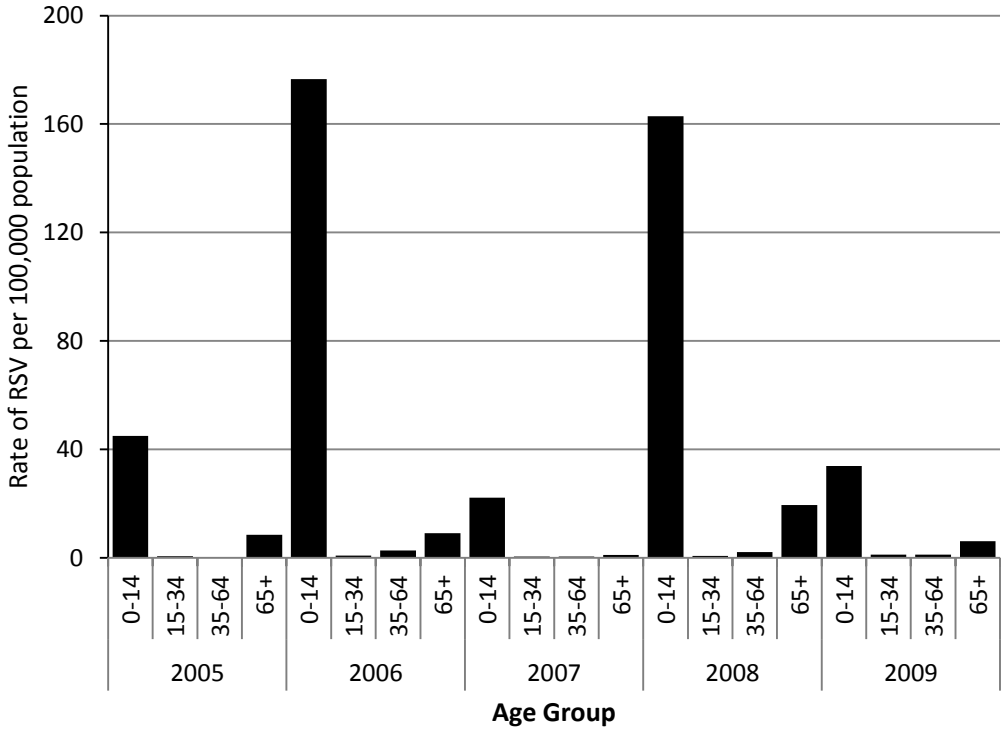


Figure 4.23: Rates of RSV by age group before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

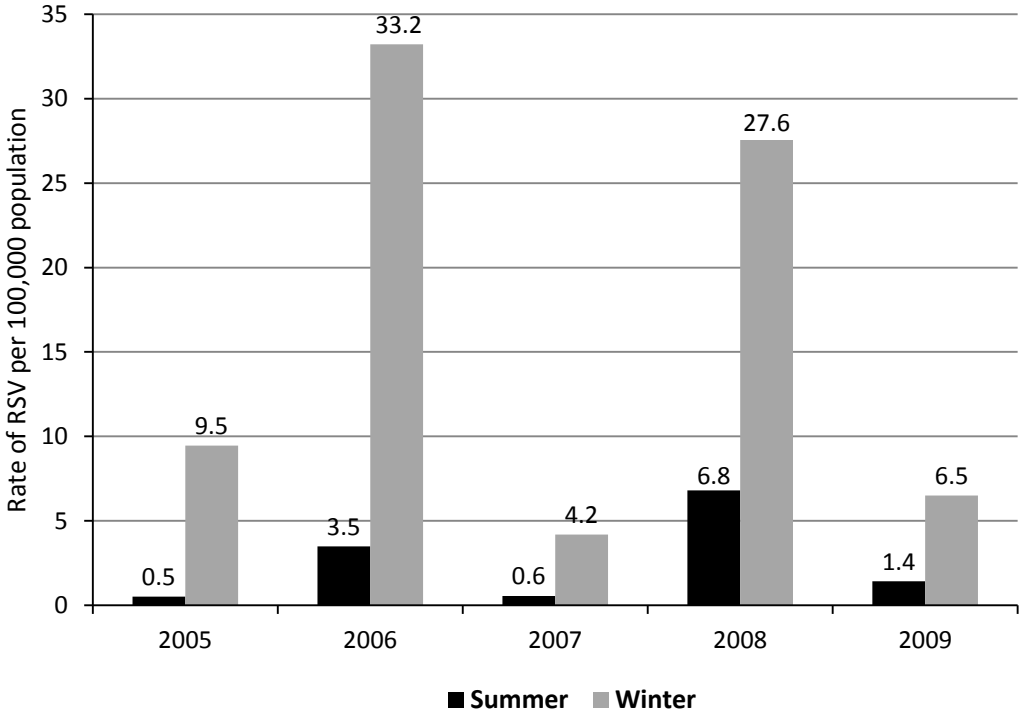


Figure 4.24: Rates of RSV by season before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

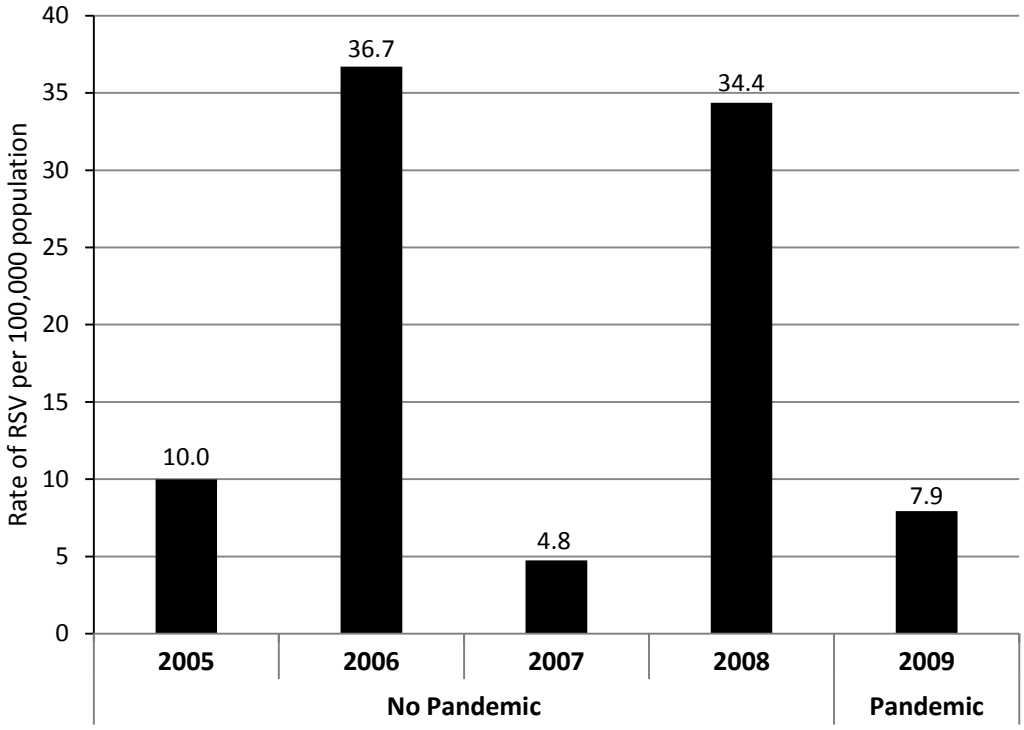


Figure 4.25: Rates of RSV before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

### 4.3.6 Adenovirus

Before and during pandemic, the incidence rates of adenovirus were apparently high among males (Figure 4.26). Moreover, the virus was more dominant among children younger than 15 years old (Figure 4.27).
Figure 4.28 shows that the incidence rates of adenovirus were fluctuating over summer and winter before pandemic. During pandemic, however, the rate was considerably higher in summer than in winter (4.6 cases per 100,000 population; 95% CI: 0.4 – 8.9 vs. 1.8 cases per 100,000 population; 95% CI: -0.8 – 4.4).

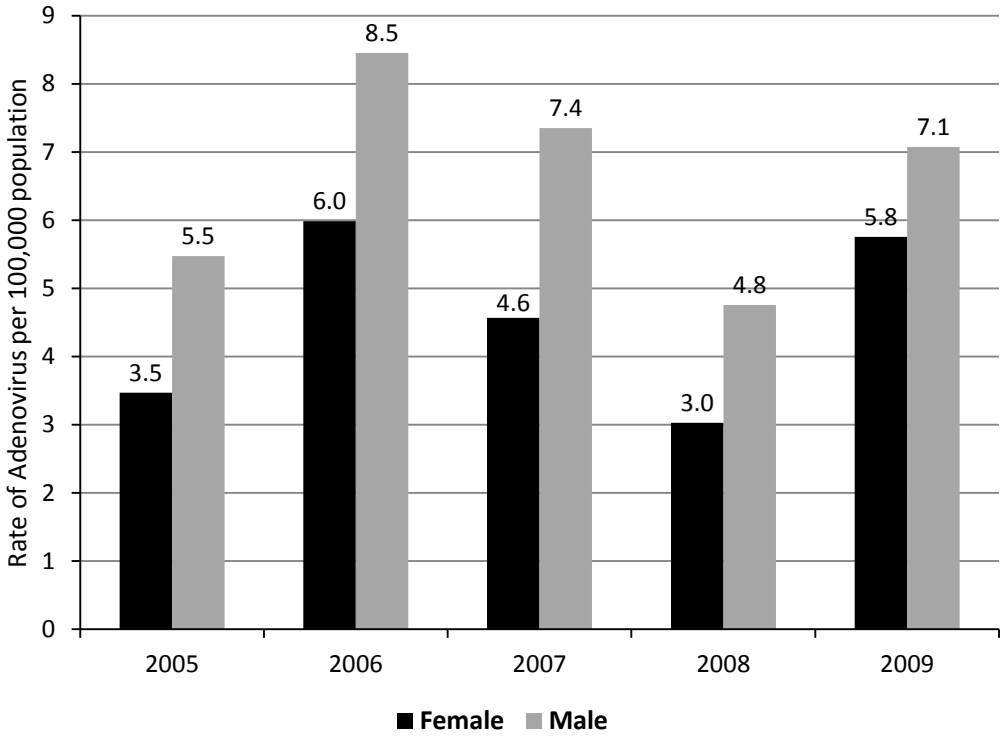


Figure 4.26: Rates of Adenovirus by sex before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

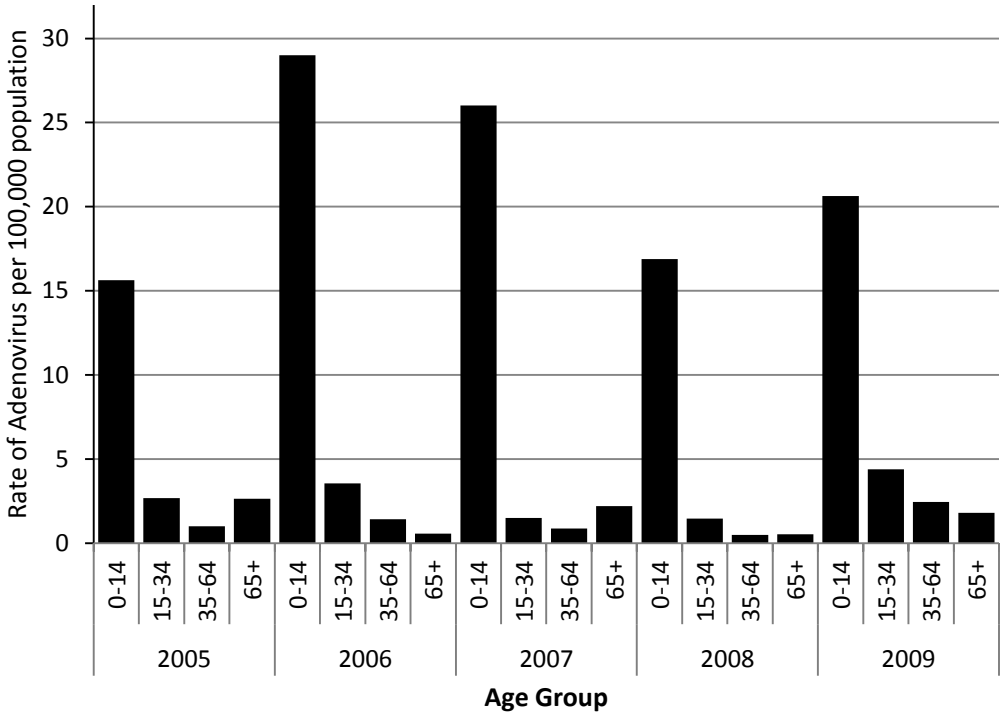


Figure 4.27: Rates of Adenovirus by age group before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

