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The Descriptive Epidemiology of Influenza Vaccination and Adverse Events of Influenza Vaccination in Alberta for the 2010-2011 Vaccination Season

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The Descriptive Epidemiology of Influenza Vaccination and Adverse Events of Influenza Vaccination in Alberta for the 2010-2011 Vaccination Season

by

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Abstract

Objective: The objective of this study was to estimate influenza vaccination coverage and describe the occurrence of adverse events related to influenza vaccination in Alberta by attributes of age, sex, geographical indicators (urban or rural), immigrants versus non-immigrants, and provider type for the 2010-2011 vaccination season.

Methods: The study used aggregate data from the Alberta's publicly funded immunization system. Denominators for influenza vaccination coverage were obtained from the health care insurance registry. Descriptive analysis included proportions to describe patterns in rates and events by attributes.

Results: Variation in influenza vaccination coverage and adverse events was observed by age, sex, place of residence and in relation to being immigrant and non-immigrant. Among young children and immigrants, there were missing values of adverse events.

Conclusions Influenza vaccination coverage rates for the overall population, for all age groups, and for rural and immigrant population are low. Reporting of adverse events is incomplete.

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List of Abbreviations

Symbol	Definition
AE	Adverse Events
AEFI	Adverse Events Following Immunization
AH	Alberta Health
AHS	Alberta Health Services
AHCIP	Alberta Health Care Insurance Plan
AIS	Alberta Immunization Strategy
ARI	Adverse Reaction to Immunization
CAEFI	Canadian Adverse Events Following Immunization
CCHS	Canadian Community Health Survey
CHREB	Conjoint Health Research Ethics Board
CI	Confidence Interval
CIC	Citizenship and Immigration Canada
CSR	Central Stakeholder Registry
GBS	Guillain Barré Syndrome
HA	Haemagglutinin

HCW	Healthcare Workers
HIA	Health Information Act
ICD	International Classification of Diseases
IHDA	Interactive Health Data Application
IIP	Alberta’s Influenza Immunization Policy
Imm/ARI	Immunization and Adverse Reactions to Immunization
LAIV	Live Attenuated Influenza Virus Vaccine
LTC	Long-Term Care
NACI	National Advisory Committee on Immunization
PHAC	Public Health Agency of Canada
PHN	Personal Health Number
SD	Standard Deviation
SESE	Supplemental Enhanced Service Event
SSPE	Subacute Sclerosing Panencephalitis
TIV	Trivalent Inactivated Vaccine
UTD	Up-To-Date

WHO	World Health Organization

Chapter One: Introduction

This chapter provides the background information on the purpose, objectives, research questions, the statement of problem and the rationale for this study.

1.1 Purpose

The purpose of this study is to describe the epidemiology of influenza vaccination coverage and adverse events of influenza vaccination for all ages (6 months or older) in the province of Alberta for the October 2010-April 2011 vaccination season.

1.2 Objectives

The objectives of this research are:

1. To estimate influenza vaccination coverage in Alberta by attributes of age, sex, geographical indicators (urban or rural), immigrants versus non-immigrants, and provider type for the October 2010-April 2011 vaccination season; and
2. To describe the occurrence of adverse events related to influenza vaccination in Alberta by attributes of age, sex, geographical indicators (urban or rural), and immigrants versus non-immigrants for the October 2010-April 2011 vaccination season.

1.3 Research Questions

The research questions are:

1. What are the proportions of people in Alberta vaccinated against influenza for the October 2010-April 2011 vaccination season by: age-group, sex, rural versus urban, immigrants versus non- immigrants, and provider type?

2. Among those vaccinated against influenza in Alberta for the October 2010-April 2011 season, what proportion (by age, sex, rural versus urban, immigrants versus non-immigrants) incurred one or more adverse events following influenza vaccination?

1.4 Statement of Problem

Influenza is an acute viral disease of the respiratory tract characterized by fever, headache, myalgia, prostration, coryza, sore throat and cough.[1] Influenza affects people of all ages and is an important cause of morbidity, hospitalization, and utilization of medical services. In Canada, between 2000 and 8000 Canadians die of influenza and its complications annually, depending on the severity of the season.[2] There are three types of influenza virus: A, B and C. The influenza morbidity and mortality of concern to humans is from type A and type B influenza viruses.[3] The focus of this thesis is on vaccination coverage of humans against influenza A and B as there is no vaccine for influenza C.

Influenza A and B viruses change antigenically each year, thus a new vaccine must be reformulated each year; people need annual vaccination. If the vaccine antigen does not closely match the circulating strains of virus, protection against infection would not be very good and influenza outbreaks may occur.[3]

Influenza vaccination is the most effective way of protecting oneself against influenza infection.[1] Surveillance relevant to an immunization program should include surveillance of coverage, adverse events, and burden of disease.[4-8] Vaccination coverage and adverse event monitoring are necessary indicators for population-based influenza vaccination programs.[9] Monitoring of vaccination coverage is important in order to determine the extent to which the total population is reached with the vaccine (i.e. detect changes in the reach of the program) and identify under-vaccinated subpopulations.[10,11] Adverse events monitoring is important for addressing vaccine safety concerns.[5,12] Annual measurement of vaccine effectiveness is also important for influenza because, as mentioned above, the disease and thus the vaccine change every year.

There is a large body of literature that studies influenza vaccination coverage and adverse events following influenza vaccination, however, few have focused on the need for improved methods of vaccine coverage and adverse event monitoring in the general population. The World Health Organization (WHO) has highlighted the usefulness and importance of assessing influenza vaccine coverage and adverse events following influenza vaccination.[7,13]

By using the administrative data from Alberta's publicly funded and administered health-care system, this study attempts to estimate values for influenza vaccine coverage indicators and to describe adverse events related to influenza vaccination for the period October 1, 2010-April 30, 2011.

1.5 Study Rationale

There are limited data to assess vaccination coverage in Canada and for the most part estimations of seasonal vaccination coverage are primarily available from the Canadian Community Health Survey (CCHS) which assesses immunization status for seasonal influenza vaccination only for people aged 12 years or older.[14] There are two limitations at least from using this national data. First of all, the CCHS does not capture data on influenza vaccination from those under the age of 12 years and residents of long-term health care facilities, and secondly survey data are based upon respondents' unvalidated self-reports.

The CCHS excludes young children and older age groups who are known to have a high proportion of influenza vaccination and in whom the risk of complications from influenza infections is very high.[15]Consequently, the overall influenza coverage rate is underestimated. Self-reports of influenza vaccination are subject to respondent bias.Studies have shown that influenza vaccine self-reports have high sensitivity and low specificity, suggesting that the real coverage rates may be lower than those reported in the CCHS.[16-19] Furthermore, self-reports of influenza vaccination in CCHS did not capture data on adverse events.

However, there are also limitations to the currently available Alberta data. Although in Alberta, data are available from the actual vaccination records, there are also problems with these data. Alberta Health Services (AHS) produces annual influenza vaccination reports and zonal reporting of coverage rates from each of the five AHS zones.[20-23]These reports are based on the reporting requirements for formerly Alberta Health and Wellness, now Alberta Health (AH) and provide information regarding influenza vaccination rates by priority reason codes.[24]

These reports do not provide information on influenza vaccination coverage and adverse events for all age groups nor vaccination rates by attributes of sex, geographical indicators (urban or rural), nor for immigrants versus non-immigrants, nor provider type. There may be differences in vaccination coverage by these attributes as has been noticed elsewhere: e.g., between rural and urban areas [25,26]and between foreign and non- foreign born individuals. [27,28]It is important to be able to identify subpopulations that are less likely to be vaccinated for future targeted interventions to increase vaccination coverage. It is also important to be able to identify subpopulations that are more likely to be vulnerable to adverse events following influenza vaccination and to address vaccine safety concerns in those groups. This information is needed to be able to address the reach of the influenza vaccination program and vaccine safety concerns in the population.

Children under the age of 9 years require two doses of influenza vaccine as a primary series for adequate protection. [29]An important methodological issue in measuring coverage in children younger than 9 years of age, i.e. the proportion of children vaccinated with 1 versus 2 doses, is critical for understanding the extent of protection offered by the influenza vaccination of young children.[30]This issue also needs to be addressed in the surveillance program.

This study will fill in the gaps in our knowledge of influenza vaccination coverage and safety by providing baseline analyses against which changes in vaccination coverage and adverse events of influenza vaccination can be monitored and evaluated. Further, in order to improve vaccination rates in Alberta, the vaccination data in this study may be helpful to vaccination program managers who may wish to be able to identify groups with low coverage for future targeted interventions and to identify population groups that are especially vulnerable to adverse events following influenza vaccination in Alberta. The findings from this study may also identify strengths and limitations in the current Alberta surveillance system.

Chapter Two: Background and Literature Review

2.1 Introduction

This chapter provides the background information on the influenza vaccination program in the context of health service delivery in Alberta. The chapter also addresses the epidemiology of influenza including the clinical features, burden of disease, control and prevention of influenza. The chapter also summarises previous literature on reporting of adverse events following influenza vaccination in the Alberta context. Finally, a review of previous literature and methodological issues related to influenza vaccination coverage is presented.

Section 2.2 provides a brief overview of the health service delivery in Alberta as it relates to immunization programs in general. Section 2.3 addresses influenza vaccination programs beginning with WHO recommendations and then focuses on the Alberta situation.

2.2 Vaccination in Alberta

AHS is the provincial health authority responsible for planning and delivery of health services, including vaccination services to Alberta residents. Administratively, AHS is made up of five zones (North, South, Central, Calgary and Edmonton) that replaced the former nine regional health authorities. AH is the provincial health ministry and is responsible for procuring vaccines for the provincial immunization programs and setting policies and guidelines for immunization delivery.

Alberta's comprehensive publicly-funded vaccination programs include influenza vaccine and routine immunization schedule that routinely vaccinate against 14 diseases in children and youth and against 4 diseases in adults.[31] AH sets the program standards for surveillance and targets for immunization rates.[31]

Unlike in other provinces, in Alberta routine childhood vaccinations are exclusively administered by the AHS public health.[32] AHS public health provides publicly funded influenza vaccine to community providers (e.g., pharmacists and physicians). Community providers must sign an agreement that they will account for the vaccine provided, and refer children under the age of 9 years to public health for influenza vaccination.[33]Monitoring of vaccine delivery/coverage in this age group underlines the importance of provider type to immunization surveillance and this is an important reason for estimating coverage by provider type. Information regarding influenza vaccination rates by provider type will help the AHS assess the extent to which this age group is reached with the vaccine.

2.3 Influenza Vaccination Programs: Surveillance and Monitoring

2.3.1 WHO influenza surveillance and monitoring: recommendations

WHO has identified the components of a well-functioning immunization program to include service delivery, cold chain and logistics, immunization coverage, vaccine safety and adverse events following immunization (AEFI), monitoring and surveillance, and strategic indicators.[8] WHO recommends that member states conduct surveillance and monitoring to describe critical features of influenza epidemiology including risk groups, transmission characteristics, and impact.[34]

“The influenza surveillance and monitoring activity collects and analyzes virological and epidemiological data from countries, areas and territories around the world to monitor global trends in influenza transmission and inform selection of influenza strains for vaccine production."[34]

2.3.2 Alberta's influenza vaccination surveillance and monitoring

2.3.2.1 History of publicly funded influenza program in Alberta

The Alberta's Influenza Immunization Policy (IIP) provides the provincial guidelines for planning and delivery of seasonal influenza vaccines to Albertans[24] while the Alberta Immunization Strategy (AIS) proposes targets for them.[31]Each year, AH takes into consideration the National Advisory Committee on Immunization (NACI) recommendations in the context of Alberta and revises IIP if appropriate. AHS Public Health assumes the sole responsibility for the delivery of the Alberta influenza immunization program and in collaboration with authorized community providers administer vaccines to the general public. AHS public health and community providers are held accountable for vaccine utilization, cold chain maintenance, and recording and reporting of influenza vaccination data and adverse events.[24]

The landscape of publicly funded programs including immunization is changing in Alberta. Prior to 2004, persons 65 years or older or persons aged 6 months or older with a chronic health condition placing them at higher risk of complications of influenza were provided with free influenza vaccines in Alberta. In line with the recommendations of the NACI, in 2004 healthy children aged 6 to 23 months were added to public funding starting for the 2004-2005 season.[35] In 2008, funding was expanded to include healthy children aged up to 59 months (i.e., "< 6 years of age") starting for the 2008-2009 season, and in spring 2009, further expansion to include all persons aged 6 months or older starting for the 2009-2010 season took place.

Alberta's IIP has been a universal publicly funded program since 2009 and individuals 6 months of age and older who reside, employed or go to school in Alberta are eligible to receive provincially funded influenza vaccine under the IIP.[24] Out-of province/ country individuals (i.e. individuals, who do not reside, are not employed or who do not go to school in Alberta) are not eligible for Alberta's provincially funded influenza vaccine and have to pay a fee to get the vaccine.[24]

The scope and responsibility for influenza immunization program delivery and targets are also changing in Alberta. While the AHS Public Health messaging targets children under 9 years of age, specifically children aged 6-23 months, the role of pharmacists in influenza vaccination in Alberta is becoming more visible than previously was the case. For example, for the 2011-2012 influenza season, pharmacists provided 90,000 Albertans with the influenza vaccine compared to 43,000 Albertans in 2010-2011 influenza season.[22,36]

The provincial targets set for the annual influenza season coverage are as follows: 75% for both seniors aged 65 years and over and children aged 6-23 months and 95% for residents of long term care facilities.[31,37]A comparison of the coverage rates among these priority groups for the six influenza seasons for which data were available[38] showed that the rates for residents of long term facilities have hovered around the 90-95% range, while the rates fluctuated between 56-62% for seniors aged 65 years and over and 16-

64% for children aged 6-23 months respectively.[31,38]Thus Alberta's influenza rates have been consistently below the target for the latter population groups.[38]

In 1999, AH implemented the Adverse Reaction to Immunization (ARI) system for the collection of adverse reaction to immunization events.[39]This system uses the vaccine code to identify the vaccine administered to the person who had the adverse reaction during a related or an associated historical vaccination.[39] The Immunization and Adverse Reactions to Immunization Database (Imm/ARI) captures both the vaccination and adverse events data from 2006 forward from all areas of the province except for First Nations persons who are immunized on-reserve.