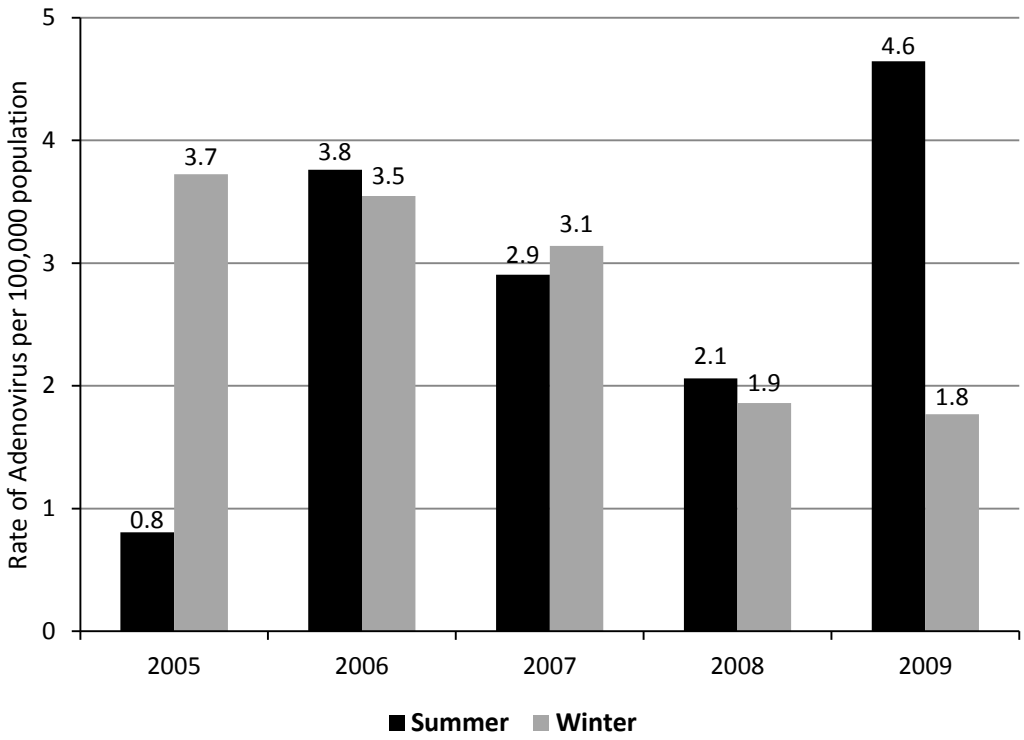


Figure 4.28: Rates of Adenovirus by season before and during the 2009 pandemic in the Province of Alberta from April 1, 2005 to January 31, 2010

### 4.3.7 Summary of respiratory viruses before and during pandemic

In summary, influenza virus-A, parainfluenza, and hMPV were noticeably increased during the 2009 pandemic. Except influenza virus-B, other respiratory viruses included in this study had more effect on children than on adults before and during the 2009 pandemic. Influenza virus A, hMPV, parainfluenza virus, and RSV had more effect on females than males during the 2009 pandemic. Influenza viruses-A, hMPV, parainfluenza virus, and adenovirus demonstrated more increase in summer than in winter during the 2009 pandemic.

## 4.4 Ecological investigation of the 2009 pandemic

This section describes the results of an ecological study that was carried out to investigate the impact of a set of demographic and health risk factors on the incidence of influenza A(H1N1)pdm09. The analysis was performed based on linking the laboratory data with the health profile of Alberta residents obtained from the CCHS data. Only the individuals of ages 15 years or older were included in the analysis.

### 4.4.1 Factors associated with the incidence of influenza A(H1N1)pdm09

The results from univariate Poisson regression (Table 4.1) showed significant association between influenza A(H1N1)pdm09 and demography, geography, health status, health habits, and health care service.

Females had 20% increased risk of developing influenza A(H1N1)pdm09 in comparison to males (RR = 1.20, 90% CI: 1.15–1.19; $p < 0.0001$). Compared to elderly people aged 65 years and older, the 15-to-34-year-old age group had about 4-fold increased risk of developing influenza A(H1N1)pdm09 and the 35-to-64- year-old age group had 1.7 times increased risk of developing influenza A(H1N1)pdm09.

There was significant association between influenza A(H1N1)pdm09 and geography. In comparison to residents of Edmonton, Chinook (HR1) and David Thompson (HR4) residents had 10% increased risk of developing influenza A(H1N1)pdm09. On the contrary, Calgary (HR3) and Aspen (HR7) residents had 10% decreased risk of developing influenza A(H1N1)pdm09. Residents of Palliser (HR2), East Central (HR5), and the Northern Lights (HR9) had more decreased risk of developing influenza A(H1N1)pdm09 that varies between 20% and 50%.

Having a diagnosis of asthma had 11% increased risk of developing influenza A(H1N1)pdm09 in comparison to non-asthmatics (RR= 1.11, 90% CI:

1.05–1.13; p <0.0001). Having a diagnosis of chronic bronchitis had 6% increased risk of developing influenza A(H1N1)pdm09 compared to the group without chronic bronchitis (RR= 1.06, 90% CI: 1.04–1.09; p <0.0001). Diabetics had 4% increased risk of developing influenza A(H1N1)pdm09 than non-diabetics (RR= 1.04, 90% CI: 1.02–1.06; p <0.0001). Having a diagnosis of heart diseases or history of cancer had 2% increased risk of developing influenza A(H1N1)pdm09 compared to the group without these medical conditions (RR= 1.02, 90% CI: 1.00–1.04; p = 0.08). Having mood disorder had 4% increased risk of developing influenza A(H1N1)pdm09 compared to the group without mood disorder (RR= 1.04, 90% CI: 1.02–1.06; p <0.0001). The presence of obesity had 22% increased risk of developing influenza A(H1N1)pdm09 and the overweight group had 33% increased risk of developing influenza A(H1N1)pdm09 (RR= 1.33, 95% CI: 1.26–1.40; p <0.0001) in comparison to the group with normal weight and body mass index.

Having regular physical activity had 2% less the risk of developing influenza A(H1N1)pdm09 compared to the group with occasional or infrequent physical activity (RR= 0.98, 90% CI: 0.96–1.01; p = 0.06). Daily and regular smokers had 10% increased risk of developing influenza A(H1N1)pdm09 in comparison to non-smokers (RR= 1.10 2, 90% CI: 1.07–1.14; p <0.0001).

The group with access to regular medical doctors had 4% increased risk of developing influenza A(H1N1)pdm09 compared to the group without regular medical doctors (RR= 1.04, 95% CI: 1.02 –1.06; p <0.0001). The group of perceived poor health had 11% less the risk of developing influenza A(H1N1)pdm09 in comparison to the group perceived good health (RR= 0.78, 95% CI: 0.61–1.00; p = 0.05). Having a history of receiving flu shot had 10% less the risk of developing influenza A(H1N1)pdm09 in comparison to the group who never had flu shot (RR= 0.90, 95% CI: 0.88–0.93; p <0.0001).

**Table 4.1: Factors associated with the incidence of influenza A(H1N1)pdm09: Results from univariate Poisson regression model ‡**

| Parameter | Level | Relative Risk (RR) | 95% CI LCL | 95% CI UCL | *p*-Value |
|---|---|---|---|---|---|
| ***Geo-Demography*** | | | | | |
| Sex | Female | 1.20 | 1.15 | 1.19 | <0.0001 |
| | Male** | 1.00 | | | |
| Age Group | 15-34 | 4.80 | 4.39 | 5.28 | <0.0001 |
| | 35-64 | 2.70 | 2.42 | 2.92 | <0.0001 |
| | ≥ 65** | 1.00 | | | |
| Health Region | HR1 | 1.10 | 1.00 | 1.18 | 0.06 |
| | HR2 | 0.80 | 0.67 | 0.85 | <0.0001 |
| | HR3 | 0.90 | 0.9 | 0.98 | <0.0001 |
| | HR4 | 1.10 | 1.00 | 1.14 | 0.04 |
| | HR5 | 0.70 | 0.58 | 0.74 | <0.0001 |
| | HR6** | 1.00 | | | |
| | HR7 | 0.90 | 0.84 | 1.00 | 0.06 |
| | HR8 | 1.10 | 0.98 | 1.17 | 0.14 |
| | HR9 | 0.50 | 0.41 | 0.58 | <0.0001 |
| ***Health Status*** | | | | | |
| Asthma | YES | 1.11 | 1.05 | 1.13 | <0.0001 |
| | NO** | 1.00 | | | |
| Chronic Bronchitis | YES | 1.06 | 1.04 | 1.09 | <0.0001 |
| | NO** | 1.00 | | | |
| Obesity | Obese | 1.22 | 1.16 | 1.29 | <0.0001 |
| | Overweight | 1.33 | 1.26 | 1.40 | <0.0001 |
| | Normal** | 1.00 | | | |
| Diabetes | YES | 1.04 | 1.02 | 1.06 | <0.0001 |
| | NO** | 1.00 | | | |
| Cancer | YES | 1.02 | 1.00 | 1.04 | 0.08 |
| | NO** | 1.00 | | | |
| Heart Disease | YES | 1.02 | 1.00 | 1.04 | 0.08 |
| | NO** | 1.00 | | | |
| Mood Disorder | YES | 1.04 | 1.02 | 1.06 | <0.0001 |
| | NO** | 1.00 | | | |
| COPD | YES | 1.01 | 0.98 | 1.02 | 0.93 |
| | NO** | 1.00 | | | |
| Hypertension | YES | 0.99 | 0.97 | 1.01 | 0.58 |
| | NO** | 1.00 | | | |
| ***Health Habits*** | | | | | |
| Physical Activity | Regular | 0.98 | 0.96 | 1.01 | 0.06 |
| | Occasional** | 1.00 | | | |
| Smoker Type | Daily | 1.10 | 1.07 | 1.14 | <0.0001 |
| | Occasional | 0.99 | 0.96 | 1.01 | 0.33 |
| | No Smoking** | 1.00 | | | |
| Drinker Type | Occasional | 1.02 | 0.98 | 1.03 | 0.6 |
| | Regular | 1.01 | 0.97 | 1.03 | 1.0 |
| | No Drink** | 1.00 | | | |

| | | | | | |
|---|---|---|---|---|---|
| ***Health Care Service*** | | | | | |
| Regular Medical Doctor | YES | 1.04 | 1.02 | 1.06 | <0.0001 |
| | NO** | 1.00 | | | |
| Perceived Health | Good | 0.89 | 0.85 | 0.92 | <0.0001 |
| | Poor** | 1.00 | | | |
| Flu Shot | YES | 0.90 | 0.88 | 0.93 | <0.0001 |
| | NO** | 1.00 | | | |

‡ The fit of the negative binomial model was adequate for the data. The deviance statistics were between 1.10 and 1.21 indicating no evidence of over-dispersion.

**Reference used for comparison

Table 4.2 contains the results from a multiple negative binomial model that included age, sex, and health risk factors obtained by linking the laboratory data with the CCHS data. After controlling for sex and age group, there was a significant association between asthma and influenza A(H1N1)pdm09 (RR= 1.06, 90% CI: 1.01–1.07; p = 0.04). Of all health risk factors examined, asthma was the only statistically significant factor. In addition, females had 20% increased risk of developing influenza A(H1N1)pdm09 in comparison to males. Moreover, the 15-to-34-year-old age group had about 4-fold increased risk of developing pH1N1 and the 35-to-64-year-old age group had 1.7 times increased risk of developing influenza A(H1N1)pdm09 in comparison to elderly people aged 65 years and older.

**Table 4.2: Factors associated with the incidence of influenza A(H1N1)pdm09: Results from the multiple negative binomial regression‡**

| Parameter | Level | Relative Risk (RR) | 95% CI LCL | 95% CI UCL | *p*-Value |
|---|---|---|---|---|---|
| Sex | Female | 1.20 | 1.16 | 1.22 | <0.0001 |
| | Male** | 1.00 | | | |
| Age Group | 15-34 | 4.90 | 4.45 | 5.36 | <0.0001 |
| | 35-64 | 2.70 | 2.46 | 2.96 | <0.0001 |
| | ≥ 65 ** | 1.00 | | | |
| Asthma | YES | 1.06 | 1.01 | 1.07 | 0.04 |
| | NO** | 1.00 | | | |

‡ The fit of the negative binomial model was adequate for the data. The deviance statistic was 1.12 indicating no evidence of any overdispersion.

**Reference used for comparison

### 4.4.2 Association between demographic factors and incidence of influenza A(H1N1)pdm09

Table 4.3 contains the results from a multiple negative binomial model that included health region, age, and sex as predictors. The association between influenza A(H1N1)pdm09, sex, age, and geography was statistically significant. The analysis here was performed based on the laboratory data only.