2.4 Epidemiology of Influenza

2.4.1 Clinical features of influenza

Influenza is an acute viral disease of the respiratory tract characterized by fever, headache, myalgia, prostration, coryza, sore throat and cough.[1]The virus is spread from person-to person by droplets, particularly small particle aerosols produced when people cough or sneeze.[3,34]

The incubation period averages 2 days, with a range of 1-4 days.[3] Most infected people recover within one to two weeks, while infection in the very young, the elderly, and those with underlying medical conditions can lead to severe complications such as pneumonia and possibly death.[34]

2.4.2 Virology of influenza

There are three types of influenza viruses: A, B and C. Influenza A viruses infect a range of mammalian (e.g. pigs and horses) and avian species, whereas type B and C infections are largely restricted to humans.[40]Only types A and B viruses cause human disease of any concern.[40]

Influenza viruses frequently undergo changes in the antigenicity of their major surface proteins through two distinct processes known as antigenic “drift” and “shift” .[3,41] Minor mutations causing small changes (“antigenic drift”) in the HA (Haemagglutinin) gene enables the virus to evade immune recognition, resulting in seasonal influenza outbreaks during inter-pandemic years.[40] Antigenic drift, which may occur in one or more influenza vaccine components, generally requires seasonal influenza vaccines to be reformulated annually.[1]

2.4.3 Burden and impact of influenza

Worldwide, influenza illness causes a high burden of suffering and results in substantial societal cost in terms of lost productivity, health service utilization, school and work absenteeism, affecting individuals and families. [42,43]Influenza occurs globally with an annual attack rate estimated at 5–10% in adults and 20–30% in children.[40] Rates of influenza infection are highest in children, but rates of serious illness and death are highest in older persons (> 65 years) and persons with underlying medical conditions.[40]

Influenza infection is the most common vaccine-preventable disease among children in Canada.[35] Children under two years suffer the highest influenza attack rates (30-50%), which are associated with high rates of health care utilization[44] and a risk of hospitalization during influenza season similar to that of high-risk individuals and the elderly.[35]

2.5 Control and Prevention of Influenza

2.5.1 Influenza vaccine and vaccination against seasonal (epidemic) influenza

Although hand hygiene and antiviral drugs have a limited role in influenza prevention and control, the cornerstone of prevention is vaccination.[1] "Vaccines should be administered using the recommended dose, route, site and schedule to optimize vaccine effectiveness and reduce the risk of local reactions or other adverse events."[45]

Due to frequent antigenic change (antigenic drift) resulting from point mutations that occur during viral replication, influenza vaccines are reformulated each year based upon recommendations from WHO international surveillance.[46] Trivalent inactivated vaccine (TIV) and live attenuated influenza virus vaccine (LAIV) are developed each year for protection against the expected predominant influenza strains.[40] Both vaccines contain the predicted antigenic variants of influenza viruses.[40]

In Canada, for the 2010-2011 season (the study period), the TIV manufactured as per WHO recommendations contained three components that offered protection to three individual strains. The composition of the TIV was as follows: A/California/7/2009(H1N1)-like, A/Perth/16/2009(H3N2)-like, and Brisbane/60/2008 (Victoria lineage)-like antigens.[47] While the B component remains unchanged from the 2009-2010 seasonal TIV, the A (H1N1) component was derived from the 2009 H1N1 pandemic virus and the A (H3N2) component was new.[47] In Alberta, for the 2010-2011 season, only TIV was used.[22]

2.6 Reporting of Adverse Events Following Influenza Vaccination

2.6.1 Importance of monitoring adverse events

All vaccines can cause adverse events and no vaccine is perfectly safe or effective.[48] As the reports of vaccine adverse events are becoming increasingly frequent, vaccine safety concerns have become increasingly prominent in immunization programs.[48]Therefore, surveillance and monitoring for adverse events after vaccination is a critical component of an immunization program.[4-6,49]

Vaccines can be considered as a public good being provided not only for the benefit of the individual but also for public protection.[48,49]Although generally speaking, vaccines have to a large extent been demonstrated to be safe, there have been clear instances of vaccine-associated harm.[50,51] Therefore, the overall comparison of vaccine adverse events and benefits from the vaccination program should be evaluated. On a population basis, the risk-benefit ratio is evaluated by expert committees whose mandate is to maximize the benefit for the whole population by averaging risks and benefits and placing greater value on patient safety.[48]

Despite the public health benefit of vaccination, concerns over vaccine safety may be the most important issue to affect immunization coverage[5] and the success[52] and sustainability of an immunization program.[12,48]As a public health issue, these vaccination concerns could undermine immunization program and may, in turn result in harm through resurgence of disease as vaccination coverage declines.[5,50] Therefore they must be addressed in order to ensure that the public confidence is maintained in the safety and efficacy of vaccines.[50]

Because vaccines are typically administered not only to large populations, but also to otherwise healthy individuals, lower rates of adverse events could translate into important numbers of cases at a population level.[48,50] This makes events occurring at ~1 in 10,000 to 1 in 1,000,000 doses of concern for vaccines.[48] Vaccine pre-licensing trials are designed to be able to establish safety by detecting events occurring in the range of 1 in 10,000 reactions, but cannot reliably detect rarer reactions.[5,53] This is why it is important to do post-marketing surveillance, i.e. include AEFI monitoring as part of surveillance related to an immunization program.

2.6.2 Monitoring of adverse events following immunization (AEFI)

Passive surveillance systems have been developed in different countries to routinely monitor for such events. They rely on voluntary reports from vaccination stakeholders such as physicians, community providers, other health-care professionals, vaccine companies or sponsors and the public.[6] In Canada, AEFIs are reported to the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) either directly or through the provincial/ territorial public health departments.[54] This database is managed by the Public Health Agency of Canada (PHAC).

WHO defines an adverse event following immunization (AEFI) as “a medical incident that takes place after an immunization, causes concern and is believed to be caused by immunization.”[55,56] It may be related to the vaccine itself or its handling or administration.[56] The event reported may be caused by immunization (causally related) or may have been coincidentally related to timing of immunization without necessarily being caused by the vaccine or the immunization process.[6]

WHO classifies AEFI outcomes as 'serious' and 'non-serious' based on the outcome or action.[55] A serious AEFI is defined as a report that, according to the reporter, resulted in life-threatening illness, hospitalization, prolongation of hospitalization, persistent or significant disability, or death, or an intervention to prevent one of these outcomes.[55,57,58]

2.6.2.1 Alberta: AEFI monitoring

Alberta currently uses a paper-based passive reporting system to monitor AEFI. AEFI data are reported on a form ('Report of Adverse Reaction to Immunizing Agents- attached see Appendix) and submitted to the AH's Surveillance and Assessment Branch Immunization Program. Currently, all the five AHS zones collect AEFI data on paper forms that are filled out by hand and then submitted to AH where they are later entered into the electronic database.

AEFI reports are sent from the AH's Imm/ARI electronically every 2 weeks to the PHAC. Case reports on AEFI are collected from the provincial and territorial health departments, health care professionals and the pharmaceutical industry.[59]The data are stored in the Canadian Adverse Events Following Immunization (CAEFI) database and are used to detect adverse events that may require more in-depth investigation.[54]

2.7 Published literature on influenza vaccination coverage in Canada

There are limited published data to assess influenza vaccination coverage in Canada. A scoping review of published literature on influenza vaccination coverage in Canada performed in 2012 showed that the literature on influenza vaccination was not limited to coverage measurements but also addressed themes that were relevant to the surveillance of influenza vaccination programs.[60]Of the 113 articles reviewed by the authors, 42% actually measured influenza vaccination coverage.[60]

Moreover, the authors identified the following themes in the literature: adverse events (8%); communication, knowledge, attitude, perception regarding influenza immunization (15%); influenza-related hospitalizations, visits and attack rates (8.8%) and other 26.6%.[60] However, there is a paucity of Canadian research to inform about the variations in influenza vaccination coverage in terms of populations (e.g. immigrants, age groups, rural) and health disparities.

For the most part estimations of seasonal vaccination coverage are primarily available from the CCHS which assesses immunization status for seasonal influenza vaccination only for people aged 12 years or older [14] (see for the section 1.5 for a discussion of the limitations of CCHS). To some extent, provincial variations in the proportion of people aged 12 or older receiving an influenza vaccination in 2003 reflect public funding of immunization.[61] The proportion in Alberta (29.1%) was above the national figure (25.5%) in 2010/2011 and had risen substantially since 2003 (from 23%).[14]

The literature suggests that influenza vaccination rates are low in Canada [14] and in the general population.[62] Canadian influenza vaccine coverage studies targeting the over-64 age group have recorded values as high as 45-69% [14,15,63], which are comparable to those reported by other European countries and the United States of America.[64-66] This contrasts with 14-32% influenza vaccine coverage in the general Canadian population.[14,15,63] In 2003, 67% of seniors (age 65 years or older) reported having had an influenza vaccination the previous year-almost unchanged from 2000/01 [61], but declined to 59.1% in 2010/11.[14] And in Alberta, the 2003 figure was 64%, with a significant decline to 58.9% in 2010/11.[20,61]The proportion of people aged 12 years or older with chronic conditions who had an influenza vaccination was below the national figure (47%) in Alberta (37%) in 2003.[61]

It is important for researchers to understand the methodological issues around influenza vaccination coverage in order to contribute findings that are meaningfully comparable over time and across studies and provinces. Several methodological issues in estimating influenza vaccination have been addressed in the published literature (see section 2.9 on details Methodological Issues in Estimating Vaccination Coverage).Methodologically important issues that are particularly problematic for making comparisons result from the lack of standardization in data collection methodology and reporting definitions [67](see section 2.9 on details Methodological Issues in Estimating Vaccination Coverage).

2.8 Epidemiology of Influenza vaccination

2.8.1 Influenza vaccination coverage

Vaccination coverage can be described simply as the proportion of defined groups that are vaccinated in a geographical area by a certain point in time.[9]For influenza, factors such as age, number of doses, and timeliness of doses and schedule of vaccination should be taken into consideration due to clear differences in the protection against influenza infection.[29,30,68,69]

Immunization coverage is a key measure of immunization system performance.[8] Immunization coverage rates are considered a sensitive indicator of the health of a population and the capacity of a health system to deliver essential services, and their measurement is required to monitor programs and progress towards national immunization targets.[10,11] If measured on an ongoing basis, coverage rates can be used to detect changes in the reach of immunization programs and identify underimmunized subpopulations.[10-11]

2.8.2 Monitoring influenza vaccination coverage in Alberta

Prior to Fall 2009, Alberta's targeted annual influenza vaccination relied on age- and risk-based recommendations of vaccines for persons 65 years or older or person aged 6 months; or older with a chronic health condition placing them at a higher risk of complications of influenza, or healthy children aged up to 59 months (i.e., "< 6 years of age").Annual AH reports have shown not only that the influenza coverage rates were below the targets but the rates have gradually declined among persons aged 65 years and older and children aged 6-23 months from the 2004-2005 season to the 2011-2012 season.[38] Because rates of serious illness are highest in these targeted groups [40], Alberta's universal publicly funded influenza vaccination program uses the priority reason codes to identify this high-risk population and estimate coverage rates for this population.

Monitoring of coverage rates among low- and high- risk groups is essential in order to determine if low coverage levels clearly indicate a problem of public health to reach the target groups.Vaccination of high-risk persons during the vaccination season is important in order to increase the proportion of high-risk Albertans protected against influenza and to reduce the transmission of viruses in the population by reducing the transmission levels among contacts of high –risk persons.[70] Individuals who are healthy also benefit from influenza vaccination.[71]

One of the challenges facing influenza vaccination programs is to identify all the children aged under nine years who require two doses of influenza vaccine as a primary series. Monitoring of coverage rates in this age group is important to ensure that they are adequately protected against influenza.[30]

2.9 Methodological Issues in Estimating Vaccination Coverage

2.9.1 Overview of methodological issues

There are several challenges in measuring vaccination coverage and comparisons across studies are challenging due to a lack of standardization in data collection methodology and reporting definitions.[67] Measurements are being made but they are not made using the same methods over time and across place. Some of these challenges relate to the definitions of 'vaccinated' (the numerator), the type of vaccination status measures,[72] whether studies reported complete or partial or combined rates,[67,73] who is included (the denominator), the data sources for the numerator and denominator, [67] and whether cross sectional or birth cohort data are used.[74]

An important methodological issue for immunization coverage assessment in children is whether the method of counting immunization doses accounts for appropriate timing and age using the minimum spacing criteria and the minimum age criteria stipulated by the vaccination schedules.[72,75] This is because differences in measurements could result from the differences in vaccines, vaccine doses, different age and spacing criteria (i.e. whether vaccinations are excluded if given earlier than the minimal age or shorter intervals than recommended by the vaccination guideline) and the purpose of assessment.[75-77]

An important methodological issue in measuring coverage in children younger than nine years of age relates to the number of appropriate doses of the vaccine they received, i.e. whether they received a single dose in the year after completion of a primary series (complete coverage) or received only a single dose in the year (partial coverage). The proportion of children vaccinated with 1 versus 2 doses is critical for understanding the extent of the protection offered by the influenza vaccination of young children.[29,30,68,69] The terms 'complete' or 'full' (i.e. two doses), 'partial' (i.e. one dose), and 'combined' (i.e. one or more doses) influenza vaccination coverage) only relate to children aged less than nine years.[67,73,78,79]

The estimation and interpretations of influenza coverage rates can be challenging. The challenges are as follows:

- Definitions of 'vaccinated' (the numerator)
- Who is included in the vaccination (the denominator)
- Generating estimates of numerators
- Selection of the appropriate indicators for coverage rates (i.e. receipt of influenza vaccine: 1 dose, 2 doses 28 days apart in children < nine years of age, 1 or more doses, etc.)
- Data sources

2.9.2 Definitions of 'Vaccinated'

The main difficulties in estimation of influenza vaccination coverage is defining 'vaccinated' and generating appropriate numerator and denominator data counts. These relate to the number of doses required [29,30,68,69], whether doses are administered and counted according to the recommended vaccination guidelines or not [47], and the timeliness of the doses in terms of both the influenza season and the time interval between the two dose administrations.[79,80]

For the study influenza season (2010-2011), the Canadian National Advisory Committee on Immunization (NACI) recommended two doses of seasonal TIV to children under age 9 with no prior TIV, with an interval of 4 weeks.[47] Children under 9 years of age who received one dose or more doses of TIV in the past are recommended to receive one dose per season thereafter. This recommendation applies whether or not the child received monovalent pandemic 2009 influenza A (pH1N1) vaccine in 2009-2010. For reasons related to immunological priming, NACI further recommended a two-dose schedule for previously unvaccinated children under 2 years of age and also stated that two doses may need to be considered in the second season for these children regardless of their vaccination history if there is a major antigenic (B lineage) change in vaccine component between sequential seasons.[47] However, NACI awaits further corroborative evidence for this recommendation for the older children.[47]

Because influenza vaccinations are provided annually within certain time period, delivering 2 doses of vaccine to all previously unvaccinated children under 2 years of age within a short period of time may also be logistically challenging.[30,67,81,82] For children under 9 years of age, for reasons related to immunological priming, children who had received only 1 dose may not be adequately protected.[47] For this reason when assessing vaccination coverage it is important to determine whether or not a child is adequately vaccinated (i.e. has received 2 doses) according to this definition. [29,30,68,69] Studies have shown that a large proportion of children did not receive the required second dose necessary to achieve a protective response.[78,80,83,84]

Studies have also demonstrated clear differences in the protection between receipt of one and two doses of influenza vaccine. In studies primarily designed to assess influenza vaccine effectiveness, Ritzwoller *et al.* (2005) and Shuler *et al.* (2007) independently demonstrated that receipt of two doses provided adequate protection against influenza illness while receipt of one dose did not achieve a significant reduction in illness among children 6-23 months of age.[29,69] These studies provided corroborative evidence for the recommendation of the second dose for optimal protection against influenza.

The definition of 'vaccinated' in several studies included having 'one or more doses'. Estimating vaccination coverage in this way may not take the dose schedule into consideration. This may amount to counting 'crude vaccinations' which may ultimately lead to overestimated coverage since it does not inform about the level of protection in the community.[85]

Other studies have made a clear distinction between receipt of 1 and 2 doses and estimated vaccination rates for receipt of 1 and 2 doses respectively.[79,80] For example, Moran et al.2009[67] conducted a telephone survey of influenza vaccination in a sample of 4854 Ontario children aged 6 months -11 years from 3029 households using a random digit dialing. The authors estimated coverage rates for receipt of at least 1 dose and 2 doses of influenza vaccine among children aged 6-23 months. In an attempt to compare the coverage rates for Ontario children aged 6-23 months with estimates from other provinces, the authors noted that only the combined rates (complete and partial coverage) could be reported since the extraction of appropriate number of doses was not possible.

Furthermore, the authors noted that the coverage estimates from these four provinces (Ontario, Manitoba, Saskatchewan, and Alberta) not only were estimated using varying denominator definitions, but also used varying numerator data sources. The differences in the coverage rates among children aged 6-23 months by provinces were in a large measure caused by the differences in methodology, which, in turn, may flow from the differences in the goals and purposes of the vaccination programs. This study underscores the need for consistent definitions, and standardization in data collection methodology if comparisons of influenza coverage rates are to be meaningful across Canadian provinces.

Therefore, the definitions of 'vaccinated' or 'not vaccinated 'for children should take into consideration the number of doses administered in a specified time period due to the clear differences in protection against influenza infection. This will also facilitate the comparisons of the study results.

2.9.3 Data Sources

Estimation of coverage depends on the availability of both the numerators and denominators. Influenza vaccination data are available from several sources including surveys, medical records, vaccination cards, administrative data, vaccination registries, immunization information systems, and insurance/billing records. However, the quality of the data can vary and careful consideration is needed when deciding to use any particular data source. Each data source has its advantages, limitations, and validity for assessing influenza vaccination coverage.

2.9.3.1 Numerator data sources

The numerator is a count of persons vaccinated obtained from a data source. Survey is one of the most common methods for the assessment of the prevalence or incidence of various health conditions in a population.[86] The prevalence or incidence estimates obtained from surveys depend on many factors such as the accuracy of self-reports and the sampling strategy.

Household surveys are the probably the most commonly used data source for numerator counts in the assessment of influenza vaccination rates. They rely primarily on parental recall and immunization cards are often used to elicit vaccination history. The main limitations of surveys are low response rates, recall bias, selection bias, [67] non-participation bias and inability to assess specific subpopulations.[87]The Canadian Community Health Survey (CCHS), which assesses immunization status for seasonal influenza vaccination only for people aged 12 years or older, is a self-reported survey data based on the respondent's response to the receipt of influenza vaccine in the past 12 months.[14]

2.9.4 Denominator Data Sources

The denominator is a count of persons included in the calculation of coverage rates, i.e. persons eligible for vaccination. The selection of a denominator may involve differences in the target population, the sampling strategy, and other special criteria such as who is included or excluded.[76]

Denominator data (counts) are can be challenging to generate. As there is no single ideal source for denominator data, several potential denominator data sources should be identified for generating vaccination coverage rates for influenza. Ideally, the data source for the denominator should have the potential to represent the population eligible for influenza vaccine in a geographical area by a specific time point or period of interest.This will take into consideration that influenza vaccine is not administered to children less than 6 months of age.

A cross-sectional survey captures the experience of a defined birth cohort, thus allowing for a retrospective reconstruction of vaccination history up to the time of a survey.[99] Assessment of childhood vaccination usually involves defining a birth cohort and the coverage is then assessed in one defined cohort. This usually involves specifying an interval of dates of births and children whose dates of birth fall within this interval will be included in the assessment. For example, one study of the assessment of influenza vaccination coverage among children aged 6-23 months following the 2002-2003 influenza season surveyed only parents of children aged 6-23 months born between December 1, 2000 and March 31, 2002.[98]

2.9.5 Validity and reliability of administrative data and immunization registries

Administrative data are described as "electronic data records that are typically generated at the time of hospital discharge or provision of other services."[88] The use of healthcare administrative databases in research is becoming increasingly common.[88] Although not originally collected for research purposes, administrative data can be used as a tool for planning and surveillance because of their availability in an electronic format as well as timeliness and large population coverage.[88]

Administrative data in general are commonly used to identify people with chronic diseases for research. The quality of data in the administrative databases varies widely in the amount of research. Great emphasis has been placed on hospital discharge abstracts, less emphasis on physician claims, and almost no emphasis on nursing home data.[89] The quality of immunization registries has also received little attention.[89] The quality of data is a reflection of both the completeness of a dataset and its accuracy.[89]

Ballard et al. (1997) [17] assessed the validity of reporting of influenza immunizations in administrative data compared with medical record reviews and surveys in the 1994-1995 and the 1995-1996 influenza vaccination seasons in the United States. They found medical record review-based documentation of influenza immunizations in 83% of cases from the influenza immunizations in administrative data, with a higher percentage of immunizations not documented in the medical record than in the administrative data (19.3% vs 13.3% respectively). Moreover, the estimated influenza vaccination coverage rate increased when the survey data were added.

The authors concluded that “telephone surveys resulted in higher and probably more valid estimates of influenza immunization rates than did analysis of administrative data and medical records.”[17] This study highlights the fact that people may obtain influenza vaccination from diverse sources leading to inability to capture many vaccinations from any single source. The possible scattering of medical records across different databases and service providers may also have contributed to the failure to capture many vaccinations.[72]

The quality of the physician claims has also been compared with the survey responses and clinical measures to assess their reliability using diagnosis as the most examined variable.[89] However, few available studies focussed on the validity of the physician claims for influenza vaccinations. Wang *et al*. (2009) and Kwong *et al*. (2007) validated the Ontario Health Insurance Plan (OHIP) billing claims against self-reported influenza vaccination in the CCHS data.[90,91] These two studies used a single physician billing fee code and/or a combination of fee codes to define influenza vaccinations in the OHIP databases. Both studies found that the physicians billing claims were highly specific for influenza vaccination, but only fairly sensitive.

The authors suggested that the rates of influenza vaccination in OHIP data might be underestimated since 35% of individuals are not vaccinated in doctor's offices; their vaccinations would not be expected to be captured in OHIP dataset. It was recommended that the use of codes specific for influenza vaccines would result in a more accurate determination of coverage.[90,91]Another limitation of the physician claims is that since the billing codes have not been validated, the physician claims might not give an accurate picture of preventive health services utilization for influenza vaccination.[90]

Immunization registries are described as "confidential, population-based computerized systems that contain information regarding children's vaccinations."[92] The data from immunization monitoring can be used for timely monitoring of influenza vaccination rates while also tracking multiple doses.[93] "A registry with added capabilities, such as vaccine management, adverse event reporting, lifespan vaccination histories, and linkages with electronic data sources, is called an immunization information system (IIS)."[94]

In 1988 Manitoba established an immunization registry at the inception of the Manitoba Immunization Monitoring System (MIMS).[95]MIMS contains the immunization records of every Manitoba resident with a valid Manitoba Health personal health identification number and includes the data from all immunization providers. [95]MIMS is capable of measuring and augmenting coverage among an entire population of children and can be programmed to produce reminder letters on a monthly basis using parents' or legal guardians' address.[95,96]

Roberts *et al.* (1994) validated the childhood immunizations recorded in MIMS against chart review and found the immunization data to be highly accurate.[96] "Comparisons between physician and MIMS records have shown excellent agreement, with 2% or fewer immunizations coded incorrectly and service dates matching 98% of the time."[96] The likely limitations in MIMS are as follows: "There are several points in the immunization data entry process where errors can occur, producing erroneous immunization records in MIMS. These include physician coding and data entry errors at the physician billing level, MIMS data entry clerk input errors, public health line listing errors, etc."[95]

2.9.6 Validity of self-reported influenza vaccination

There is extensive literature on self-reported information to determine influenza vaccination coverage. Apart from issues such as survey response rates and sample representativeness, the validity and reliability of the responses often come into question. In these studies, medical records data (immunization record review) are frequently used to confirm vaccination status. Studies comparing parental reports of influenza vaccination with immunization record review in young children have found good levels of agreement but over reporting by parents often occurs.[97,98] The results suggest that self-reported vaccination status may be both reliable and valid.[16-19]

2.9.7 Urban/ Rural Indicators Comparisons

Estimation of rural and urban influenza coverage is of interest because studies in Canada have shown that geographic location (urban/rural) can influence the quality of health care. [100,101] In Canada, it has been shown that rural residents on average have shorter life expectancies and are less healthy than urban residents.[100] It is therefore important to understand the factors that influence health service utilization in rural population.

This study used the postal code information contained in the AHCIP (Alberta Health Care Insurance Plan) Central Stakeholder Registry (CSR) as geographic indicator of residence (urban/rural).AHCIP Central Stakeholder Registry is largely based on self-reported information and is prone to errors which may limit the accuracy of the data. The accuracy of data will reflect the information the applicants for AHCIP provide. Errors could also arise from data entry and /or interpretation by data entry staff.

It is also important to note that there are differences in the methods used by AH and Statistics Canada to define geographic populations.[102] One of the major differences lies in assigning geographic location of residents.[102] AH uses the mailing postal code of residence for geographic placement of residents and this can be different from the physical address, especially in rural areas where post offices boxes are used.[102] The Census uses the physical address of the residents which has greater precision than the postal codes.[102]

There are several limitations in using postal codes as geographic indicators of residence.These include the following: “the residential mailing postal code used in AHCIP Registry may not always reflect an individual’s physical residential address.”[102] “Postal code-derived populations from the AHCIP Registry underestimate the rural populations, and in some cases, even report no residents in these geographic units.”[102]

2.9.8 Immigrants versus foreign born versus ethnicity

The literature suggests that there may be differences in vaccination coverage between foreign and non- foreign born individuals or between immigrants and non-immigrants.[27,28] It is important to discover if coverage rate varies by subgroups or among different populations. If this is so, this may suggest a need to target interventions to those specific groups if there are disparities or a need for increased culturally competent public health immunization interventions to increase coverage among those specific groups.[28]

For the purposes of this study, immigrants are persons who are listed in the Alberta immigrant registry and whose place of birth is outside Canada. Immigrants are persons who have acquired the landed immigrant status in Canada.[27] Foreign born persons are persons whose country of origin is outside Canada.

Based on research in Canada, studies have shown that immigrants or children identified as immigrants were more likely to have received influenza vaccination.[15,103,104] or were more likely to be up-to date (UTD) for routine childhood vaccinations at two years.[27] Other studies of influenza and childhood vaccination coverage have produced contradictory findings, whereby immigrants and foreign born children were less likely to have received the influenza vaccine.[28,105,106]

Factors that may account for these opposing findings include differences in sample populations among studies [15,27,103,104], whether the study adjusted for other possible covariates [15,27,103,104], and whether the study relates to ethnicity rather than immigration.[28,107]

2.9.9 Male/ Female Comparisons

Studies of influenza vaccination coverage have shown that women were more likely than men to have received the influenza vaccine.In studies using multivariate logistic regression models to identify the effect of sex, holding other characteristics equal, men had significantly low odds of vaccination compared with women.[61,108]

2.10 Summary of Literature Review

Influenza is a disease of public health importance and influenza vaccination provides protection against influenza. Measuring vaccine coverage and monitoring adverse events following vaccination are key indicators for influenza vaccine program evaluation and useful aid in program management and decision making.