After controlling for sex and age group, and compared to the residents of Edmonton, residents of Palliser (HR2) and the East Central (HR5) regions of Alberta had 22% decreased risk of developing influenza A(H1N1)pdm09, whereas the residents of the Northern Lights region (HR9) had 57% decreased risk (RR= 0.43, 95% CI: 0.33–0.57; $p < 0.0001$).

In comparison to elderly people aged 65 years and older, children younger than 15 years old had more than 7-fold increased risk of developing influenza A(H1N1)pdm09, the 15-to-34-year-old age group had about 4-fold increased risk of developing influenza A(H1N1)pdm09, and the 35-to-64-year-old age group had 1.7 times increased risk of developing influenza A(H1N1)pdm09. Furthermore, females had 12% increased risk of developing influenza A(H1N1)pdm09 in comparison to males (RR= 1.12, 95% CI: 1.02–1.24; $p = 0.02$).

**Table 4.3: Association between demographic factors and incidence of influenza A(H1N1)pdm0: Results from the multiple negative binomial regression ‡**

| Parameter | | Relative Risk(RR) | 95% CI | *p*-Value |
|---|---|---|---|---|
| Sex | Female | 1.12 | 1.02 – 1.24 | 0.02 |
| | Male** | 1.00 | | |
| Age Group | | | | |
| | 0-14 | 8.37 | 6.83 – 10.25 | < 0.0001 |
| | 15-34 | 4.90 | 4.00 – 6.00 | < 0.0001 |
| | 35-64 | 2.72 | 2.22 – 3.34 | < 0.0001 |
| | ≥ 65** | 1.00 | | |
| Health Region | HR1 | 0.91 | 0.75–1.11 | 0.37 |
| | HR2 | 0.78 | 0.63–0.98 | 0.03 |

| | | | | |
|---|---|---|---|---|
| | HR3 | 0.90 | 0.76–1.06 | 0.19 |
| | HR4 | 1.06 | 0.89–1.26 | 0.53 |
| | HR5 | 0.79 | 0.63–0.98 | 0.03 |
| | HR6** | 1.00 | | |
| | HR7 | 0.99 | 0.82–1.20 | 0.91 |
| | HR8 | 0.95 | 0.78–1.16 | 0.61 |
| | HR9 | 0.43 | 0.33–0.57 | <0.0001 |

‡ The fit of the negative binomial model was adequate for the data. The deviance statistic was 1.14 indicating no evidence of any over-dispersion.

**Reference used for comparison

HR1= Chinook Regional Health Authority
HR2= Palliser Health Region
HR3= Calgary Health Region
HR4= David Thompson Regional Health Authority
HR5= East Central Health
HR6= Capital Health
HR7= Aspen Regional Health Authority
HR8= Peace Country Health
HR9= Northern Lights Health Region

# CHAPTER FIVE

# DISCUSSION AND CONCLUSIONS

## 5.1 Discussion

In the thesis, association between influenza A(H1N1)pdm09 and geography, age, sex, and asthma was found statistically significant. The risk of developing influenza A(H1N1)pdm09 varied among Alberta zones. Children younger than 15 years old were at seven times higher risk of the disease compared to the elderly people aged 65 years and older. The 15-to-34-year-old age group had about 4-fold increased risk and the 35-to-64-year-old age group had 1.7-fold increased risk in comparison to elderly people aged 65 years and older. These findings were supported by many earlier studies that suggested disproportionately effects of influenza A(H1N1)pdm09 in young adults and children [178].

Children have emerged as highly vulnerable groups to influenza A(H1N1)pdm09 infection [107]. A study conducted by Ertek et al. [179] in Turkey concluded that influenza A(H1N1)pdm09 virus has mainly affected children aged 5-14 years old. Glatman-Freedman et al. [180] performed a systematic review and meta-analysis using 50 articles that reported outbreak investigations with direct measurements of attack rates of influenza A(H1N1)pdm09 pandemic among children at various settings including schools, households, travel and social events. The authors concluded that children have higher attack rates of influenza A(H1N1)pdm09 than adults. They speculated that the reasons could be due to “lack of immunity from previous exposure to similar influenza viruses as well as virological, host characteristics, behavioral, environmental and other factors” that affect children more than adults [180]. Other studies [112, 181-183] indicated that the highest rates of hospital admission in Canada, the United States, Australia, and the United Kingdom

during the 2009 pandemic were reported among children less than five years of age. Further, the Center for Disease Control and prevention (CDC) considered young children 6 months to four years old as amongst the top-priority groups to receive vaccine doses for A(H1N1)pdm09 [247].

Contrary to children, elderly people aged 65 years and older had the lowest odds of being infected by influenza A(H1N1)pdm09. Although people of this age group may suffer from some immunological deterioration, Hancock et al. [184] found that those people have had the advantage of having pre-existing cross-reactive antibodies to A(H1N1)pdm09 viruses acquired during the aging process through infection and/or immunizations. Klein et al. [107] indicated that the reduced number of infections in individuals aged ≥ 65 years arose in part from the fact that "antibodies generated to pre-1950 H1N1 viruses cross react with 2009 H1N1, resulting in limited protection from 2009 H1N1 infection." Hancock et al. made their conclusion based on measuring the cross-reactive antibodies to pandemic A(H1N1)pdm09 virus in stored serum samples collected from individuals who either donated blood or were vaccinated with recent seasonal or 1976 swine influenza vaccines. In their study, Hancock et al. did not find evidence of cross-reactive antibodies to influenza A(H1N1)pdm09 in individuals under 35 years of age.

In this thesis, boys had increased risk of influenza A(H1N1)pdm09 compared to girls until the age of 14 years; this pattern was reversed from 15 to 64 years with females having higher risk than males. Boys under 15 years of age reported increased risk of having influenza A(H1N1)pdm09 compared to girls. Many studies [185, 186,187,188] indicated that this may be due to less immune response to influenza A(H1N1)pdm09 virus in boys than in girls. However, the mechanisms that underlie differences between sexes are complicated and can be influenced by genetic, immunological, hormonal, and behavioral factors [185]. Females usually generate higher innate and adaptive immune responses compared to males [185,189-191], which can speed up virus clearance and

reduce virus load. Yet, the sex-based differences in immune responses to infectious diseases are poorly understood and insufficiently investigated in the literature [186,192].

Females between 15 and 64 years were at 12% higher risk of infection with influenza A(H1N1)pdm09 than males. A few studies [193,186,185] reported comparable patterns of male-female differences in the incidence of influenza A(H1N1)pdm09 that were age-dependent. A study conducted by Klein [193] indicated that "the incidence, severity and case fatality rates following infection appear to differ between males and females, but often are age-dependent and vary between countries." Other studies [194,193,195-199, 185] reported higher rates of hospitalization among females in the reproductive age between 15 and 49 years old. In addition, pregnancy has shown to be associated with increased risk of severe complications following influenza A(H1N1)pdm09 infection [200-207]. Several studies [107,113,117,118,121,123,124] indicated that females, especially pregnant women, may have less immune response to influenza A(H1N1)pdm09 virus than males. In addition, the immune response to viruses can vary with changes in hormone concentrations caused by natural fluctuations over the menstrual or estrous cycle, contraception use, pregnancy, and menopause [185,208]. Moreover, the biological changes in the respiratory, cardiovascular, and immune systems during pregnancy, make pregnancy itself a risk factor for severe disease [200,209-211,193]. However, many of the infected females of the reproductive age during the 2009 pandemic were not pregnant [107]. This may be attributable to potential comorbidity with other factors associated with the increased incidence of infection.

The subsequent reversal of the virus impact on adults can potentially be due to several reasons. As a rule, the expression of most diseases originates from a combination of genetic vulnerability, massive endocrine changes during puberty, and environment [212]. Studies have also shown that females tend to

seek medical care more frequently than males of the same age [186,213,214], and this can result in more reporting of illness by females.

Having a diagnosis of asthma were at 6% increased risk of influenza A(H1N1)pdm09 in comparison to those without asthma. No association was found between A(H1N1)pdm09 and other factors (i.e., air quality, smoking, drink, obesity, mood disorder, perceived health, physical activity, and financial status) that have been also investigated in this study. Of the 64 A(H1N1)pdm09-confirmed deaths reported to Alberta Health [215], 23 cases (~36%) had asthma. Individuals living with asthma, especially those with poorly controlled asthma, may have more severe influenza A(H1N1)pdm09 than others who do not have asthma [216]. However, the association between influenza A(H1N1)pdm09 and asthma can be confounded with age. O'Riordan et al. [217] conducted a study on children with influenza A(H1N1)pdm09 admitted to a large pediatric hospital in Ontario. They found that asthma was more likely to be a significant risk factor for severe illness among children than among those with seasonal influenza. Other studies concluded similar results [218-221]. Two more studies conducted in Australia, New Zealand and USA [80,216,222] concluded that the majority of individuals (73%) who developed severe influenza A(H1N1)pdm09 and admitted to inpatient care or ICU had underlying chronic conditions, among which asthma was the most common comorbid condition. Salas et al. [216] indicated that the mechanism of the possible influence of asthma on the severity of influenza A(H1N1)pdm09 is unclear and needs to be investigated. Several studies showed evidence of impairments of the innate and acquired immunity among individuals with asthma [223-227]. Such impairments can potentially "compromise the host's ability to clear microbial organisms (viruses or bacteria) from the airways, increasing the risk of invasive infection" [216].

Although several studies demonstrated above affirmed that influenza A(H1N1)pdm09 occurred more frequently among children with asthma during the 2009 pandemic, Erbas et al. [228] did not support this conclusion and

suggested that individuals with asthma have more frequent access to health care facilities than others without asthma; for instance, to follow-up for disease status or progress, for newly observed symptoms, or for treatment modification. Erbas et al. claimed that during the 2009 pandemic, individuals with asthma were more likely to come into contact with people infected with influenza A(H1N1)pdm09 at health care facilities, and thus becoming more vulnerable to infection [228] . The findings of Erbas et al claim seems convincing based on consideration of differential exposure as a confounder of the association between asthma and pandemic infections. However, their observation was based on a study that conducted on a small sample of 111 children with asthma admitted to a hospital in Australia during the peak 2010 season [228]. The potential deficiency of representation of the sample used, as well as the unavailability of data on A(H1N1)pdm09 cases during the 2009 pandemic, suggests further investigation. Moreover, caution should be used to compare these results, especially when conducting systematic reviews or meta-analysis.

Similar to the findings for influenza A(H1N1)pdm09 in this thesis, reversal patterns of age-dependent male-female differences have been reported in subjects with asthma [248]. Epidemiological studies reported a male predominance of asthma before puberty and a female predominance after puberty [212, 236, 249]. A National Study in the UK [230] reported predominance in the incidence of asthma in boys younger than 16 years of age with a reversal of the sex ratio thereafter. Other studies [231,232] reported higher rates in women through the reproductive years. The influence of gender was also reported in hospital admissions, with more boys admitted before puberty and a gender reversal evident post-puberty [233]. This can be due to the different physiology between males and females. Boys have a relative slow growth of airways compared to the growth of their lungs [234,235]. Girls, on the other hand, have balanced growth of airways to lung volume and consequently greater air flow rates at fixed proportions of total lung capacity. This sex difference reverses at puberty with an elevation of all indices of lung function in

males. Nevertheless, asthma cannot entirely explained by the structural or functional airway sex differences. For instance, inflammatory responses in the airway wall can be accountable for causing airway obstruction [236] that leads to asthma.

Air quality health index (AQHI) records collected by the Environment and Sustainable Resource Development [237] on daily basis for the entire period of pandemic were also considered as part of the thesis. However, the results were not reported because of the sparsity of data that makes the findings not generalizable. This is because the AQHI data were available only to large cities that have monitoring stations. Although ambient weather conditions and climate patterns may have direct impact on airborne transmissions that facilitate the spread of a virus over broad geographic areas [238, 246], we did not find sufficient evidence to support an association between air quality and influenza A(H1N1)pdm09 in Alberta.

In this thesis, residents of the Northern Lights of Alberta, along with the residents of the former Palliser and the East Central regions have decreased risk of developing influenza A(H1N1)pdm09 compared to Edmonton residents. To the best of my knowledge, no studies have analytically investigated the geographical variation of influenza A(H1N1)pdm09 among Alberta zones or regions (e.g., by means of inferential statistics).