Because influenza vaccination provides significant health benefits for all age and risk groups, monitoring influenza vaccination coverage in all age and risk groups will help determine if adequate levels of protection in the population are achieved. Surveillance and monitoring for adverse events after vaccination are critical components of immunization programs for addressing vaccine safety concerns.

It is important for researchers to understand the methodological issues around influenza vaccination coverage in order to contribute findings that are meaningfully comparable over time and across studies and place.

Chapter Three: Methods

3.1 Introduction

This chapter addresses the methodology used to answer the research questions. The chapter includes the study design, study population, study period, and the data sources.

3.2 Study design

This study used a retrospective observational design in which administrative data were used to describe adverse events of influenza vaccination and to estimate influenza vaccination coverage for the 2010-2011 influenza vaccination season in Alberta.

For the 2010/11 influenza season, AH's population-based dataset for influenza vaccination, that captures all ages, rural and urban areas, and influenza vaccinations administered by pharmacists and physicians, was available to the researcher. This study used all the available data for the 2010-2011influenza season.

3.3 Study population

The study population is comprised of all persons aged 6 months or older in the province of Alberta who were eligible for publicly funded influenza vaccination between October 1, 2010 and April 30, 2011inclusive.

3.4 Study period

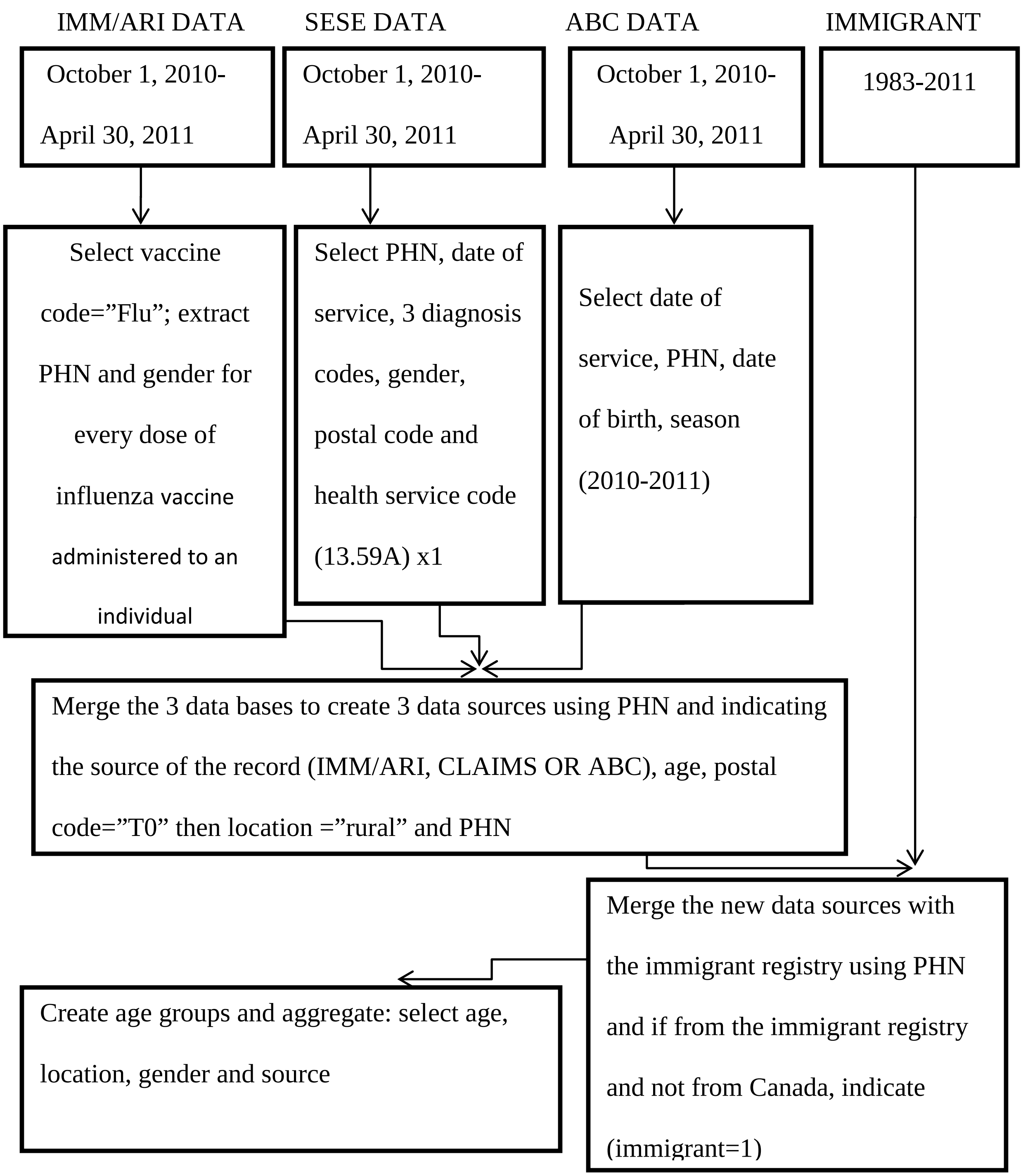
For the purpose of this research, an "influenza season" runs from October 1, 2010 to September 30, 2011.The study's "influenza vaccination season" runs from October 1, 2010 to April 30, 2011.In Alberta, first and annual doses of influenza vaccine were administered for the 2010-2011 season until April 15th, 2011 with the second dose administered until May 15th, 2011.[20] However, for this study the analyses were based on data provided to the researcher up to April 30, 2011.

3.5 Databases

Vaccination data for all persons six months of age and older were retrieved from the following three AH databases: Immunization and Adverse Reactions to Immunization (Imm/ARI) registry, the Alberta Blue Cross (ABC) database and the Fee-for-Service Administrative Claims Database (Supplemental Enhanced Service Event System-SESE). The adverse events data for influenza were retrieved from the Imm/ARI system for the 2010-11 influenza season.The fourth AH database known as the immigrant registry provided the counts of immigrants in Alberta.

The data were created as four separate files (the flu file, the second dose file, the AEFI file and the immigrant file) by AH personnel who had access to the PHN and performed the file linkage and data aggregation prior to releasing it to the researcher. The data were extracted using the PHN, which is a unique lifetime identifier. Figure 3.1 shows how the preliminary database linkages and aggregation of the flu file were performed using the PHNs for deterministic linkage.The creation of the second dose file (two influenza vaccine doses) was determined as outlined in Figure 3.1 such that subjects were counted twice in Imm/ARI using the vaccine code “FLU” during the study period.The AEFI file was extracted as a table in the Imm/ARI registry and the immigration registry is created annually from the AHCIP central stakeholder registry of new Albertans

Figure 3.1 Schematic presentation of database linkages and aggregation for the flu file



3.6 Data Sources

3.6.1 Alberta health care insurance plan (AHCIP) central stakeholder registry (CSR)

The AHCIP Central Stakeholder Registry captures over 99% of Alberta's residents and information on each insured person is maintained in a provincial registration file that contains demographic information, as well as a unique personal health number (PHN) for linking the registration file to a variety of health data sources.[109] The demographic information contained in the database includes name, address with postal code, date of birth, and sex.

The number of registrants as of mid-year registered on the AHCIP was used as the estimate for the population of Alberta in 2010. However, these estimates exclude members of the Armed Forces, Royal Canadian Mounted Police, people in federal penitentiaries, or those who opted out of the AHCIP, and persons from other provinces during their first three months in Alberta. First Nations persons are included in the AHCIP registration file but their healthcare is covered by the federal government.

3.6.2 Immunization and adverse reactions to immunization (Imm/ARI) registry

The Imm/ARI Registry is used in Alberta to collect administrative data for immunizations and adverse events. This database is managed by the AH.The Imm/ARI database contains individual level immunization records, including data on adverse events following immunization for all publicly funded vaccines. In addition to an individual record of each vaccine given, this database also includes PHN, date vaccine administered, manufacturer and lot number, dosage, site vaccine administered (e.g., right arm), method of administration (e.g., oral, subcutaneous injection), and influenza vaccine reason code (Imm/ARI priority code).

The Imm/ARI registry is still collecting data for some years but has complete data for the study period for this research. The Imm/ARI registry captures vaccines given by the public health nurses. Vaccines administered on reserves and in the context of occupational and safety and employer groups are not captured by Imm/ARI. Although influenza vaccination data for residents of long-term care (LTC) facilities are included in Imm/ARI for most but not all LTC facilities, vaccination data for AHS LTC facilities are included in Imm/ARI (Personal Communication, Kim Simmonds, Manager, Infectious Disease Epidemiology, Surveillance and Assessment Branch Family and Population Health Division Alberta Health, July 5, 2013).

For influenza vaccinations not administered in the mass clinics, the Edmonton zone records data on paper forms that are entered in an electronic system. In other zones, the public health nurses enter data into an electronic system. In the mass influenza clinics, the paper forms are completed by a public health nurse and then data entry people enter the data into the AHS source system and the data are submitted to Imm/ARI (Personal Communication, Kim Simmonds, Manager, Infectious Disease Epidemiology, Surveillance and Assessment Branch Family and Population Health Division Alberta Health, July 19, 2013).

Community providers collected influenza immunization event data on influenza immunization forms (client immunization records) in written or electronic format [33].Community providers were required to submit immunization data to AHS twice each influenza season (December 31st and March 31st).[22,33] Influenza immunization event data from physicians and pharmacists are entered into the Supplemental Enhanced Service Event System (SESE) and Alberta Blue Cross databases respectively.SESE and Imm/ARI do not communicate with each other and data are not transferred between the sources (personal communication, Larry Svenson, Director, Surveillance and Assessment, Alberta Health, January 29, 2013).The vaccine code “FLU” [39]was used to identify the reported adverse events related to influenza in Imm/ARI.

Imm/ARI is validated using the stakeholder register for the client demographics and reviewed by AHS and AH for immunization details. Finally there are data submission rules that further reduce the likelihood of incorrect data submission (Personal Communication, Kim Simmonds, Manager, Infectious Disease Epidemiology, Surveillance and Assessment Branch Family and Population Health Division Alberta Health, July 5, 2013).

3.6.3 Supplemental enhanced service event system (Physicians claims database)

The official name, since November 1993, of the physician claims database is the supplemental enhanced service event (SESE). The database is quite large, but a number of the fields are related to the claim payment process. This database includes information on the patient (e.g. PHN, date of birth, age at service, postal code), the provider (e.g. provider identifier, specialty) the service event (e.g. location, type of facility, diagnostic codes, procedure codes), and the payment (e.g. amount claimed, amount assessed application of fee modifiers) (personal communication, Larry Svenson, Director, Surveillance and Assessment, Alberta Health, January 29, 2013).

When a physician administers the seasonal vaccine to a patient who is over six months of age, a medical record of the visit is generated. This is considered to be an insured service. However, there is no vaccine-specific billing code. The physician gets paid for the service by submitting a claim to Alberta Health. To support the claim, the physician provides the PHN of the patient, the date and location of service, up to three diagnostic codes (4-digit ICD (International Classification of Diseases)-9 coding), and the procedure performed (using the Canadian Classification of Procedures) (personal communication, Larry Svenson, Director, Surveillance and Assessment, AH, January 29, 2013).

In addition to the diagnostic codes, the health service code to be billed is 13.59A (intramuscular or subcutaneous injections).[109,110] The health service code (13.59A) was the only fee code consistently used in this study to define as well as count the number of influenza vaccinations administered by physicians. In Alberta, the fee codes are not vaccine specific.

3.6.4 Alberta Blue Cross (ABC)

Alberta Blue Cross provides supplementary health and dental benefit plans for individuals and families, seniors, and large and small employers.[111] The Alberta Blue Cross database contains the record (for each person vaccinated) of vaccines administered by pharmacists and includes pharmacy claims for seniors and persons on assistance.

"Only pharmacists with the authorization to administer vaccines by injection from the Alberta College of Pharmacists (ACP) will be able to access, administer, and bill Alberta Blue Cross for provincially funded influenza vaccine"[112].

The scope of practice for pharmacists is restricted to patients aged 5 and older for vaccines other than influenza vaccine.[112] For publicly funded influenza vaccine, pharmacists have agreed to only vaccinate people over 9 years of age, i.e. the College of Pharmacists has agreed to this vaccination restriction for influenza vaccination, but only for influenza vaccination.[33,112] Data on immunizations administered by pharmacists in this study are only captured through ABC.

3.6.5 Alberta Immigrant Registry

The Alberta immigrant registry captures the counts of immigrants from 1983-2011. This registry uses the AHCIP Central Stakeholder Registry to identify people who have migrated into Alberta since 1984.[113] The datasets provided to the researcher contained aggregated data by age at immigration, sex, and year of immigration. Current data for 2010-2011 were included, which was the most relevant data for the study period. However, the data prior to 2004 were incomplete.

"This registry uses the Alberta Health Care Insurance Plan Central Stakeholder Registry (CSR) to identify people who have migrated into Alberta since 1984.Immigration information, such as country or province of origin and date of arrival is typically provided when people register for health care coverage under the Alberta Health Care Insurance Plan (AHCIP) (P.8) " [113] The AHCIP registration form collects information such as country or province of origin and date of arrival when people register for health care coverage under the AHCIP.[114]

3.7 Data Cleaning and Creation of the Analytical Sets

The data were extracted by AH personnel as four separate files (Imm/ARI) registry, the Alberta Blue Cross database and the Fee-for –Service Administrative Claims Database (Supplemental Enhanced Service Event System-SESE), and the Alberta Immigrant Registry for the 2010-2011 influenza vaccination season.The researcher was provided with aggregated anonymized data that contained all the data variables required for the study. Once the files were received, the raw data were checked for duplicate entries or any other inconsistencies. The 45 persons (approximately 0.01%) for whom data were missing on sex (missing or unknown), or age (coded as invalid values) were excluded from the file. One person (approximately 0.4%) for whom data was missing on sex (unknown) was excluded from the AEFI file.

After data cleaning, four analytical databases emerged: the flu file, the second dose file, the AEFI file and the immigrant file.The flu file was the largest and was constructed from the Imm/ARI database, SESE database, the Alberta Blue Cross database, and the Immigrant Registry.The flu file had the following variables: the age at immunization (calculated as the difference between date of birth and the date of immunization) , sex, the type of vaccination provider, which is an indicator variable to identify whether the vaccination was provided by the AHS public health nurse, by a physician, or a pharmacist; an indicator variable for the area of residence (urban versus rural), an indicator variable for immigrant status (immigrants vs. non-immigrants), and the aggregate counts of vaccination data. Table 3.1 summarizes the analytical datasets, data sources and variables.

3.8 Data File Organization

The Flu file contained aggregate counts of vaccination data by age, sex, and indicator variables for the area of residence, the type of vaccination provider, and the place of birth.It contained the influenza vaccination data for all persons 6 months and older who received at least one dose of influenza vaccine in Alberta for the 2010-2011 vaccination season.Influenza vaccination data from the Imm/ARI database, the SESE database, the Alberta Immigrant Registry, and the Alberta Blue Cross database were merged to generate the flu file.The PHN was used as the key linking variable and the linkages can be considered to be deterministic (Figure 3.1).

Table 3.1 Databases used for analysis by source of data§

Analytical Dataset	Source Database	Variables in the analytical databases
Flu file	• Imm/ARI Database • Supplemental Enhanced Service Event System (SESE) • Alberta Blue Cross Database	1) Age at immunization (in years) 2) Sex 3) Indicator variable for area of residence (rural vs. urban) 4) Indicator variable for immigrant status (immigrants vs. non-immigrants) 5) Indicator variable for vaccination provider (AHS public health, physicians & pharmacists) 6) Aggregate count of number of vaccinations given during influenza vaccination period (October 1, 2010 to April 30, 2011)

Table 3.1 Databases used for analysis by source of data, continued		
Analytical Dataset	Source Database	Variables in the analytical databases
Second dose file	• Imm/ARI Database	1) Age at immunization (in months) 2) Sex 3) Indicator variable for area of residence (rural vs. urban) 4) Indicator variable for immigrant status (immigrants vs. non-immigrants) 5) Aggregate count of number of vaccinations given during influenza vaccination period (October 1, 2010 to April 30, 2011)

Table 3.1 Databases used for analysis by source of data, continued		
Analytical Dataset	Source Database	Variables in the analytical databases
AEFI file	• Imm/ARI Database	1) Age at immunization (in years) 2) Sex 3) Indicator variable for area of residence (rural vs. urban) 4) Indicator variable for immigrant status (immigrants vs. non-immigrants) 5) AEFI severity (serious AEFI vs. non-serious AEFI) 6) Aggregate count of number of vaccinations given during influenza vaccination period (October 1, 2010 to April 30, 2011)
Immigrant file	• Alberta Immigrant Registry	1) Age at immigration (in years) 2) Sex 3) Indicator variable for area of residence (rural vs. urban) 4)Year of immigration 5) Aggregate count of number of immigrants in 2010

§The researcher was provided with aggregated data; dataset contained only aggregated data whereas the source databases contained individual record data.

The second dose file comprised aggregate counts of vaccination by age, sex, and indicator variables for the area of residence, and the place of birth. This file contained the records of influenza vaccination of children < 49 months of age who received two doses of influenza vaccine in Alberta for the 2010-2011 vaccination.There were no data on second dose for children aged 5-8 in the dataset.The data for children < nine years of age for which there was only a record of a single dose being given are in the flu file.

The AEFI file contained aggregate counts of adverse events data among those vaccinated against influenza by age, sex, and the indicator variables for severity of adverse events, the area of residence, and the immigrant status.

The immigrant file is comprised of aggregate counts of immigrants by attributes of age at immigration, sex, year of immigration, and indicator variable for area of residence.

3.9 Urban/ Rural Indicators Comparisons

The AHCIP Central Stakeholder Registry includes information on postal codes which can be used as a proxy for the area of residence. Geographical areas such as urban or rural residence were assigned by the AH personnel based on the person's postal code current at the time of data extraction in September 2012. Rural postal codes can be distinguished from urban postal codes by the character "0" (zero) in the second position.[115-116]

3.10 Influenza Vaccination Coverage Rates for One versus Two Doses

Influenza vaccine doses were counted as 1 dose (i.e. only one dose of vaccine was administered) and 2 doses (i.e. only two doses were administered). The variables 'one dose' and 'two doses' influenza vaccination were used to describe the influenza vaccination coverage of children under 9 years of age. This study did not link to influenza vaccination data of prior years to see if children had received a dose in prior year.

3.11 Adverse events following influenza vaccination

In Alberta, the reporting system is passive and paper-based. AEFI data are reported on a form (Report of Adverse Reaction to Immunizing Agents) [117] and submitted to the AH's Surveillance and Assessment Branch Immunization Program.

AHS submits AEFI reports electronically except for the Edmonton zone, which sends the paper form. All AEFI reports are reviewed at AH prior to data entry; AEFI reports are validated when entered into Imm/ARI.The current form is being revised and a new form will be implemented (Personal Communication, Kim Simmonds, Manager, Infectious Disease Epidemiology, Surveillance and Assessment Branch Family and Population Health Division Alberta Health, July 5, 2013). The AEFI reports contain information on vaccines and the dates they were administered.

AH adopts PHAC's definition of AEFI for reporting purposes. According to PHAC, "An AEFI is any untoward medical occurrence in a vaccine which follows immunization and which does not necessarily have a causal relationship with the administration of the vaccine."[118] "A causal relationship between immunization and the event that follows does not need to be proven and submitting a report does not imply or establish causality"[118] It is also important for the reported event to have a temporal association with the vaccine and it cannot be clearly attributed to other causes.[118]

The AEFI data provided were pre-coded as serious versus not-serious events by AH personnel.The serious events were coded by an immunization nurse in consultation with the chief medical officer of health. However, the duration and onset of AEFI were not taken into consideration in grading AEFI's seriousness and there is no coding manual available at this present time (Personal Communication, Kim Simmonds, Manager, Infectious Disease Epidemiology, Surveillance and Assessment Branch Family and Population Health Division Alberta Health, July 5, 2013).

There are text fields in the reporting form (patient record, immunization record, adverse events record and adverse event detail record) which are coded by AH personnel. The text fields are all recoded in numeric values except comments; for example, the adverse event might be fever, but in the database it will be coded as 01 and there is a code table to look up the numeric values.[119]

AH uses the medical diagnoses listed on the AEFI reports to classify AEFI outcomes as 'serious' and 'non-serious'events. For influenza, serious AEFI outcomes are encephalopathy, meningitis, paralysis, Guillain-Barré Syndrome (GBS), subacute sclerosing panencephalitis (SSPE), adenopathy, and anaphylaxis (Personal Communication, Kim Simmonds, Manager, Infectious Disease Epidemiology, Surveillance and Assessment Branch Family and Population Health Division Alberta Health, September 21, 2012).

3.12 Operational Definitions

For the purposes of this study:

- The 2010-2011 vaccination season was defined as the period from October 1, 2010 to May 15, 2011 in which publicly funded influenza vaccination was administered in Alberta.

- Vaccinated was defined as an entry/ a record of influenza vaccination event in any of the three databases :Imm/ARI registry, the Alberta Blue Cross database and the Fee-for –Service Administrative Claims Database (Supplemental Enhanced Service Event System-SESE) between October 1,2010 and April 30,2011 inclusive.

- Urban/rural was defined based on the residential mailing postal code in the AHCIP registry file. If the postal code had the character “0” (zero) in the second position, a person was classified as a rural resident; otherwise, as an urban resident.

- Immigrant vs.non-immigrant: If on the AHCIP registry a person was born outside Canada, the person was classified as an immigrant; otherwise as a non-immigrant if Canadian-born.

- Provider type was defined as persons or agencies who directly administered the vaccine such as public health, community physicians, and pharmacists.

3.13 Inclusion Criteria

3.13.1 Objective1: Estimating influenza vaccination coverage

People were included if they:

1) were 6 months of age or older.

2) were eligible for publicly funded influenza vaccinations given in the province of Alberta during influenza vaccination period (October 1, 2010 to April 30, 2011) as demonstrated by them having a PHN in the AHCIP stakeholder registry.

3.13.2 Objective 2: Describing the occurrence of adverse events related to influenza vaccination

People were included if they:

1) were 6 months of age or older.

2) The person has actually received an influenza vaccination during influenza vaccination period (October 1, 2010 to April 30, 2011) as demonstrated by them having a record of vaccination event in any of the three databases (Imm/ARI) registry, the Alberta Blue Cross database and the Fee-for –Service Administrative Claims Database (Supplemental Enhanced Service Event System-SESE).

3.14 Exclusion Criteria

3.14.1 Objective1: Estimating influenza vaccination coverage

Children vaccinated against influenza under six months of age were counted as having received a non-effective dose and were removed from all analyses. Influenza vaccines that were administered after April 30, 2011 were considered outside of the study's defined influenza vaccination season and did not count in the estimations of vaccination coverage. Consequently, persons (including children) who received their first or only dose of vaccine after April 30, 2011were excluded from the estimations of vaccination coverage.

3.14.2 Objective 2: Describing the occurrence of adverse events related to influenza vaccination

The same exclusion criteria for objective 1 apply to objective 2.

3.15 Data Analysis

The researcher classified each person who received influenza vaccine or incurred an adverse event following vaccination with the influenza vaccine into age groups. There were 15 mutually exclusive categories that were useful for describing counts and rates for coverage (objective # 1).Because of the paucity of adverse events, the age groups were collapsed into 6 mutually exclusive categories for objective # 2.

3.15.1 Objective1: Estimating influenza vaccination coverage

For this objective, two separate analyses were made. First, counts and the proportions of persons vaccinated (i.e. who received at least one dose of vaccine and children < 9 years) were estimated by attributes of age, age group, sex, urban and rural residence, immigrant and non-immigrant, and in relation to vaccine provider type (AHS public health, physicians & pharmacists). Second, coverage for each sex and for age specific groups, and by attributes of urban and rural residence, immigrant and non-immigrant, and in relation to vaccine provider type, were estimated.

Influenza vaccination coverage rates were determined by estimating the number of individuals who received the vaccine as a proportion of the total number of individuals eligible to receive the influenza vaccine (all Albertans aged 6 months and older). For example, the overall influenza vaccination coverage rate (all age-groups combined) for Alberta was calculated using the formula:

- Number of individuals who received one dose of influenza vaccine / 2010 mid-year population estimate for Alberta.

Coverage rates for specific age groups were estimated as follows:

- Number of individuals who received the vaccine in a particular age group (e.g. children 6-23 months) / Number of individuals in that age group (e.g. children 6-23 months).

Similarly, coverage rate for each sex and for specific age groups was determined separately for males and females, rural and urban residents, immigrants and non-immigrants, and in relation to vaccine provider type.

The proportion of persons who received one, two or one or more doses was estimated in four separate analyses:

1) First, the influenza vaccination coverage (point estimates and its 95% confidence interval) was estimated for the general population (i.e. an overall estimate for Alberta) and

2) Second, by attributes of age, sex, geographical indicators (urban or rural), immigrants versus non-immigrants, provider type for the 2010-2011 vaccination season. Numerator counts for specific rates (i.e. age and sex specific rates, and age-specific rates by geographical indicators (urban or rural), and immigrants versus non-immigrants) were

taken from the aggregate counts of vaccinations that represent the three numerator data sources in the flu file.

3) Third, the proportion of children who received one and two doses of influenza vaccine was estimated. Age –sex specific counts of children who received one and two doses of influenza vaccine from the flu file and second file were used as numerators.

4) Finally, patterns in the coverage by different age groups, sex, type of residence (rural versus urban), and immigrants versus non-immigrants and provider type were analyzed.

In sensitivity analyses, the coverage rates were repeated after excluding the residents of the long-term care (LTC) facilities and healthcare workers (HCW) who had been vaccinated.[20]

3.15.2 Objective 2: Describing the occurrence of adverse events related to influenza vaccination

For this objective, two separate analyses were made. In the first analysis, counts and proportion of persons who incurred one or more adverse events following influenza vaccination were presented by attributes of age, sex, geographical indicators (urban or rural), and immigrants versus non-immigrants. In the second analysis, age-specific rates were estimated.

Rates of adverse events were determined by estimating the number of individuals who incurred one or more adverse events following influenza vaccination as a proportion of the total number of individuals 6 months or older who received one dose of influenza vaccine. For example, the overall rate of adverse event for Alberta was calculated using the formula:

- Number of individuals who incurred one or more adverse events following influenza vaccination / Number of individuals 6 months or older who received at least one dose of influenza vaccine.

Rates of adverse events for specific age groups were estimated as follows:

- Number of individuals who incurred one or more adverse events following influenza vaccination in a particular age group (e.g. children aged 6-23 months) / Number of individuals 6 months or older who received at least one dose of influenza vaccine in that age group (e.g. children 6-23 months).

Similarly, rates of adverse events for each sex and for specific age groups were determined separately for males and females, rural and urban residents, immigrants and non-immigrants, etc. Rates were expressed as events per 100,000 persons vaccinated.

The proportion of persons who incurred one or more adverse events following influenza vaccination was estimated in three separate analyses:

1) First, the proportion of individuals (point estimate and its 95% confidence interval) who incurred one or more adverse events following influenza vaccination in Alberta for the 2010-2011 vaccination season was estimated.

2) Second, the proportions of individuals who incurred one or more adverse events following influenza vaccination by specific age groups, sex, type of residence (rural

versus urban), and immigrants versus non-immigrants (point estimates and their 95% confidence intervals) was estimated; and

3) Third, patterns in the adverse events following influenza vaccination by different age groups, sex, type of residence (rural versus urban), and immigrants versus non-immigrants were analyzed.