Several studies investigated the geographic distribution of influenza A(H1N1)pdm09 and reported significant association with both the incidence and mortality rates [168,169-172, 173-176]. Such geographic variation may also have impact on the transmission and spread of the disease. Besides, vulnerability to influenza A(H1N1)pdm09 infection varied among individuals from different groups and races. Wenger et al. [174] reported that Alaska Native people and Asian/Pacific Islanders were two to four times more likely to be infected with influenza A(H1N1)pdm09 and hospitalized than white Caucasians. A study from

China using the data from 30 provinces on climate, geography, and demography showed that regional variation in influenza was associated with climatic conditions [177]. On the other hand, Wenger et al [174] indicated that the reasons for geographical changes in influenza A(H1N1)pdm09 during pandemic in Alaska were not clear. Storms et al. [168] investigated laboratory-confirmed data for influenza A(H1N1)pdm09 from 80 countries (47 temperate and 33 tropical–subtropical) that have 5.5 billion (80%) of the world's population and examined the correlation between geography (i.e., central latitude and climatic regions) and proportion of influenza A(H1N1)pdm09. The authors found that the activity of influenza A(H1N1)pdm09 was associated with the latitude; the temperate countries had higher intensity (higher median peak) but shorter duration of influenza A(H1N1)pdm09 activity than tropical–subtropical countries during pandemic [174]. Furthermore, the impact of geography on influenza 2009 pandemic might be confounded by other factors, including access to health care and socio-economic attributes [168,169]. Wesche et al. [170] reported that people living in remote areas, such as First Nations, Inuit, and Métis were at a higher risk of A(H1N1)pdm09. The authors claimed that this may be due to lack of running water, overcrowding, access to health care facilities, and poor nutrition, which all increase the likelihood of infection [170].

## 5.2 Strengths and Limitations

### 5.2.1 Strengths

The main strengths of this study include the availability of a large province-wide dataset for respiratory infectious diseases over a 6-years period (2004-2009), together with all influenza A(H1N1)pdm09 laboratory-confirmed cases. The linkage of these laboratory data with other data from different sources facilitated exploring the distribution patterns and epidemiologic characteristics of influenza A(H1N1)pdm09 using ecological analysis. In addition, this study provided an opportunity to investigate the behavior of a new influenza strain in Alberta; a province that is ranked as the fourth highly populated province in

Canada [239] with a population of 4,025,100 in 2013. Moreover, the major part of the analysis conducted in this thesis was population-based, which provided more validity, generalizability, and a broad view to the results. Further, this study was unique in its approach of analyzing laboratory population-based data on A(H1N1)pdm09 along with the other common respiratory viruses. This approach allowed investigating the behavior of these respiratory viruses (i.e., influenza virus A, influenza virus B, parainfluenza virus, hMPV, RSV, and adenovirus) before and during pandemic. Also, the study demonstrated the morbidity of influenza A(H1N1)pdm09 as impacted by sex and age, which was always overlooked in other studies on the same topic due to unavailability of population-based pandemic data.

### 5.2.2 Limitations

A limitation of this research comes from its ecological part. Linking the laboratory data with the CCHS data may result in having divergent groups (e.g., zones) that cannot be effectively compared. This is because the laboratory data were collected from the entire population of Alberta of all ages (i.e., population-based) whereas the CCHS data were generated by random sampling from subjects aged 12 years and older. In addition, there was a time gap between the two collection procedures. Cycle 4.1 CCHS data were collected between 2007 and 2008 whereas the laboratory data were collected in a real-time like fashion during the 2009 outbreak. With this limitation, an ecological approach was adopted to investigate the potential association between influenza A(H1N1)pdm09 and a set of health risk factors. Although ecological studies have their weaknesses [240,241], they are still useful for public health surveillance to measure exposures at a group rather than an individual level [241]. In spite of this drawback, the findings of this thesis were sufficiently consistent with those acknowledged by other studies [216,242,243-245,186,192].

In addition, a number of factors may affect the concluded results. For instance, cases with influenza A(H1N1)pdm09 reported to the ProvLab may not

include the entire population of pandemic cases in Alberta. Specifically, individuals from disadvantaged groups (e.g., First Nations and individuals living in remote areas) may have the disease, and even die from it, without seeking health care service. As a result, no specimens are submitted for testing. Further, specimens submitted to the ProvLab might be confounded with disease severity and access to health care facilities. Such factors can mislead the results and contribute to underestimating the measured effects. The comparison of circulatory respiratory viruses before and during the 2009 pandemic can be confounded with changes in testing patterns during the pandemic.

### 5.3 Conclusions

In this study, associations between influenza A(H1N1)pdm09 virus and four factors (geography, age, sex, and asthma) were found significant and consistent with findings from other relevant studies. Association between sex and age was observed; a switch in the vulnerability to A(H1N1)pdm09 occurred in females between 15 to 64 years of age to have higher risk than males. These factors can be considered as risk factors or, at least, as important measures to consider when developing health care strategies for the prevention and control of influenza pandemics. Consideration of these factors can result in a more effective public health preparedness and responses to future influenza pandemics.

# BIBLIOGRAPHY


1 World Health Organization. WHO Handbook for Journalists: Influenza Pandemic. WHO Outbreak Communication, WHO, Geneva, 2005, accessed on April 15, 2014, from http://www.who.int/csr/don/Handbook_influenza_pandemic_dec05.pdf

2 P. Effler. Every Year Is an Influenza Pandemic for Children: Can We Stop Them? Pediatrics, vol. 130, 2012, pp. 554-557.

3 J. Nguyen-Van-Tama, A. Hampson. The Epidemiology and Clinical Impact of Pandemic Influenza. Vaccine, vol. 21, 2003, pp.1762–1768.

4 R. Rüttimann, P. Bonvehí, D. Vilar-Compte, R. Isturiz, J. Labarca, E. Vidal. Influenza among the elderly in the Americas: A Consensus Statement. Rev Panam Salud Publica, vol. 33, no. 6, 2013.

5 A. Monto, L. Comanor, D. Shay, W. Thompson. .Epidemiology of Pandemic Influenza: Use of Surveillance and Modeling for Pandemic Preparedness. JID, vol. 194, Suppl 2, 2006, pp. S95-S97.

6 D. Carcione, C. Giele, G. Dowse, D. Mak, L Goggin, et al. Comparison of Pandemic (H1N1) 2009 and Seasonal Infl uenza, Western Australia, 2009. Emerging Infectious Diseases, vol. 16, no. 9, 2010, pp. 1388-1395.

7 F. Southwick, Infectious Diseases: A Clinical Short Course, Second Edition. McGraw-Hill, 2007.

8 An Advisory Committee Statement (ACS). Statement on Seasonal Influenza Vaccine for 2011–2012. Public Health Agency of Canada, 2012, accessed on April 15, 2014, from file:///C:/Users/elamy/Downloads/-sites-webphac-htdocs-archives-acs-dcc-5-eng.pdf

9 World Health Organization. Influenza (Seasonal), Fact Sheet No 211, WHO, Geneva, 2012, accessed on April 15, 2014, from http://www.novartisvaccines.com/downloads/flucelvax/Seasonal_Influenza_Fact_Sheet.pdf

10 K. Kuszewski, L. Brydak. The Epidemiology and History of Influenza. Biomed & Pharmacother, vol. 54, 2000, pp. 188-95.

11 P. Kupperberg. The Influenza Pandemic of 1918–1919. InfoBase Publishing, New York, 2008.

12 The Standing Senate Committee on Social Affairs, Science and Technology Senate. Canada's Response to the 2009 H1N1 Influenza Pandemic. The Senate of Canada, 2010, accessed on April 15, 2014, from http://www.parl.gc.ca/content/sen/committee/403/soci/rep/rep15dec10-e.pdf

13 Alberta Health. Public Health Notifiable Disease Management Guidelines: Influenza. Government of Alberta, 2012, accessed on April 15, 2014, from http://www.health.alberta.ca/documents/Guidelines-Influenza-2012.pdf

14 D. Heymann. Control of Communicable Diseases Manual. Washington, DC, American Public Health Association, 19th ed., 2008.

15 J. Treanor. Influenza Viruses, Including Avian Influenza and Swine Influenza. In G. Mandell, J. Bennett, R. Dolin (eds): Principles and Practice of Infectious Diseases, 7th ed. Philadelphia: Churchill Livingstone Elsevier, 2010, pp. 2265–2288.

16 M. Chan. World now at the start of 2009 Influenza Pandemic. World Health Organization, WHO Media Center, Geneva, 2009, accessed on April 15, 2014, from http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/

17 Edwin D. Kilbourne. Influenza Pandemics of the 20th Century. Emerging Infectious Diseases , vol. 12, no. 1, 2006, accessed on April 15, 2014, from http://wwwnc.cdc.gov/eid/article/12/1/pdfs/05-1254.pdf

18 K. Jeffery, Taubenberger, H. Harvey, M. Memoli. The 1918 Influenza Pandemic: Lessons for 2009 and the Future. Crit Care Med, vol. 38, no. 3, 2010, accessed on April 15, 2014, from http://journals.lww.com/ccmjournal/Fulltext/2010/04001/The_1918_influenza_pandemic__Lessons_for_2009_and.2.aspx

19 United States Department of Health and Human Services. The Great Pandemic: The United States in 1918-1919, accessed on April 15, 2014, from http://www.flu.gov/pandemic/history/1918/

20 E. Kilbourne. Influenza Pandemics of the 20th Century. Emerg Infect Dis., 2006, accessed on April 15, 2014, from http://wwwnc.cdc.gov/eid/article/12/1/05-1254_article.htm

21 D. Henderson, B. Courtney, T. Inglesby, E. Toner, J. Nuzzo. Public Health and Medical Responses to the 1957-58. Biosecur Bioterror, vol. 7, no. 3, 2009, pp. 265-73.

22 F. Dunn. Pandemic Influenza in 1957: Review of International Spread of new Asian Strain. JAMA, vol. 166, no. 10, 1958, pp. 1140-1148.

23 S. Knobler, A. Mack, A. Mahmoud, S. Lemon (eds.). The Threat of Pandemic Influenza: are we ready?. Workshop summary / prepared for Forum on Microbial Threats, Board on Global Health, Washington, 2005, accessed on April 15, 2014, from http://www.ncbi.nlm.nih.gov/books/NBK22156/pdf/TOC.pdf

24 World Health Organization. Pandemic (H1N1) 2009. Update 80, WHO, 2009, accessed on April 15, 2014, from http://www.who.int/csr/don/2009_12_23/en/index.html

25 N. Mishra. Emerging influenza A/H1N1: Challenges and development. The Health, vol. 2, no. 1, 2011, pp. 16-22.

26 World Health Organization. Pandemic (H1N1) 2009. Update 105, WHO, Geneva, 2010, accessed on November 28, 2012, from http://www.who.int/csr/don/2010_06_18/en/print.html

27 Canadian Health Services Research Foundation, "Myth: The Aging Population Will Overwhelm the Healthcare System," Myth busters. CHSRF, Ottawa, 2001.

28 Public Health Agency of Canada. *FluWatch*. PHAC, Ottawa, 2010, accessed on Nov. 28, 2012, from http://www.phac-aspc.gc.ca/fluwatch/index-eng.php?utm_source=RedirectURL&utm_medium=EngURL&utm_content=Fluwatch

29 Canadian Institute for Health Information. Health Care in Canada 2010. CIHI, 2010, accessed on April 15, 2014, from https://secure.cihi.ca/free_products/HCIC_2010_Web_e.pdf

30 Treasury Board of Canada Secretariat. Supplementary Estimates (B), 2009-10, for the Fiscal Year Ending March 31st 2010. TBS, Ottawa, 2010.

31 P. Waldie and C. Alphonso. Cost of Vaccinating Nation Hits $1.5-Billion and Climbing. *The Globe and Mail*, November 12, 2009.

32 B. Sander et al. "Is a Mass Immunization Program for Pandemic (H1N1) 2009 Good Value for Money? Evidence From the Canadian Experience. Vaccine, vol. 28, no. 38, 2010, pp. 6210–6220.

33 The Health Quality Council of Alberta (HQCA). Review of Alberta's Response to the 2009 H1N1 Influenza Pandemic. Government of Alberta, 2010.

34 Government of Alberta. Review of Deaths Occurring in Alberta During the 2009 Influenza Pandemic. Government of Alberta, 2012 accessed on April 15, 2014, from http://www.health.alberta.ca/documents/2009-Pandemic-Deaths-Review.pdf

35 E. Padlan. The pandemic 2009 (H1N1) Swine Influenza Virus is Mild Compared to the Pandemic 1918 (H1N1) Virus because of a Proline-to-Serine Substitution in the Receptor-Binding Site of its Hemagglutinin – A Hypothesis. Med Hypotheses, 2009.

36 Public Health Agency of Canada. FluWatch report: March 16 to 22, 2014 (Week 12). PHAC, Ottawa, 2014, accessed on April, 8, 2014 from http://www.phac-aspc.gc.ca/fluwatch/13-14/w12_14/pdf/fw2014-12-eng.pdf

37 Public Health Agency of Canada. Notice to Health Care Professionals – Influenza A(H1N1)pdm09 Predominant Seasonal Influenza Strain. PHAC, Ottawa, 2014, accessed on April, 8, 2014 from http://www.phac-aspc.gc.ca/influenza/ah1n1-eng.php

38 World Health Organization. Standardization of Terminology of the Pandemic A(H1N1)2009 virus. WHO, Geneva, 2010, accessed on April 15, 2014 from http://www.who.int/influenza/gisrs_laboratory/terminology_ah1n1pdm09/en/

39 Canadian Institute for Health Information. The Impact of the H1N1 Pandemic on Canadian Hospitals. Report, CIHI, 2010, accessed on April 15, 2014, from https://secure.cihi.ca/free_products/H1N1_AIB_final_EN.pdf

40 World Health Organization. FluNet Summary. WHO, Geneva, 2014, accessed on April 15, 2014 from http://www.who.int/influenza/gisrs_laboratory/updates/summaryreport/en/

41 World Health Organization. H1N1 in Post-Pandemic Period. WHO, Geneva, 2010, accessed on April 15, 2014 from http://www.who.int/mediacentre/news/statements/2010/h1n1_vpc_20100810/en/

42 Centers for Disease Control and Prevention. People at High Risk of Developing Flu–Related Complications. CDC, Atlanta, accessed on April 15, 2014, from http://www.cdc.gov/flu/about/disease/high_risk.htm

43 M. Rothberg, S. Haessler. Complications of Seasonal and Pandemic Influenza. Crit Care Med., vol. 38, 2010, pp. e91–7.

44 M. Van Kerkhove, K. Vandemaele1, V. Shinde1, et al. Risk Factors for Severe Outcomes Following 2009 Influenza A (H1N1) Infection: A Global Pooled Analysis. PLoS Med.2011 Jul;8(7):e1001053.

45 L. Vaillant, G. La Ruche1, A. Tarantola, P. Barboza1. Epidemiology of Fatal Cases Associated with Pandemic H1N1 Influenza 2009. Eurosurveillance, vol. 14, no. 33, 2009.

46 M. Madjid, I. Aboshady, et al. Influenza and Cardiovascular Disease: A Causal Relationship? Texas Heart Institute Journal, vol. 31, no. 1, 2004.

47 L. Simonsen, R. Taylor, C. Viboud, Mark A Miller, L. Jackson. Mortality Benefits of Influenza Vaccination in Elderly People: an Ongoing Controversy. Lancet Infect Dis., vol. 7, 2007, pp. 658–66.

48 The World Health Organization. Influenza (Seasonal). Fact sheet No. 211, WHO, Geneva, 2009, accessed on Nov. 28, 2012, from http://www.who.int/mediacentre/factsheets/fs211/en/

49 W. Thompson, D. Shay, E. Weintraub, et al. Mortality Associated with Influenza and Respiratory Syncytial Virus in the United States. JAMA, vol. 289, 2003, pp. 179–86.

50 W. Thompson, D. Shay, E. Weintraub, et al. Influenza-Associated Hospitalizations in the United States. JAMA, vol. 292, 2004, pp. 1333–1340.

51 D. Schanzer, T. Tam, J. Langley, et al. Influenza-Attributable Deaths, Canada 1990-1999. Epidemiol Infect., vol. 135, no. 7, 2007, pp. 1109-1116.

52 E. Brooks, C. Bryce, C. Avery, C. Smelser, D. Thompson, K. Nolte. 2009 H1N1 Fatalities: The New Mexico Experience. J Forensic Sci, vol. 57, no. 6, 2012.

53 Peter Doshi. Bulletin of the World Health Organization. The elusive definition of pandemic influenza. Bulletin of the World Health Organization. vol. 89, 2011, pp. 532-538.

54 C. Potter. A History of Influenza. Journal of Applied Microbiology, vol. 91, no. 4, 2001, pp. 572-579.

55 R. Garten, C. Davis, C. Russell, et al. Antigenic and Genetic Characteristics of Swine-Origin 2009 A(H1N1) Influenza Viruses Circulating in Humans. Science, no. 325, 2009, pp.197-201.

56 J. Taubenberger, D. Morens: 1918 influenza: the Mother of All Pandemics. Emerg Infect Dis., no. 12, 2006, pp.15-22.

57 L. Wessel, Y. Hua, J. Wu, S. Moghadas. Public Health Interventions for Epidemics: Implications for Multiple Infection Waves. BMC Public Health, vol. 11, suppl 1:S2, 2011.

58 I. Cameron and D. Montizambert. The 1918-1919 Spanish Influenza Pandemic in Canada. Canadian Family Physician, vol. 56, 2010, pp. 453-454.

59 Centers for Disease Control and Prevention. Update: Swine Influenza A(H1N1) Infections– California and Texas. Morbidity and Mortality Weekly Report, CDC, no. 58, 2009, accessed on Nov. 28, 2012, from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm58d0424a1.htm

60 World Health Organization. Swine influenza—update 3. WHO, Geneva, 2009, accessed on Nov. 28, 2012, from http://www.who.int/csr/don/2009_04_27/en/index.html

61 M. Chan. Swine Influenza: Statement by WHO Director. WHO, Geneva, 2009, accessed on Nov. 28, 2012, from http://www.who.int/mediacentre/news/statements/2009/h1n1_20090425/en

62 World Health Organization. Pandemic (H1N1) 2009— update 94. WHO, Geneva, 2010, accessed on Nov. 28, 2012, from http://www.who.int/csr/don/2010_04_01/en/index.html

63 World Health Organization. Pandemic (H1N1) 2009–update 112. WHO, Geneva, accessed on Nov. 28, 2012, from www.who.int/csr/don/2010_08_06/en/index.html

64 M. Girard, J. Tam, O. Assossou, M. P. Kieny. The 2009 A (H1N1) Influenza Virus Pandemic: A Review. Vaccine, no. 28, 2010, pp. 4895–4902.

65 S. Sullivan, R. Jacobson, W. Dowdle, G. Poland. 2009 H1N1 Influenza. Mayo Clin Proc., vol. 85, no. 1, 2010, pp. 64-76.

66 G. Chowell, J. Hyman, L. Bettencourt, C. Castillo-Chavez (eds.). Mathematical and Statistical Estimation Approaches in Epidemiology. Springer Dordrecht Heidelberg, 2009.

67 J. Juno, K. Fowke, Y. Keynan. Epidemiology of the 2009 Pandemic Influenza A (H1N1). National Collaborating Centre for Infectious Diseases (NCCID), Manitoba, 2011.

68 A. Tuite, A. Greer, M. Whelan, A. Winter, B. Lee, P. Yan, et al. Estimated Epidemiologic Parameters and Morbidity Associated with Pandemic H1N1 Influenza. Can Med Assoc J, vol. 182, no. 2, 2010, pp. 131-136.

69 Y. Yang, J. Sugimoto, E. Halloran, N. Basta, D. Chao, L. Matrajt, G. Potter, E. Kenah, I. Longini. The Transmissibility and Control of Pandemic Influenza A (H1N1) Virus. Science, vol. 326, no. 5953, 2009, pp. 729-733.

70 D. Balcan, H. Hu, B. Goncalves, P. Bajardi, C. Poletto, J. Ramasco, et al. Seasonal Transmission Potential and Activity Peaks of The New Influenza A(H1N1): A Monte Carlo Likelihood Analysis Based on Human Mobility. BMC Medicine, 2009, pp.7-45.

71 J. Lessler, N. Reich, C. Cummings. Outbreak of 2009 pandemic influenza A (H1N1) at a New York City School. New Engl J Med., vol. 361, no. 27, 2009, pp. 2628-36.

72 L. Rvachev, I. Longini Jr. Mathematical Biosciences, vol. 75, no. 3, 1985.

73 I. Longini. Mathematical Biosciences, vol. 82, no. 19, 1986.

74 C. Mills, J. Robins, M. Lipsitch. Nature, 2006, pp. 432:904.

75 R. Brookmeyer. Incubation Period of Infectious Diseases. In: P. Armitage, T. Colton, (Eds.), Encyclopedia of Biostatistics. Wiley, New York, 2006, pp. 2011–2016.

76 V. Farewell, A. Herzberg, K. James, L. Ho, G. Leung. SARS Incubation and Quarantine Times: When is an Exposed Individual Known to be Disease Free? Stat. Med, vol. 24, 2005 pp. 3431–3445.

77 P. Sartwell. The distribution of Incubation Periods of Infectious Diseases. Am. J. Hyg., vol. 51, 1950, pp. 310–318.

78 R. Brookmeyer, X. You. A Hypothesis Test for the End of a Common Source Outbreak, 2006.

79 P. Fine, The Interval between Successive Cases of an Infectious Disease. Am. J., 2003.

80 D. Haydon, M. Chase-Topping, et al. The Construction and Analysis of Epidemic Trees with Reference to the 2001 UK Foot-and-Mouth Outbreak. Proc Biol Sci., vol. 270, no. 1511, 2003, pp. 121–127.

81 J. Lloyd-Smith, S. Schreiber, P. Kopp, W. Getz. Superspreading and the Effect of Individual Variation on Disease Emergence. Nature, vol. 438, 2005, pp. 355–359.

82 F. Dawood, A. Iuliano, C. Reed, et al. Estimated Global Mortality Associated with the first 12 Months of 2009 Pandemic Influenza A H1N1 Virus Circulation: A Modeling Study. The Lancet Infectious Diseases, vol. 12, no. 9, 2012, pp. 687-695.

83 J. Michalove, T. Ndahwouh, O. Diop, et al, eds. Delayed Pandemic H1N1 Transmission in West Africa, May 2009–March 2010. Options for the Control of Influenza VII Conference, Hong Kong, 2010, pp. 3–7.

84 E. Miller, K. Hoschler, P. Hardelid, E. Stanford, N. Andrews, M. Zambon. Incidence of 2009 Pandemic Influenza A H1N1 Infection in England: a Cross-sectional Serological Study. Lancet, vol. 375, 2010, pp.1100–08.

85 J. Ortiz, K. Lafond, T. Wong, T. Uyeki. Pandemic Influenza in Africa, Lessons Learned from 1968: A Systematic Review of the Literature. Influenza Other Respi Viruses, vol. 6, 2012, pp. 11–24.

86 C. Cohen, L. Simonsen, J. Kang, et al. Elevated Influenza-related Excess Mortality in South African Elderly Individuals, 1998–2005. Clin Infect Dis., vol. 51, 2010, pp. 1362–69.

87 N. Johnson, J. Mueller. Updating the Accounts: Global Mortality of the 1918–1920 "Spanish" Influenza Pandemic. Bull Hist Med, vol. 76, 2002, pp. 105–15.

88 G. La Ruche, A. Tarantola, P. Barboza, L. Vaillant, J. Gueguen, M. Gastellu-Etchegorry. The 2009 Pandemic H1N1 Influenza and Indigenous Populations of the Americas and the Pacific. Euro Surveill., vol. 14, no. 42, 2009.

89 C. Murray, A. Lopez, B. Chin, D. Feehan, K. Hill. Estimation of Potential Global Pandemic Influenza Mortality on the Basis of Vital Registry Data from the 1918–20 Pandemic: a Quantitative Analysis. Lancet, vol. 368, 2006, pp.2211–18.

90 H. Nair, W. Brooks, M. Katz, et al. Global Burden of Respiratory Infections due to Seasonal Influenza in Young Children: A Systematic Review and Meta-Analysis. Lancet, vol. 378, 2011, pp.1917–30.

91 Centers for Disease Control and Prevention. CDC Estimates of 2009 H1N1 Influenza Cases, Hospitalizations, and Deaths in the United States, April 2009–February 13. CDC, Atlanta, 2009, accessed on April 15, 2014 from http://www.cdc.gov/h1n1flu/estimates/April_February_13.htm

92 O. Fléchelles, R. Fowler, P. Jouvet. H1N1 Pandemic: Clinical and Epidemiologic Characteristics of the Canadian Pediatric Outbreak. Expert Rev Anti Infect Ther. vol. 11, no. 6, 2013, pp. 555-563

93 A. Suryaprasad, J. Redd, K. Hancock, A. Branch, E. Steward-Clark, J. Katz, A. Fry, J. Cheek. Influenza Serology Working Group. American

Indian and Alaska Native Pandemic Influenza A (H1N1) Investigation Team. Severe Acute Respiratory Infections Caused by 2009 Pandemic Influenza A (H1N1) among American Indians--southwestern United States. Influenza Other Respir Viruses, 2013, vol. 7, no. 6, pp. 1361-1369.

94 Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. Clinical Aspects of Pandemic 2009 Influenza A (H1N1) Virus Infection. N Engl J Med, vol. 362, 2010, pp. 1708-19.