3.16 Statistical Analysis

All data manipulations and analyses were done using STATA intercooled 11.0 statistical software.[120] 95% CIs were calculated for coverage rates and for rates of adverse events. 95% CIs around a point estimate were used to determine a statistically significant difference between two age groups. If the intervals do not overlap, it can be concluded that the point estimates are different and the two age- groups are statistically different. If the intervals do overlap, we cannot conclude anything because either the point estimates could be different or the point estimates could be similar.

Chi-square tests were used to determine the statistical significance of the difference between two proportions. In exploratory analyses, influenza vaccination coverage for the receipt of one dose was compared to the receipt of two doses among children aged < 49 months with respect to age group, gender, and immigrant vs. non-immigrant. All exploratory analyses were carried out at alpha=0.05 for descriptive purposes. Data were presented as frequencies, proportions, rates and mean ± standard deviation (SD).

3.17 Denominators for Estimating Vaccination Coverage

For all analyses, denominators were counts of persons of the corresponding age group who were eligible for an influenza vaccine. Ideally, the data source for the denominator should have the potential to represent the population eligible for influenza vaccine in Alberta. This will take into consideration that influenza vaccine was not administered to children less than 6 months of age.

Denominator data for influenza vaccination coverage rates were retrieved from AH‘s Interactive Health Data Application (IHDA) population estimates which was based on mid-year population estimates (June 30, 2010) from the AHCIP Central Stakeholder Registry.[121] The AHCIP registry was deemed the most appropriate denominator source for age-, sex-, and geography-specific influenza vaccination coverage in Alberta for the following reasons: completeness (captures over 99% of Alberta’s residents), data are updated regularly, quality assurance is in place to account for migration of people into and out of the province, and all registrants’ dates of birth are recorded.

In the AHCIP data, all children aged zero to one year were included. For this study, the population counts for children aged less than one year was divided into half to represent the population of children aged six months to less than one year.

3.18 Numerator and Denominator Data Sources for Adverse Events

For this study, Imm/ARI was the only database that contained the adverse events (AE) records. The numerator was a count of all persons 6 months or older vaccinated as recorded in the AEFI file that experienced adverse events (AE) following influenza immunization for the 2010/2011 vaccination season.

The Imm/ARI database, the SESE database and the Alberta Blue Cross database were used as the denominator data for describing the occurrence of adverse events. The denominator was a count of all influenza vaccine doses administered to persons 6 months or older as recorded in the aggregate counts of vaccination in flu file for the 2010/2011 vaccination season. The numerator for research question #1 was the denominator for research question #2.

3.19 Potential Data Sources for Denominators for Immigrants and Non-immigrants

As there was no single ideal source for denominator data for non-immigrants and immigrants, several potential denominator data sources were identified for generating vaccination coverage. They were: the Alberta immigrant registry (1983-2011) [113], 2006 Census-20% Sample Data (Alberta) [122] and Citizenship and Immigration Canada (CIC): Alberta-permanent residents by country of citizenship[123]. In order to determine the denominator for immigrants, the number of immigrants in 2010 was estimated by adding up the number of immigrants in the immigrant registry from 1984-2008 and the number of immigrants in the CIC data: Alberta-permanent resident by country of citizenship data from 2009-2010. [123] The two data sets were mutually exclusive and the number of immigrants was estimated by adding up within the data sets.

The number of non-immigrants was estimated by subtracting the number of immigrants from 2010 mid-year population estimate for Alberta. This decision was made after a critical appraisal of several data sources (Table 3.2). The Alberta immigrant registry was selected as the best choice for the purpose of this thesis because it contains the current and most relevant data for the study period (2010) and was also used to identify the denominator counts.

3.20 Ethical Considerations

Ethical review and approval was sought through the Conjoint Health Research Ethics Board (CHREB). Ethical approval was given on March 16, 2012.This study complied with the use of the health information as outlined in the Health Information Act (HIA) Guidelines and Practices Manual.[124]

Specifically, the analytic dataset represented a minimum dataset and contained only those variables that the researcher needed to analyze his research questions. The minimum amount of information that might be potentially be identifying was extracted. A minimal dataset was considered both ethical and efficient. Respect for persons was assured by extracting a minimum amount of information, linking data and removing identifiers.

Only the AH employees, who were data custodians under the HIA were authorized to be aware of the identifying information such as PHN and names, accessed the information. The data files that were released to the researcher have had the PHN stripped and were anonymized aggregate data. In this way, the researcher cannot track unique individuals within the dataset.There were no individual level benefits to study participants but there is social benefit.

Table 3.2 Assessment of Data Sources for Denominators for Immigrants & Non-Immigrants

Data Source	AH Immigrant Registry	2006 Census-20% Sample Data (Alberta)	Citizenship and Immigration Canada (CIC): Alberta-permanent resident by country of citizenship
Advantages	• Current & most relevant data for the study period (2010) • No data on non-immigrants • Data stratified by age at immigration, sex & year of immigration • Data are validated	• Complete data for immigrants and non-immigrants • Data stratified by sex, age groups, immigration status & place of birth • Data includes all categories of immigrants	• Current & most relevant data for the study period (2010) • No data on non-immigrants • Complete data for permanent residents for a particular year by country of citizenship

Table 3.2 Assessment of Data Sources for Denominators for Immigrants & Non-Immigrants, continued

Data Source	AH Immigrant Registry	2006 Census-20% Sample Data (Alberta)	Citizenship and Immigration Canada (CIC): Alberta-permanent resident by country of citizenship
Limitations	• Incomplete data: data since 1983 but complete since 2004 • Data for immigrants for a particular year, not for the total number of immigrants	• Data not current for the study period (2010) • Will need population projections for denominators corresponding to inter-censal years • Data may not account for current reality due to population shifts since 2006 census, i.e. emigration, deaths, etc.	• Data not stratified by age at immigration, sex & year of immigration • Incomplete data for immigrants, likely excludes non-permanent (i.e. temporary) residents

Table 3.2 Assessment of Data Sources for Denominators for Immigrants & Non-Immigrants, continued

Data Source	AH Immigrant Registry	2006 Census-20% Sample Data (Alberta)	Citizenship and Immigration Canada (CIC): Alberta-permanent resident by country of citizenship
Feasibility	• Valid source for immigrants • Should not as a sole source because of the limitations above	• Valid source for both immigrants and non-immigrants • Should not as a sole source because of the limitations above	• Valid source for immigrants • Should not as a sole source because of the limitations above

Chapter Four: Results

4.1 Introduction

Study results are presented in this chapter according to the objectives. The objectives are as follows:

(1) To estimate influenza vaccination coverage in Alberta by attributes of age, sex, geographical indicators (urban or rural), immigrants versus non-immigrants, and provider type for the 2010-2011 vaccination season; and

(2) To describe the occurrence of adverse events related to influenza vaccination in Alberta by attributes of age, sex, geographical indicators (urban or rural), and immigrants versus non-immigrants for the 2010-2011 vaccination season.

4.1.1 Descriptive and Bivariate Analyses

The descriptive analyses included tabulation of frequency distributions of the baseline characteristics of persons in terms of age, age groups, sex, place of residence, immigrants versus non-immigrants and provider type. For the 2010-2011 influenza season, estimates for coverage and adverse events are determined for the general population (i.e. an overall estimate for Alberta).The proportions of individuals vaccinated by age groups, sex, type of residence (rural versus urban), and immigrants versus non-immigrants (point estimates and their 95% confidence intervals) are presented. Coverage estimates were also determined for children who received one and two doses of influenza vaccine.

Among those vaccinated against influenza for the 2010-2011 vaccination season, the proportions of individuals who incurred one or more AE following influenza vaccination by age- groups, sex, type of residence (rural versus urban), and immigrants versus non-immigrants (point estimates and their 95% confidence intervals) were also estimated. Finally, patterns in the coverage and adverse events by age groups, sex, type of residence (rural versus urban), and immigrants versus non-immigrants were analyzed.

4.2 Objective1: Estimating influenza vaccination coverage

Findings for this objective will be presented in two sections. In the first section, the numbers of persons vaccinated are presented by attributes of age, sex, geographical indicators (urban or rural), immigrants versus non-immigrants, and provider type. The second section focuses on coverage.

The 45 persons (approximately 0.01%) for whom data were missing on sex (missing or unknown), or age (coded as invalid values) were excluded from all analyses. Data for the 640,268 individuals, who received one dose of vaccine in 2010-2011 influenza season and for whom there was no missing data for sex, age, place of residence, immigrants and non-immigrants, and vaccination provider, were analyzed.

4.2.1 Description of study population

Table 4.1 shows the distribution of demographic characteristics of individuals in the study sample. The final study population sample comprised 640, 268 individuals who received at least one dose of influenza vaccine in Alberta for the 2010-2011 vaccination season.Of those vaccinated, the majority of individuals vaccinated were female (56%),

Table 4.1 Demographic characteristics of individuals 6 months of age and older who received at least one dose of influenza vaccine, Alberta, 2010-2011 vaccination season

Characteristics	N= 640,268
Age at vaccination (years)	
Mean (SD)	49.9 (27.7)
Median	50
Range	< 1, 109
Sex	
Male	43.9%
Female	56.1%
Residence	
Urban	84.9%
Rural	15.1%
Non-immigrants and immigrants	
Non-immigrants	87.0%
Immigrants	13.0%
Vaccine provider	
AHS public health	81.4%
Physicians	11.8%
Pharmacists	6.8%

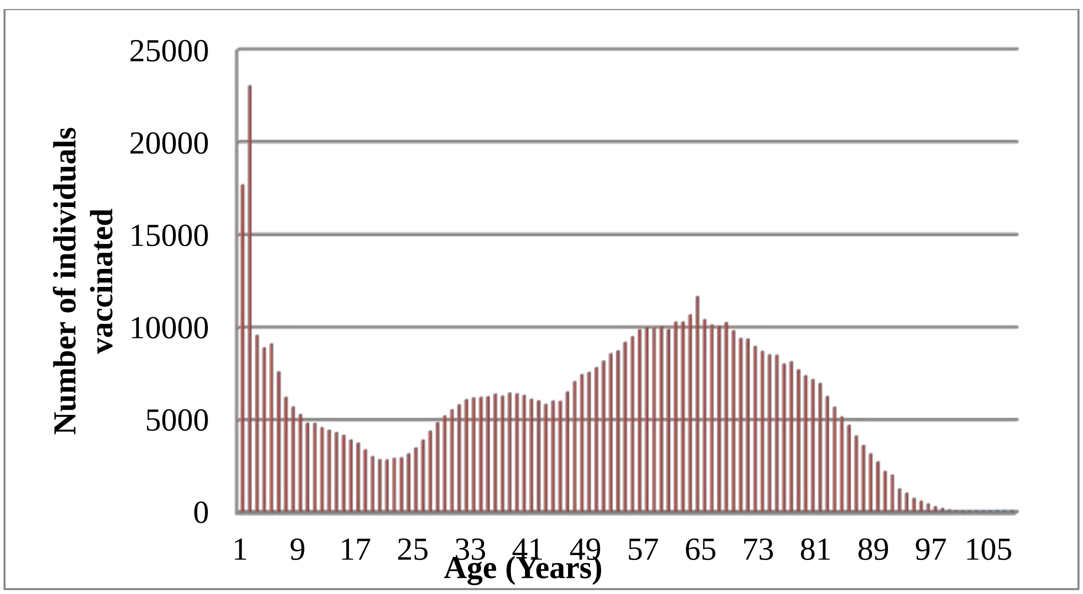
*SD Standard Deviation

The median age was 50 years (range: < 1-109 years) and 85% resided in urban areas.Non-immigrants and immigrants made up 87% and 13% of the study population respectively.

4.2.2 Frequency distribution of vaccinations

The number of persons who received at least one dose of vaccine varied greatly by age, age group, sex, urban and rural residence and in relation to vaccine provider type. As shown in Figures 4.1 and 4. 2, the number of persons vaccinated and the proportions vaccinated varied by age and age- groups respectively.

Figure 4.1 Number of persons 6 months of age and older who received at least one dose of influenza vaccine in Alberta, 2010-2011 vaccination season, by age in years



It is clear that there are peaks in the 0.5-<2 and 65+ age- groups. Among those vaccinated, children aged 6-23 months and children < 9 years accounted for 6.4% and 15.4% respectively.The highest and lowest proportions of vaccinations were administered to those in the 65 years and older (29%) and the 20-24 (2.4%) age groups.In general, more females (56%) than males (44%) were vaccinated. Similar proportions of male and female children aged 6-23 months or 10-14 years were vaccinated. However, for all age groups older than 10-14 years, more females than males were vaccinated (Figure 4.3).

Across all age categories, more urban residents than rural residents were vaccinated. The 65 years and older age group accounted for the highest proportion of vaccinations in both urban and rural areas (Figure 4.4).