95 L. Donaldson, P. Rutter, B. Ellis, et al. Mortality from Pandemic A/H1N1 2009 Influenza in England: Public Health Surveillance Study. BMJ, vol. 339, b5213, 2009.

96 J. Louie, M. Acosta, K. Winter, et al. Factors Associated with Death or Hospitalization due to Pandemic 2009 Influenza A(H1N1) Infection in California. JAMA, vol. 302, 2009, pp.1896-902.

97 The ANZIC Influenza Investigators. Critical Care Services and 2009 H1N1 Influenza in Australia and New Zealand. N Engl J Med, vol. 361, 2009, pp.1925-34.

98 WHO Working Group for Risk Factors for Severe H1N1pdm Infection. Risk factors for severe outcomes following 2009 Influenza A (H1N1) infection: A Global Pooled Analysis. Appeal PMEDICINE-D-10-00373. WHO, Geneva, 2011, accessed on April 15, 2014 from www.who.int/influenza/surveillance_monitoring/Risk_factors_H1N1.pdf

99 R. Libster, J. Bugna, S. Coviello, et al. Pediatric Hospitalizations Associated with 2009 Pandemic Influenza A (H1N1) in Argentina. N Engl J Med., vol. 362, 2010; pp. 45-55.

100 J. McKenna, A. Bramley, J. Skarbinski, et al. Asthma in Patients Hospitalized with Pandemic Influenza A(H1N1)pdm09 Virus Infection–United States, 2009. BMC Infectious Diseases, vol. 13, no. 57, 2013.

101 T. Kwan-Gett, A. Baer, J. Duchin. Spring 2009 H1N1 Influenza Outbreak in King Country Washington. Disaster Med Pub Health Preparedness, vol. 3, 2009, pp. S109–16.

102 F. Dawood, S. Jain, L. Finelli, M. Shaw, S. Lindstrom, R. Garten, et al. Emergence of a Novel Swine-Origin Influenza A (H1N1) Virus in Humans. N Engl J Med, vol. 360, 2009, pp. 2605–15.

103 T. Nguyen-Van J. Epidemiology of Influenza. Oxford: Blackwell Science, 1998.

104 M. Sovero , J. Garcia , A. Laguna-Torres, et al. Short Report: Genetic Analysis of Influenza A/H1N1 of Swine Origin Virus (SOIV) Circulating in Central and South America. Am. J. Trop. Med. Hyg., vol. 83, no. 3, 2010, pp. 708–710.

105 CDC. Serum Cross-Reactive Antibody Response to a Novel Influenza A (H1N1) Virus After Vaccination with Seasonal Influenza Vaccine. MMWR, vol. 58, no. 19, 2009, pp. 521-524

106 D. Knox, C. Schacht. Choices in Relationships: An Introduction to Marriage and the Family. Cengage Learning, 11 ed., 2011, pp. 64–66.

107 S. Klein, C. Passaretti, M. Anker, P. Olukoya, Andrew Pekosz. The Impact of Sex, Gender and Pregnancy on 2009 H1N1 Disease. Biol Sex Differ., 2010, pp. 1-5.

108 S. Klein, C. Roberts, eds. Sex Hormones and Immunity to Infection. Springer Verlag, Berlin, 2010.

109 M. Anker, ed. In Epidemic-Prone Infectious Diseases City: World Health Organization Press, 2007, pp. 1-40.

110 Public Health Agency of Canada. Leading Causes of Death. PHAC, Ottawa, 2014, accessed on April 15, 2014 from http://www.phac-aspc.gc.ca/publications-eng.php

111 World Health Organization. Women and health: Today's Evidence Tomorrow's Agenda. WHO, Geneva, 2009, accessed on April 15, 2014 from http://www.who.int/gender/women_health_report/en/

112 A. Campbell, R. Rodin, R. Kropp, Y. Mao, Z. Hong, J. Vachon, J. Spika, L. Pelletier. Risk of Severe Outcomes Among Patients Admitted to Hospital with Pandemic (H1N1) Influenza. CMAJ, vol. 182, no. 4, 2010.

113 S. Lapinsky: H1N1 Novel Influenza A in Pregnant and Immunocompromised Patients. Crit Care Med., vol. 38, 2010, pp. e52-e57.

114 World Health Organization. Sex, Gender and Influenza in Achieving Gender Equality and Health Equity. WHO Library Cataloguing-in-Publication Data, WHO, Geneva, 2010, accessed on April 15, 2014 from www.who.int/publications/2010/9789241500111_eng.pdf

115 A. Creanga, T. Johnson, S. Graitcer, L. Hartman, T. Al-Samarrai, A. Schwarz, S. Chu, et al., Severity of 2009 Pandemic Influenza A (H1N1) Virus Infection in Pregnant Women. Obstetrics & Gynecology, vol. 115, no. 4, 2010, pp. 717-726.

116 World Health Organization. Weekly Epidemiological Record-Transmission Dynamics and Impact of Pandemic Influenza A (H1N1) 2009 Virus. WHO, Geneva, vol. 84, no. 46, 2009, pp.477–484, accessed on April 15, 2014 from http://www.who.int/wer/2009/wer8446/en/

117 D. Jamieson, M. Honein, S. Rasmussen, J. Williams, D. Swerdlow, M. Biggerstaff, et al. H1N1 2009 Influenza Virus Infection During Pregnancy in the USA. Lancet, vol. 374, 2009, pp. 451–8.

118 J. Louie, M. Acosta, D. Jamieson, M. Honein, The California Pandemic Working Group. Severe 2009 H1N1 Influenza in Pregnant and Postpartum Women in California. N Engl J Med., vol. 362, 2010, pp. 27-35.

119 D. Skowronski, G. De Serres. Is Routine Influenza Immunization Warranted in Early Pregnancy? Vaccine, vol. 27, 2009, pp. 4754–4770.

120 M. Beck. Influenza and Obesity: Will Vaccines and Antivirals Protect? JID, vol. 205, 2012.

121 D. Jamieson, et al. H1N1 2009 Influenza Virus Infection During Pregnancy in the USA. Lancet, vol. 374, 2009, pp. 451–458.

122 J. Louie, M. Acosta, D. Jamieson, M. Honein. Severe 2009 H1N1 Influenza in Pregnant and Postpartum Women in California. N Engl J Med., vol. 362, 2010, pp. 27-35.

123 L. Mosby, S. Rasmussen, D. Jamieson. Pandemic Influenza A (H1N1) in Pregnancy: A Systematic Review of the Literature. Am J Obstet Gynecol., 2011.

124 Public Health Agency of Canada. Recommendations for pH1N1 Vaccine in Pregnancy. PHAC, Ottawa, 2009, Accessed on April 15, 2014 from www.phac-aspc.gc.ca/alert-alerte/h1n1/vacc/pregvaccgrossvacc-eng.php

125 Zarychanski R, Stuart TL, Kumar A, et al. Correlates of Severe Disease in Patients with 2009 Pandemic Influenza (H1N1) Virus Infection. CMAJ 2010; 182:257-64.

126 World Health Organization. Obesity and Overweight. WHO, WHO Factsheet 311, Geneva, 2010, Accessed on April 15, 2014 from http://www.who.int/mediacentre/factsheets/fs311/en/

127 J. Louie, M. Acosta, M. Samuel, R. Schechter, D. Vugia, K. Harriman, B. Matyas, the California Pandemic (H1N1) Working Groupa. A Novel Risk Factor for a Novel Virus: Obesity and 2009 Pandemic Influenza A (H1N1). Obesity and 2009 H1N1 Influenza, CID, vol. 52, 2011, pp. 301-312.

128 J. Kwong, M. Campitelli and L. Rosella. Obesity and Respiratory Hospitalizations During Influenza Seasons in Ontario, Canada: A Cohort Study. Obesity and Influenza Hospitalization, CID, vol. 53, 2011.

129 H. Paich, P. Sheridan, J Handy, E. Karlsson, S Schultz-Cherry, M. Hudgens, T. Noah, S. Weir, M. Beck. Overweight and Obese Adult Humans Have a Defective Cellular Immune Response to Pandemic H1N1 Influenza A Virus. Obesity, vol. 21, 2013, pp. 2377-2386.

130 J. Louie, M. Acosta, M. Samuel, et al. A Novel Risk Factor for a Novel Virus: Obesity and 2009 Pandemic Influenza A (H1N1). Clin Infect Dis., vol. 52, 2011, pp. 301-312.

131 O. Morgan, A. Bramley, A. Fowlkes, et al. Morbid Obesity as a Risk Factor for Hospitalization and Death due to 2009 Pandemic Influenza A(H1N1) Disease. PLoS One, vol. 5, no., e9694, 2010.

132 Centers for Disease Control and Prevention. Intensive-Care Patients with Severe Novel Influenza A (H1N1) Virus Infection–Michigan, June 2009. MMWR Morb Mortal Wkly Rep 58, 2009, pp. 749-752.

133 O. Morgan, A. Bramley, A. Fowlkes, et al. Morbid Obesity as a Risk Factor for Hospitalization and Death due to 2009 Pandemic Influenza A(H1N1) Disease. PLoS One, vol. 5, no. 3, e9694. 2010.

134 D. Mertz, T. Kim, J. Johnstone, P. Lam, et al. Populations at Risk for Severe or Complicated Influenza Illness: Systematic Review and Meta-Analysis. BMJ, vol. 347, no. f5061, 2013.

135 A. McGeer, K. Green, A. Plevneshi, A. Shigayeva, et al. Antiviral Therapy and Outcomes of Influenza Requiring Hospitalization in Ontario, Canada. Clin Infect Dis., vol. 45, 2007, pp. 1568-75.

136 D. Moore, W. Vaudry, D. Scheifele, et al. Surveillance for Influenza Admissions Among Children Hospitalized In Canadian Immunization Monitoring Program Active Centers, 2003-2004. Pediatrics, vol. 118, no. 3, 2006, pp. e610-e619.

137 Centers for Disease Control and Prevention. FluView: A Weekly Influenza Surveillance Report Prepared by the Influenza Division. CDC, Atlanta, 2009, accessed on April 15, 2014 from http://www.cdc.gov/flu/weekly/

138 S. Bagshaw, et al. Acute Kidney Injury Among Critically Ill Patients with Pandemic H1N1 Influenza A in Canada: Cohort Study. BMC Nephrology, vol. 14, no. 123, 2013.

139 J. Louie, M. Acosta, K. Winter, et al. Factors Associated with Death or Hospitalization due to Pandemic 2009 Influenza A(H1N1) Infection in California. JAMA, vol. 302, 2009, pp. 1896–902.

140 T. Hanslik, P. Boelle, A. Flahault. Preliminary Estimation of Risk Factors for Admission to Intensive Care Units and for Death in Patients infected with Influenza A(H1N1)2009 Virus, France, 2009-2010. PLoSCurr, vol. 2, RRN1150, 2010.

141 T. Watanabe. Renal Complications of Seasonal and Pandemic Influenza A Virus Infections. Eur J Pediatr, vol. 172, 2013, pp. 15-22.

142 B. Lee, S. Mukhi, J. May-Hadford, S. Plitt, M. Louie, S. Drews. Determination of the relative economic impact of differentmolecular-based laboratory algorithms for respiratory viral pathogen detection, including Pandemic (H1N1), using a secure web based Platform. Virology Journal, vol. 8, no. 277, 2011, pp. 1-11.

143 S, Wong, K, Pabbaraju, B. Lee, J. Fox. Enhanced Viral Etiological Diagnos of Respiratory System Infection Outbreaks by Use of a Multitarget Nucleic Acid Amplification Assay. Journal Of Clinical Microbiology, vol. 47, no. 1 2009, pp. 3839–3845.

144 J. Thomas, D. Weber. Epidemiologic Methods for the Study of Infectious Diseases. Oxford University Press, Inc., 2001.

145 D. Swerdlow, L. Finelli, C. Bridges. 2009 H1N1 Influenza Pandemic: Field and Epidemiologic Investigations in the United States at the Start of the Fir Pandemic of the 21st Century. Clinical Infectious Diseases, vol. 52, no. s1, 2011.

146 Canadian Institute for Health Information. H1N1 in Canada—A Context for Understanding Patients and their Use of Hospital Services. CIHI, Ottawa, 2010, accessed on April 15, 2014 from https://secure.cihi.ca/free_products/HCIC_2010_Web_e.pdf

147 P. Lagace-Wiens, E. Rubinstein, A. Gumel. Influenza Epidemiology—Past, Present, and Future. Crit Care Med., vol. 38, no. 4, 2010.