Figure 4.2 Proportions of persons 6 months of age and older who received at least one dose of influenza vaccine in Alberta, 2010-2011 vaccination season, by age group

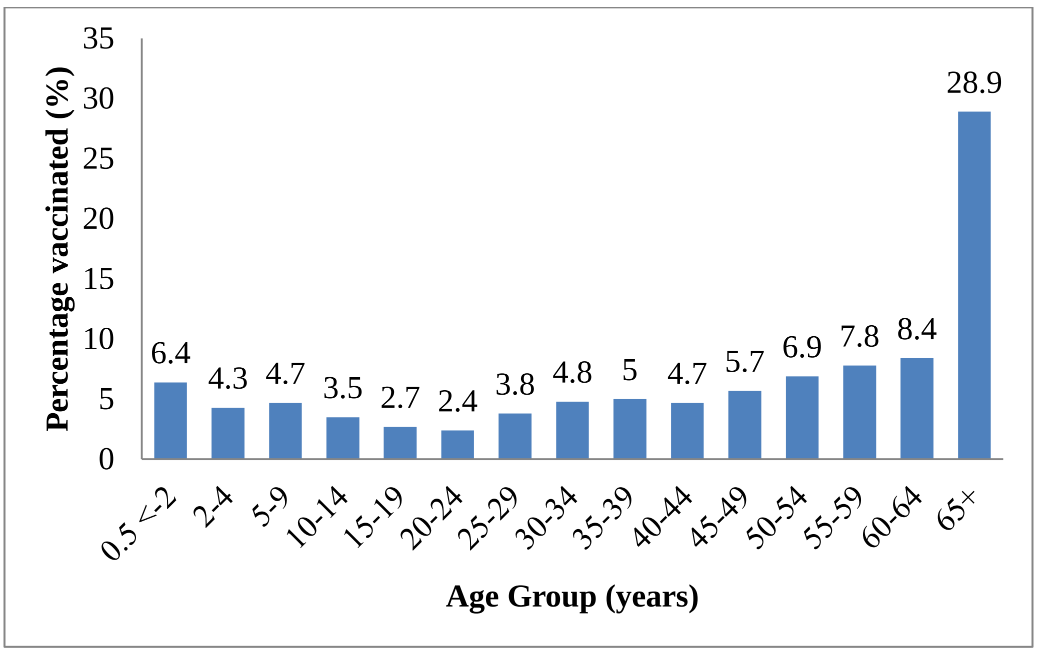
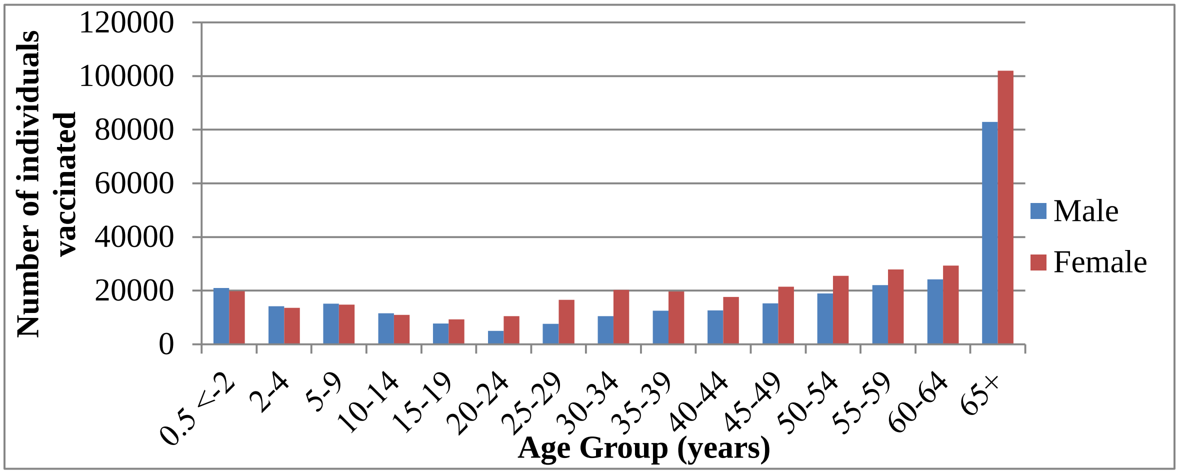


Figure 4.3 Number of persons 6 months of age and older who received at least one dose of influenza vaccine in Alberta, 2010-2011 vaccination season, by sex and age group



As shown in Figure 4.5, more non-immigrants than immigrants were vaccinated among all age groups, particularly among children aged 4 years or less.

Figure 4.4 Number of persons 6 months of age and older who received at least one dose of influenza vaccine in Alberta, 2010-2011 vaccination season, by rural and urban residence and age group

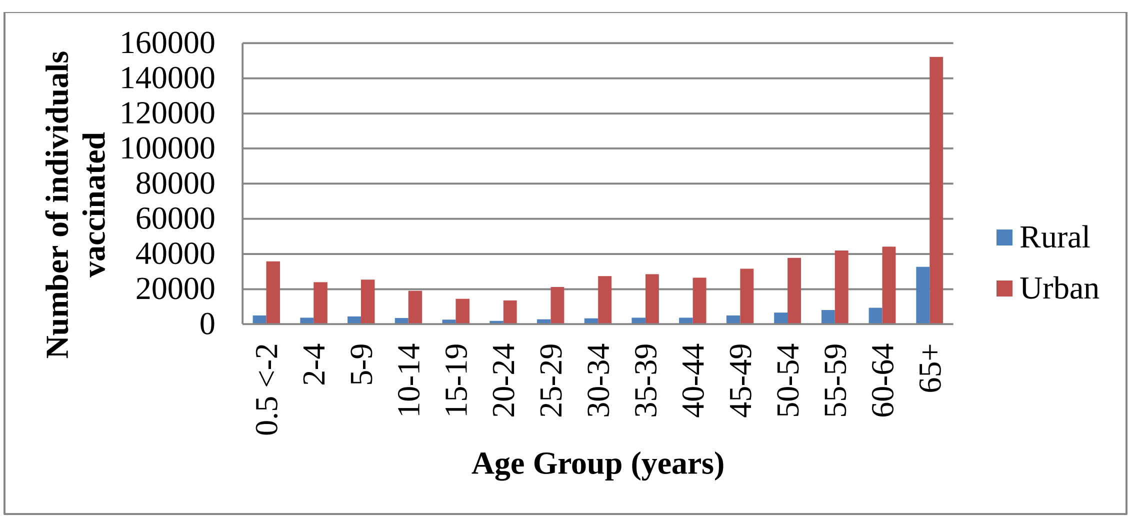


Figure 4.5 Number of persons 6 months of age and older who received at least one dose of influenza vaccine in Alberta, 2010-2011 vaccination season, by non-immigrants and immigrants and age group

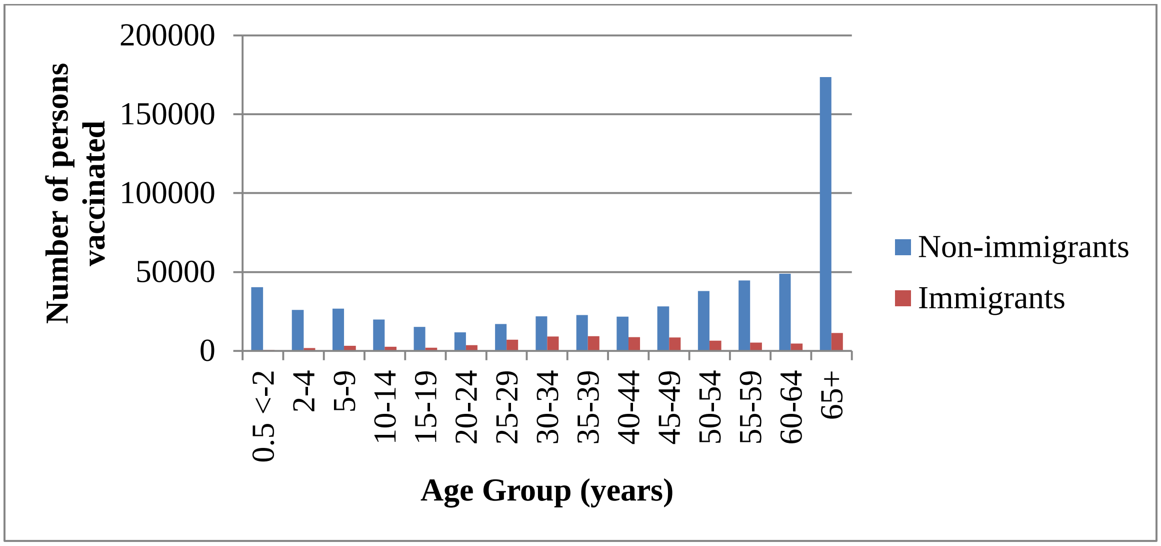
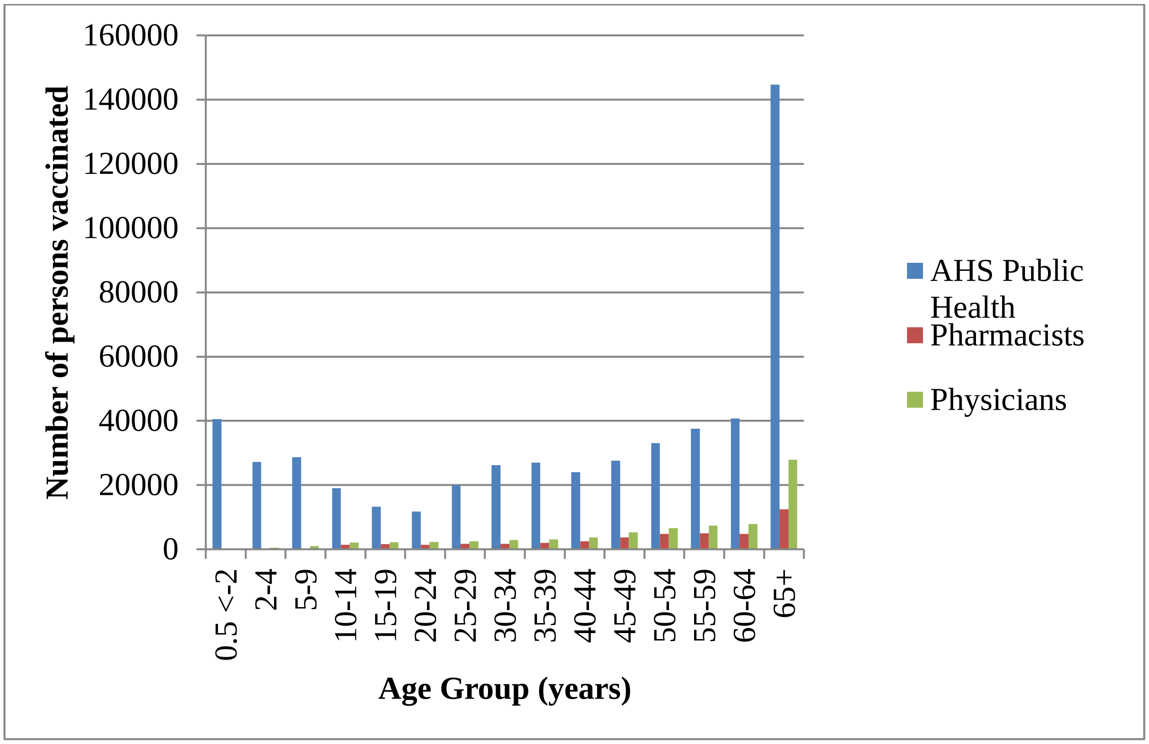


Figure 4.6 depicts the pattern of health services utilization for influenza vaccination. The majority of vaccinations were administered by public health nurses across all age groups. Overall, 81.4% of the influenza vaccinations were administered by AHS public health in contrast to 11.8% and 6.8% administered by physicians and pharmacists respectively (Table 4.1).

Figure 4.6 Number of persons 6 months of age and older who received at least one dose of influenza vaccine in Alberta, 2010-2011 vaccination season, by provider type and age group



4.2.3 Influenza vaccine coverage for the overall population (all age groups combined)

For the 2010-2011 vaccination season in Alberta, the overall influenza vaccination coverage among individuals who received at least one dose of influenza vaccine was estimated to be 17.2%. Table 4.2 depicts the vaccine coverage rates by demographic characteristics.

Females had a higher coverage rate than males. Vaccine coverage rates were higher in urban than in rural areas. Rates were also higher for non-immigrants than immigrants. Of the three vaccine providers, influenza vaccination administered by the public health nurses had the highest coverage, followed by physician vaccinations and vaccinations administered by the pharmacists in that order.

Table 4.2 Influenza vaccination coverage (percent) and corresponding 95% confidence intervals among persons 6 months of age and older who received at least one dose of influenza vaccine in Alberta, by sex, rural and urban residence, and non-immigrants vs. immigrants, 2010-2011 influenza season

Variable	Population	Total vaccinated	% (95% CI)
Overall coverage (all age groups combined)	3,716,520*	640,268	17.2 (17.1-17.3)
Sex			
Male	1,848,843	281,042	15.2 (15.1-15.3)
Female	1,842,002	359,226	19.5 (19.4-19.6)
Residence			
Urban	2,995,515	543,456	18.1(18.0-18.2)
Rural	721,005	96,812	13.4 (13.3-13.5)

Table 4.2 Influenza vaccination coverage (percent) and corresponding 95% confidence intervals among persons 6 months of age and older who received at least one dose of influenza vaccine in Alberta, by sex, rural and urban residence, and non-immigrants vs. immigrants, 2010-2011 influenza season, continued

Variable	Population	Total vaccinated	% (95% CI)
Non-immigrants and Immigrants			
Non-immigrants	3,514,010	556,834	17.6 (17.6-17.7)
Immigrants	562,510	83,434	14.8 (14.7-14.9)
Vaccination provider			
AHS public health	3,690,845§	521,425	14.1 (14.0-14.2)
Physicians	3,690,845§	75,626	2.0 (2.0-2.1)
Pharmacists	3,690,845§	43,217	1.1 (1.1-1.2)

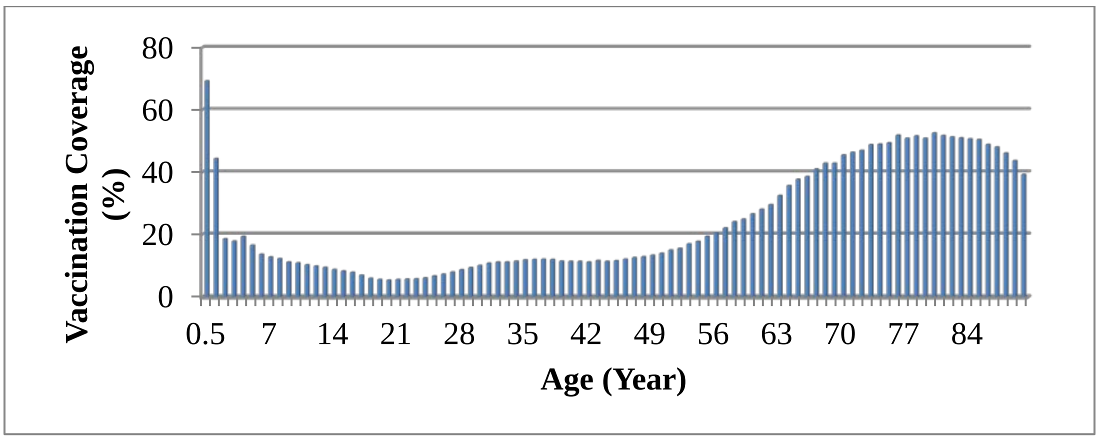
* Alberta 2010 mid-year population § population eligible for vaccination excluding children < 6 months

In the sensitivity analyses using the total population eligible for influenza vaccine in Alberta as the denominator, when the counts of persons vaccinated from the LTC facilities were excluded, the estimated coverage rate decreased slightly from 17.2 to 16.8% (95% CI: 16.8-16.9). However, when the analysis was done excluding the counts of HCW vaccinated, the estimated coverage rate decreased significantly from 17.2 to 15.1% (95% CI: 15.1-15.2). In the sensitivity analyses, when the population eligible for influenza vaccine in LTC facilities was excluded from the total population, there was a slight decrease in the estimated coverage-from 17.2 to 16.9% (95% CI:16.9-17.0). However, when the analysis was repeated excluding the population eligible for influenza vaccine in HCW from the total population, the estimated coverage rate decreased significantly from 17.2 to 16.1% (95% CI: 16.0-16.1).