148 Statistics Canada. CCHS 2007-2008: Data Dictionary. Public Use Microdata File, 2009, accessed on April 15, 2014 from http://www23.statcan.gc.ca/imdb-bmdi/pub/document/3226_D6_T9_V7-eng.pdf

149 Statistics Canada. Canadian Community Health Survey (CCHS) – 2007-2008 CCHS Microdata File User Guide. Statistics Canada, Ottawa, 2009, accessed on April 15, 2014 from http://www23.statcan.gc.ca/imdb-bmdi/pub/document/3226_D7_T9_V4-eng.pdf

150 Statistics Canada. Canadian Community Health Survey (CCHS). 2007-2008 Public Use Microdata File. Approximate Sampling Variability Tables. Statistics Canada, Ottawa, 2009, accessed on April 15, 2014 from http://www23.statcan.gc.ca/imdb-bmdi/pub/document/3226_D7_T9_V4-eng.pdf

151 Statistics Canada. Canadian Community Health Survey, 2008 Questionnaire, I. Statistics Canada, Ottawa, 2008, accessed on April 15, 2014 from http://www23.statcan.gc.ca/imdb-bmdi/instrument/3226_Q1_V5-eng.pdf

152 Statistics Canada. Canadian Community Health Survey (CCHS). Derived Variable Specifications. Statistics Canada, Ottawa, 2010, accessed on April 15, 2014 from http://www23.statcan.gc.ca/imdb-bmdi/pub/document/3226_D71_T9_V1-eng.pdf

153 Statistics Canada. 2006 Community Profiles. Catalogue no. 92-591-XWE. Statistics Canada, Ottawa, 2008, accessed on Jan 1, 2014 from http://www12.statcan.gc.ca/census-recensement/2006/dp-pd/prof/92-591/index.cfm?Lang=E

154 Interactive health Data Application. Alberta Health. Government of Alberta, accessed on April 15, 2014 from http://www.ahw.gov.ab.ca/IHDA_Retrieval/

155 SAS/STAT® 9.3 User's Guide: The GLIMMIX Procedure (Chapter). SAS Institute Inc. 2011.

156 B. Karazsia, M. van Dulmen. Regression Models for Count Data: Illustrations using Longitudinal Predictors of Childhood Injury. Journal of Pediatric Psychology, vol. 33 no.10, 2008.

157 A. Cameron, P. Trivedi. Econometric Models Based on Count Data: Comparisons and Applications of some Estimators and Tests. Journal of Applied Econometrics, vol. 1, 1986, pp. 29–53.

158 D. Fekedulegn, M. Andrew, J. Violanti, T. Hartley, L. Charles, C. Burchfiel. Comparison of Statistical Approaches to Evaluate Factors. Associated With Metabolic Syndrome. The Journal of Clinical Hypertension, vol. 12, no. 5, 2010, pp. 365-73.

159 G. Bouche, B. Lepage, V. Migeot, P. Ingrand. Application of Detecting and Taking Overdispersion into Account in Poisson Regression Model. Revue d'epidemiologie et de Sante Publique, vol. 57, no. 4, 2009, pp. 285-96. [in French]

160 W. Garner, E. Mulvey, E. Shaw. Regression Analysis of Counts and Rates: Poisson, Overdispersed Poisson, and Negative Binomial Models. Psychological Bulletin, vol. 118, 1995, pp. 392-404.

161 N. Breslow. Tests of Hypotheses in Overdispersed Poisson Regression and other Quasi-Likelihood Models. Journal of the American Statistical Association, vol. 85, 1990, pp. 565-571.

162 M. Sturman. Multiple Approaches to Analyzing Count Data in Studies of Individual Differences: The Propensity for Type I Errors, Illustrated with the Case of Absenteeism Prediction. Educational and Psychological Measurement, vol. 59, 1990, pp. 414–430.

163 A. Agresti. An Introduction to Categorical Data Analysis. Second Edition, John Wiley& Sons, Inc., 2007.

164 J. Hausman, B. Hall, Z. Griliches. Econometric Models for Count Data with an Application to the Patents-R&D Relationship. Econometrica, vol. 52, 1984, pp. 909–938.

165 J. Lloyd-Smith. Maximum Likelihood Estimation of the Negative Binomial Dispersion Parameter for Highly Overdispersed Data, with Applications to Infectious Diseases. PLoS ONE, vol. 2, no., 2: e180, 2007.

166 J. Lloyd-Smith, S. Schreiber, P. Kopp, W. Getz. Superspreading and the Effect of Individual Variation on Disease Emergence. Nature, VOL. 438, 2005, PP. 355–359.

167 T. Harris. The Theory of Branching Processes. Dover, New York, 1989.

168 A. Storms, M. Van Kerkhove, E. Azziz-Baumgartner, W. Lee, M. Widdowson, N. Ferguson, A. Mountsa. Worldwide Transmission and Seasonal Variation of Pandemic Influenza A(H1N1)2009 Virus Activity during the 2009–2010 Pandemic. Influenza and Other Respiratory Viruses, John Wiley & Sons Ltd., vol. 7, no. 6, 2013.

169 F. Gonzalez-Candelas, J. Astray, J. Alonso, et al. Sociodemographic Factors and Clinical Conditions Associated to Hospitalization in Influenza A (H1N1) 2009 Virus Infected Patients in Spain, 2009–2010. PLoS One, vol. 7, 2012, e33139.

170 S. Wesche, R. Ryan, C. Carry. First Nations, Inuit and Métis: Respiratory Health Initiatives Environmental Scan. National Aboriginal Health Organization, Ottawa, 2011, accessed on April 15, 2014 from http://www.naho.ca/documents/naho/english/2011_04_Lung-Health-E-Scan.pdf

171 G. Chowell, S. Echevarría-Zuno, C. Viboud, et al. Epidemiological Characteristics and Underlying Risk Factors for Mortality during the Autumn 2009 Pandemic Wave in Mexico. PLoS One.

172 G. Chowell, A. Ayala, V. Berisha, et al. Risk Factors for Mortality among 2009 A/H1N1 Influenza Hospitalizations in Maricopa County, Arizona, April 2009 to March 2010. Computational and Mathematical Methods in Medicine, vol. 2012, no. 914196, 2012.

173 Liu Y, Wang W, Li X, Wang H, Luo Y, et al. Geographic Distribution and Risk Factors of the Initial Adult Hospitalized Cases of 2009 Pandemic Influenza A (H1N1) Virus Infection in Mainland China. PLoS ONE, vol. 6, no. 10, 2011, e25934.

174 J. Wenger, L. Castrodale, D. Bruden, et al. 2009 Pandemic Influenza A H1N1 in Alaska: Temporal and Geographic Characteristics of Spread and Increased Risk of Hospitalization among Alaska Native and Asian/Pacific Islander people. J Infect Dis., vol. 203, no. 6, 2011, pp. 828–837.

175 A. Fowlkes, P. Arguin, et al. Epidemiology of 2009 Pandemic Influenza A (H1N1) Deaths in the United States, April-July 2009. Clin Infect Dis., vol. 52, suppl 1, 2011, pp. S60–S68.

176 G. Chowell, C. Viboud, C. Munayco, et al. Spatial and Temporal Characteristics of the 2009 A/H1N1 Influenza Pandemic in Peru. PLoS One, vol. 6, no. 6, 2011, e21287.

177 H. Yu, W. Alonso, et al. Characterization of Regional Influenza Seasonality Patterns in China and Implications for Vaccination Strategies: Spatio-Temporal Modeling of Surveillance Data. PLoS Med., vol. 10, no. 11, 2013, e1001552.

178 T. Kwan-Gett, A. Baer, J. Duchin. Spring 2009 H1N1 Influenza Outbreak in King Country Washington. Disaster Med Pub Health Preparedness, vol. 3, 2009, pp. S109–16.

179 M. Ertek, R. Durmaz, D. Guldemir, A. Altas, and R. Saydam. Epidemiological, Demographic, and Molecular Characteristics of Laboratory-confirmed Pandemic Influenza A (H1N1) Virus Infection in Turkey, May 15- November 30, 2009. Jpn. J. Infect. Dis., vol. 63, 2010, pp. 239-245.

180 A. Glatman-Freedman, I. Portelli, S. Jacobs, et. al. Attack Rates Assessment of the 2009 Pandemic H1N1 Influenza A in Children and Their Contacts: A Systematic Review and Meta-Analysis. PLoS One, vol. 7, no. 11, 2012, e50228.

181 J. Bishop, M. Murnane, R. Owen. Australia's Winter with the 2009 Pandemic Influenza A (H1N1) Virus. N Engl J Med., vol. 361, 2009, pp. 2591-4.

182 Centers for Disease Control and Prevention. Fluview: 2008–2009 Influenza Season Week 39 Ending October 3, 2009. CDC, Atlanta, 2009, accessed on April 15, 2014 from www.cdc.gov/flu/weekly/weeklyarchives2008-2009/weekly39.htm

183 Health Protection Agency. HPA weekly National Influenza Report, 24 September 2009 (week 39). HPA, London 2009, accessed on April 15, 2014 from www.hpa.nhs.uk/web /HPAwebFile/HPAweb_C/1253205412438

184 K. Hancock, V. Veguilla, et al. Cross-Reactive Antibody Responses to the 2009 Pandemic H1N1 Influenza Virus. N Engl J Med., vol. 361, 2009, pp. 1945–1952.

185 S Klein, A. Hodgson, D. Robinson. Mechanisms of Sex Disparities in Influenza Pathogenesis. Journal of Leukocyte Biology, vol. 92, 2012, pp. 67-73.

186 N. Eshima., O. Tokumaru, et al. Sex- and Age-Related Differences in Morbidity Rates of 2009 Pandemic Influenza A H1N1 Virus of Swine Origin in Japan. PLoS ONE, vol. 6, no. 4, 2011, e19409.

187 World Health Organization. Addressing Sex and Gender in Epidemic-prone Infectious Diseases. WHO Library Cataloguing-in-Publication Data, WHO, Geneva, 2007, accessed on April 10, 2014, from http://www.who.int/csr/resources/publications/SexGenderInfectDis.pdf

188 R. Engler, M. Nelson, M. Klote, et al. Half- vs Full-Dose Trivalent Inactivated Influenza Vaccine (2004-2005) Age, Dose, and Sex Effects on Immune Responses. Arch Intern Med., vol. 168, 2008, pp. 2405–2414.

189 C. Roberts, W. Walker, J. Alexander. (2001) Sex-associated Hormones and Immunity to Protozoan Parasites. Clin. Microbiol. Rev. 14, 476–488.

190 A. Araneo., T. Dowell, M. Diegel, R. Daynes . Dihydrotestosterone Exerts a Depressive Influence on the Production of Interleukin-4 (IL-4), IL-5, and γ-Interferon, but not IL-2 by Activated Murine T cells. Blood, vol. 78, 1991, pp. 688-699.

191 F. Barrat, B. Lesourd, H. Boulouis , et al. Sex and Parity Modulate Cytokine Production During Murine Ageing. Clin. Exp. Immunol., vol. 109, 1997, pp. 562-568.

192 E. Fish. The X-files in Immunity: Sex-based Differences Predispose Immune Responses. Immunology, vol. 8, 2008, pp. 737–744.

193 S. Klein, C. Passaretti, M. Anker, P. Olukoya, A. Pekosz. The Impact of Sex, Gender and Pregnancy on 2009 H1N1 Disease. Biol Sex Differ., vol. 1, no. 1, 2010.

194 W. Oliveira, et al. Pandemic H1N1 Influenza in Brazil: Analysis of the First 34,506 Notified Cases of Influenza-Like Illness with Severe Acute Respiratory Infection (SARI). Euro Surveill., vol. 14, no. 42, 2009.

195 T. Klooster, C. Wielders, T. Donker, et.al. Surveillance of Hospitalizations for 2009 Pandemic Influenza A(H1N1) in the Netherlands, 5 June - 31 December 2009. Euro Surveill., vol. 15, no. 2, 2010.

196 J. Fielding, N. Higgins, J. Gregory, K. Grant, et al. Pandemic H1N1 Influenza Surveillance in Victoria, Australia, April - September, 2009. Euro Surveill., vol. 14, no. 42, 2009.

197 F. Tulloch, R. Correa, G. Guerrero, R. Samaniego, M. Garcia, et al. Armien B. Influenza Research Group. Profile of the First Cases Hospitalized due to Influenza A (H1N1) in Panama City, Panama. May-June 2009. J Infect Dev Ctries., vol. 3, 2009, pp. 811–816.

198 New South Wales Public Health Network. Progression and Impact of the First Winter Wave of the 2009 Pandemic H1N1 Influenza in New South Wales, Australia. Euro Surveill., vol. 14, no. 42, 2009.

199 J. Denholm, C. Gordon, P. Johnson, et al. Hospitalized Adult Patients with Pandemic (H1N1) 2009 Influenza in Melbourne, Australia. Med J Aust., vol. 192, 2010, pp. 84–86.

200 M. Henninger, B. Crane, A. Naleway. Trends in Influenza Vaccine Coverage in Pregnant Women, 2008 to 2012. Perm J., Spring, vol. 17, no. 2, 2013, pp. 31–36.

201 Centers for Disease Control and Prevention. 2009 Pandemic Influenza A (H1N1) in Pregnant Women Requiring Intensive Care—New York City, 2009. CDC, Atlanta, MMWR Morb Mortal Wkly Rep. 2010 Mar 26, vol. 59, no. 11, 2010, pp. 321–326.

202 A. Creanga, T. Johnson, S. Graitcer, et al. Severity of 2009 Pandemic Influenza A (H1N1) Virus Infection in Pregnant Women. Obstet Gynecol. 2010 Apr;115(4):717–26.

203 S. Ellington, L. Hartman, M. Acosta, et al. Pandemic 2009 Influenza A (H1N1) in 71 Critically Ill Pregnant Women in California. Am J Obstet Gynecol., vol. 204, suppl. 6, 2011, pp. S21–30.

204 D. Jamieson, M. Honein, S. Rasmussen, et al. Novel Influenza A (H1N1) Pregnancy Working Group. H1N1 2009 Influenza Virus Infection during Pregnancy in the USA. Lancet, vol. 374, no. 9688, 2009, pp. 451–458.

205 J. Louie, M. Acosta, D. Jamieson, M. Honein, California Pandemic (H1N1) Working Group Severe 2009 H1N1 Influenza in Pregnant and Postpartum Women in California. N Engl J Med., vol. 362, no. 1, 2010, pp. 27–35.

206 S. Rasmussen, D. Kissin, L. Yeung, et al. Pandemic Influenza and Pregnancy Working Group Preparing for Influenza after 2009 H1N1: Special Considerations for Pregnant Women and Newborns. Am J Obstet Gynecol., vol. 204, suppl. 1, 2011, pp. S13–20.

207 A. Siston, S. Rasmussen, M. Honein, et al. Pandemic H1N1 Influenza in Pregnancy Working Group Pandemic 2009 influenza A (H1N1) Virus Illness among Pregnant Women in the United States. JAMA, vol. 303, no. 15, 2010, pp. 1517–1525.

208 L. Brabin. Interactions of the Female Hormonal Environment, Susceptibility to Viral Infections, and Disease Progression. AIDS Patient Care STDS, vol. 16, 2002, pp. 211-221.

209 J. Cono, J. Cragan, D. Jamieson, S. Rasmussen. Prophylaxis and Treatment of Pregnant Women for Emerging Infections and Bioterrorism Emergencies. Emerg Infect Dis., vol. 12, no. 11, 2006, pp.1631–1637.

210 S. Wong, K. Chow, T. Leung, et al. Pregnancy and Perinatal Outcomes of Women with Severe Acute Respiratory Syndrome. Am J Obstet Gynecol., vol. 191, 2004, pp. 292–297.

211 D. Jamieson, R. Theiler, S. Rasmussen. Emerging Infections and Pregnancy. Emerg Infect Dis., vol. 12, no. 11, 2006, pp. 1638–1643.

212 T. Ninan , G. Russell. Respiratory Symptoms and Atopy in Aberdeen School Children: Evidence from two Surveys 25 Years Apart. BMJ, vol. 304, 1992, pp. 873-875.

213 K. Bertakis, R. Azari, L. Helms, E. Callahan, J. Robbins: Gender Differences in the Utilization of Health Care Services. J Fam Pract., vol. 49, 2000, pp. 147-152.

214 World Health Organization. Sex, Gender and Influenza in Achieving Gender Equality and Health Equity. WHO Library Cataloguing-in-Publication Data, WHO, 2010, accessed on April 10, 2014, from http://whqlibdoc.who.int/publications/2010/9789241500111_eng.pdf

215 Alberta Health, Alberta Health Services. Pandemic (H1N1) 2009: The Alberta Experience. Government of Alberta, 2010, accessed on April 15, 2014 from http://www.health.alberta.ca/documents/H1N1-Alberta-Experience-2010.pdf

216 C. Salas, S. Mehra, M. Crespo, Y. Juhn. Asthma and Severity of 2009 Novel H1N1 Influenza: a Population-Based Case–Control Study. J Asthma, vol. 250, no. 10, 2013, pp. 1069-76.

217 S. O'Riordan, M. Barton, Y. Yau, S. Read, Upton Allen, Dat Tran. Risk Factors and Outcomes among Children Admitted To Hospital with Pandemic H1N1 Influenza. CMAJ, vol. 182, no.1, 2010.

218 K. Ward, P. Spokes, J. McAnulty. Case-Control Study of Risk Factors for Hospitalization caused by Pandemic (H1N1) 2009. Emerg Infect Dis., vol. 17, no. 8, 2011, pp. 1409–1416.

219 D. Ploinb, C. Chidiace, F. Carratd, B. Cohena, et al. Complications and Factors Associated with Severity of Influenza in Hospitalized Children and Adults during the Pandemic Wave of A(H1N1)pdm2009 Infections. Journal of Clinical Virology, vol. 58, 2013, pp. 114– 119.

220 J. McKenna. Asthma in Patients Hospitalized with Pandemic Influenza A(H1N1)pdm09 Virus Infection–United States, 2009. BMC Infectious Diseases, 2013, pp. 13:57.

221 ANZIC Influenza Investigators, S. Webb, et al. Critical Care Services and 2009 H1N1 Influenza in Australia and New Zealand. NEngl J Med 2009; 361:1925–1934.

222 ANZIC Influenza Investigators, S. Webb, et al. Critical Care Services and 2009 H1N1 Influenza in Australia and New Zealand. NEngl J Med., vol. 361, 2009, pp. 1925–1934.

223 D. Grove, T. Burston, M. Wellby, R. Ford, I. Forbes. Humoral and cellular immunity in asthma. J Allergy Clin Immunol., vol. 55, 1975, pp. 152–163.

224 P. Wark, S. Johnston, F. Bucchieri, R. Powell, S. Puddicombe, V. Laza-Stanca, S. Holgate, D. Davies. Asthmatic Bronchial Epithelial Cells Have a Deficient Innate Immune Response to Infection with Rhinovirus. J Exp Med., vol. 201, 2005, pp. 937–947.

225 M. Contoli, S. Message, V. Laza-Stanca, et al. Role of Deficient Type III Interferon Lambda Production in Asthma Exacerbations. Nat Med., vol. 12, 2006, pp. 1023–1026.

226 N. Lahood, S. Emerson, P. Kumar, R. Sorensen. Antibody Levels and Response to Pneumococcal Vaccine in Steroid-Dependent Asthma. Ann Allergy, pp. 70, 1993, pp. 289–294.

227 J. Fischer, J. Johnson, R. Kuli-Zade, T. Johnson, S. Aung, R. Parker, B. Graham. Overexpression of Interleukin-4 Delays Virus Clearance in Mice Infected with Respiratory Syncytial Virus. J Virol., vol. 71, 1997, pp. 8672–8677.

228 B. Erbas, M. O'Sullivan, S. Dharmage, J. Druce, K. Allen, M. Tang, P. Bardin, M. Abramson. No H1N1 Detected in Children Admitted to Hospital with Asthma during the H1N1 Pandemic. American Journal of Respiratory and Critical Care Medicine, vol.186, no. 5, 2012, pp. 462.

229 E. McAnarney. Adolescent Brain Development: Forging New Links? Journal of Adolescent Health, vol. 42, 2008, pp. 321-323.

230 H. Anderson, A. Pottier, D. Strachan. Asthma from Birth to Age 23: Incidence and Relation to Prior and Concurrent Atopic Disease. Thorax, vol. 47, 1992, pp. 537-542.

231 M. Gissler, M. Jarvelin, P. Louhiala, et al. Boys have more Health Problems in Childhood than Girls: Follow-up of the 1987 Finnish Birth Cohort. Acta Paediatr, vol. 88, 1999, pp. 310-314.

232 A. Venn, S. Lewis, M. Cooper M, et al. Questionnaire Study of Effect of Sex and Age on the Prevalence of Wheeze and Asthma in Adolescence. BMJ, vol. 316, 1998, pp. 1945-1946.

233 E. Skobeloff, W. Spivey, R. Silverman, et al. The Effect of the Menstrual Cycle on Asthma Presentations in the Emergency Department. Arch Intern Med, vol. 156, 1996, pp. 1837-1840.

234 M. Rosenthal, S. Bain, D. Cramer, et al. Lung Function in White Children Aged 4 to 19 Years. Thorax, vol. 48, 1993, pp. 794-802.

235 M. Hibbert, A. Lannigan, J. Raven, et al. Gender Differences in Lung Growth. Pediatr Pulmonol., vol. 19, 1995, pp. 129-134.

236 M. Osman. Therapeutic Implications of Sex Differences in Asthma and Atopy. Arch Dis Child, vol. 88, 2003, pp. 587–590.

237 Alberta Environment. Alberta Ambient Air Data Management System (AAADMS). Data Reports. Government of Alberta, accessed on April 15, 2014, from http://www.casadata.org/index.asp

238 C. Fuhrmann. The Effects of Weather and Climate on the Seasonality of Influenza: What we Know and What we Need to Know. Geography Compass, vol. 4, no. 7, 2010, pp. 718–730.

239 Statistics Canada. Population by Year, by Province and Territory (2013).
Statistics Canada, Ottawa, 2013, accessed on April 15, 2014 from http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo02a-eng.htm

240 S. Greenland, H. Morgenstern. Ecological Bias, Confounding, and Effect Modification. International Journal of Epidemiology International Epidemiological Association, vol. 18, no. 1, 1989, pp. 269-274.

241 M. Washio, A. Oura, M. Mori. Ecological Studies on Influenza Infection and the Effect of Vaccination: Their Advantages and Limitations Vaccine, vol. 26, 2008, pp. 6470–6472.

242 J. McKenna, A. Bramley, J. Skarbinski, A. Fry, L. Finelli, S. Jain. Asthma in Patients Hospitalized with Pandemic Influenza A(H1N1)pdm09 Virus Infection–United States, 2009. BMC Infectious Diseases, vol. 13, no. 57, 2013.

243 M. Obuchi, Y. Adachi, T. Takizawa, T. Sata. Influenza A(H1N1)pdm09 Virus and Asthma. Frontiers Microbiology, vol. 4, no. 307, 2013.

244 K. Kloepfer, J. Olenec, et al. Increased H1N1 Infection Rate in Children with Asthma. Am J Respir Crit Care Med., vol. 185, no. 12, 2012, pp 1275–1279.

245 G. Chowell, S. Echevarria-Zuno, et al. Characterizing the Epidemiology of the 2009 Influenza A/H1N1 Pandemic in Mexico. PLoS Med., vol. 8, no. 5, 2011, e1000436.

246 Standards Advisory Subgroup (CSAS). Review of the UK Air Quality Index. Health Protection Agency for the Committee on the Medical Effects of Air Pollutants, UK, 2011, accessed on April 10, 2014, from http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317137023144

247 H. Boon, A. Tahir. Pandemic H1N1 2009 (Swine flu) and Pregnancy. Obstet, Gynaecol. Reprod Med., vol. 20, 2010, pp. 101-106.

248 D. Postma. Gender Differences in Asthma Development and Progression. Gender Medicine, vol. 4, suppl. B, 2007, pp. s133-s147.

249. R. Zannolli, G. Morgese. Does Puberty Interfere with Asthma? Med Hypotheses, vol. 48, 1997, pp. 27-32.

250 D. Adams, Stefan Hubscher. Systemic Viral Infections and Collateral Damage in the Liver. Am J Pathol., vol. 168, no. 4, 2006, pp. 1057–1059.

# Notification of Approval (Renewal)

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|---|---|
| Date: | July 2, 2013 |
| Amendment ID: | Pro00016132_REN3 |
| Principal Investigator: | Ambikaipakan Senthilselvan |
| Study ID: | MS3_Pro00016132 |
| Study Title: | **A Computational Epidemiology Approach for Characterizing and Modeling the Spread of Pandemic Infectious Diseases** |
| Approval Expiry Date: | August 12, 2014 |

Thank you for submitting this renewal application. Your application has been reviewed and approved.

This re-approval is valid for another year. If your study continues past the expiration date as noted above, you will be required to complete another renewal request. Beginning at 30 days prior to the expiration date, you will receive notices that the study is about to expire. If you do not renew on or before the renewal expiry date, you will have to re-submit an ethics application.

All study related documents should be retained so as to be available to the Health REB upon request. They should be kept for the duration of the project and for at least 5 years following study completion.

Sincerely,

Dr. Glen J. Pearson, BSc, BScPhm, PharmD, FCSHP

Associate Chair, Health Research Ethics Board - Health Panel

*Note: This correspondence includes an electronic signature (validation and approval via an online system).*