4.2.3.1 Age- specific influenza vaccination coverage

Figure 4.7 shows the influenza vaccination coverage rate by age and it is clear that there are peaks in the 6-23 months and 65 years and older age group; the rate was highest in <1 year olds (69.3%) and lowest in the 20 year olds (5.4%).

Figure 4.7 Influenza vaccination coverage (percent) among individuals 6 months of age and older who received at least one dose of influenza vaccine in Alberta, 2010-2011 influenza season, by age in years



Age-specific coverage estimates for one dose vaccination are presented in Figure 4.8. Children between the ages of 6 months and 23 months had the highest coverage rates (approximately 53%), while persons 65 years and older had the second highest rates (46%). The lowest rate (approximately 6%) was seen in individuals between the ages of

20 and 24 years of age. Confidence intervals for age-specific estimates did not overlap in all age groups.

4.2.3.2 Age- specific influenza vaccination coverage by sex

Age-specific estimates are presented by sex in Table 4.3. Similar coverage rates were attained by male and female children aged 6-23 months or 10-14 years. However, for all age groups older than 10-14 years, females attained higher coverage rates than males. Confidence intervals for sex-specific coverage estimates did not overlap in all age groups older than 10-14 years.

Figure 4.8 Influenza vaccination coverage (percent) and corresponding 95% confidence intervals among individuals 6 months of age and older who received at least one dose of influenza vaccine in Alberta, 2010-2011 influenza season, by age group

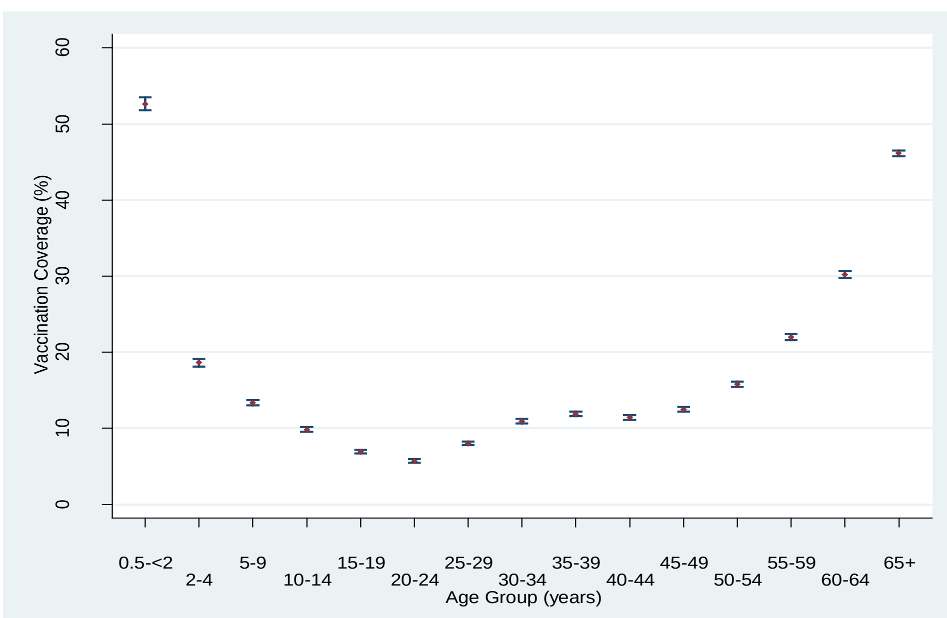


Table 4.3 Influenza vaccination coverage (percent) and corresponding 95% confidence intervals among persons 6 months of age and older who received at least one dose of influenza vaccine in Alberta, 2010-2011 influenza season, by sex and age group

Age group (years)	Male (95% CI)	Female (95% CI)
0.5 -< 2	52.6 (52.1-53.1)	52.6 (52.1-53.2)
2 – 4	18.6 (18.3-18.8)	18.7 (18.3-18.9)
5 – 9	13.2 (13.0-13.4)	13.5 (13.3-13.8)
10-14	9.8 (9.6-9.9)	9.9 (9.8-10.2)
15-19	6.1 (5.9-6.3)	7.8 (7.6-7.9)
20-24	3.7 (3.6-3.8)	7.7 (7.6-7.9)
25-29	5.1 (4.9-5.2)	10.9 (7.8-11.1)
30-34	7.4 (7.3-7.6)	14.5 (14.3-14.7)
35-39	9.1 (8.9-9.3)	14.8 (14.6-15.0)
40-44	9.4 (7.9-9.3)	13.5 (13.3-13.7)
45-49	10.3 (10.2-10.5)	14.7 (14.5-14.9)
50-54	13.3 (13.1-13.4)	18.5 (18.3-18.7)
55-59	19.0 (18.8-19.2)	25.1 (24.8-25.3)
60-64	27.1 (26.8-27.4)	33.4 (33.1-33.7)
65+	45.4 (45.2-45.6)	46.8 (46.7-47.0)

4.2.3.3 Influenza vaccination coverage by rural and urban residence and age

Coverage estimates for urban and rural residents are presented by age groups in Table 4.4. Across all age groups, coverage rates were higher for urban residents than rural residents. Among urban residents, children between the ages of 6 months and 23 months had the highest coverage rates (46.2%), while persons 65 years and older had the second highest rate (38%). The lowest rates for urban residents were seen in individuals between the ages of 20 and 24 years of age (5%).

In contrast, among rural residents, persons 65 years and older had the highest rate (8.2%), while children between the ages of 6 months and 23 months had the second highest rates (6.5%). The lowest coverage rates of 0.7% and 0.9% (<1%) were found in rural residents among 20 and 24 and 25-29 age groups respectively. Overall, urban residents (14.7%) attained higher coverage rate than rural residents (2.6%). Confidence intervals for rural and urban residents' estimates did not overlap in all age groups.

Table 4.4 Influenza vaccination coverage (percent) and corresponding 95% confidence intervals among persons 6 months of age and older who received at least one dose of influenza vaccine in Alberta, 2010-2011 influenza season, by rural and urban residence and age group

Age group (years)	Rural (95% CI)	Urban (95% CI)
0.5 -< 2	6.5 (6.3-6.7)	46.2 (45.8-46.5)
2 – 4	2.5 (2.4-2.6)	16.1 (15.9-16.3)
5 – 9	2.0 (1.2-2.1)	11.3 (11.2-11.5)
10-14	1.5 (1.4-1.6)	8.3 (8.2-8.4)
15-19	1.0 (1.0-1.1)	5.9 (5.8-6.0)
20-24	0.7 (0.6-0.7)	5.0 (4.9-5.1)
25-29	0.9 (0.9-1.0)	7.1 (6.9-7.2)
30-34	1.2 (1.1-1.3)	9.7 (9.6-9.8)
35-39	1.3 (1.3-1.4)	10.5 (10.4-10.6)
40-44	1.4 (1.3-1.4)	10.0 (9.9-10.1)
45-49	1.7 (1.6-1.8)	10.8 (10.7-10.9)
50-54	2.3 (2.3-2.4)	13.5 (13.3-13.6)
55-59	3.5 (3.4-3.6)	18.4 (18.3-18.6)
60-64	5.2 (5.1-5.4)	25.0 (24.8-25.2)
65+	8.2 (8.1-8.3)	38.0 (37.8-38.1)

4.2.3. 4 Influenza vaccination coverage by age for immigrants and non-immigrants

Influenza vaccination coverage estimates for non-immigrants and immigrants are presented by age groups in Table 4.5. It can be seen that non-immigrants had higher coverage rates than immigrants among all age groups. Among non-immigrants, children between the ages of 6 and 23 months had the highest coverage rate (52%), while persons 65 years and older had the second highest rate (43.3%). Non-immigrants between the ages of 20 and 24 years achieved the lowest coverage rate (4.3%) In contrast, among immigrants, the rates were very low. It is surprising that the lowest coverage rates of 0.6% and 2.8% were attained by immigrants among children aged 6-23 months and 65 years and older age groups respectively.

Overall, non-immigrants had (15.1%) attained higher coverage rate than immigrants (2.2%). Confidence intervals for coverage estimates for non-immigrants and immigrants did not overlap in all age groups.

4.2.3. 5 Influenza vaccination coverage by provider type and age

Influenza vaccination coverage estimates for provider types are presented by age groups in Figure 4.9. Of the three providers, vaccinations administered by public health nurses had the highest coverage rates across all age groups, while physician vaccinations had the second highest rates.

Vaccinations administered by pharmacists had the lowest rates. As the majority of children between the ages of 6 months and 23 months were vaccinated by public health nurses, this age group had the highest coverage rate (52.3%).

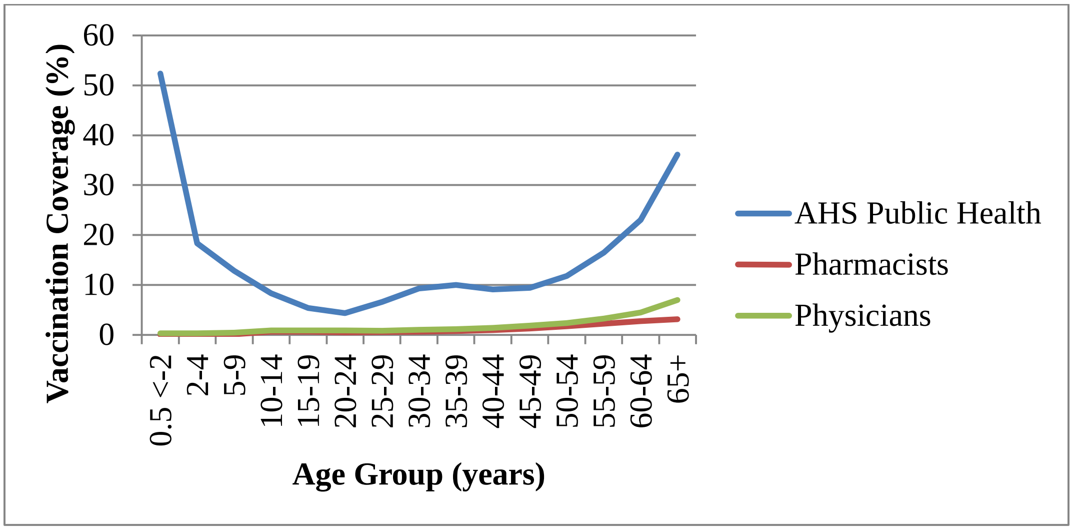
A small proportion of this age group was vaccinated by physicians (0.3%), while persons 65 years and older had the second highest rate (36%) for vaccinations administered by public health nurses.

In contrast, vaccinations administered by physicians and pharmacists had lower coverage rates. For example, the coverage rates attained by vaccinations administered by physicians and pharmacists in the 65 and older age category were approximately 7% and 3.1% respectively.Furthermore, children between the ages of 6 months and 23 months had the lowest coverage rate (0.3%) for vaccinations administered by physicians. Overall, coverage rates by providers were as follows: public health nurses (14.1%), physicians (2%) and pharmacists (1.2%).

Table 4.5 Influenza vaccination coverage (percent) and corresponding 95% confidence intervals among persons 6 months of age and older who received at least one dose of influenza vaccine in Alberta, 2010-2011 influenza season, by non-immigrants and immigrants and age group

Age group (years)	Non-immigrants (95% CI)	Immigrants (95% CI)
0.5 -< 2	52.0 (51.7-52.4)	0.6 (0.5-0.7)
2 – 4	17.5 (17.3-17.7)	1.1 (1.0-1.2)
5 – 9	11.9 (11.8-12.1)	1.3 (1.3-1.4)
10-14	8.7 (8.6-8.8)	1.1 (1.0-1.2)
15-19	6.1 (6.0-6.2)	0.7 (0.7-0.8)
20-24	4.3 (4.2-4.4)	1.3 (1.3-1.4)
25-29	5.6 (5.5-5.7)	2.3 (2.2-2.4)
30-34	7.7 (7.6-7.8)	3.1 (3.1-3.3)
35-39	8.4 (8.3-8.5)	3.4 (3.3-3.5)
40-44	8.2 (8.1-8.3)	3.2 (3.1-3.3)
45-49	9.6 (9.5-9.8)	2.8 (2.8-2.9)
50-54	13.5 (13.4-13.7)	2.2 (2.2-2.3)
55-59	19.6 (19.5-19.8)	2.3 (2.2-2.4)
60-64	27.6 (27.4-27.9)	2.6 (2.5-2.7)
65+	43.3 (44.2-44.5)	2.8 (2.7-2.9)

Figure 4.9 Influenza vaccination coverage (percent) among persons 6 months of age and older who received at least one dose of influenza vaccine in Alberta, 2010-2011 influenza season, by provider type and age group



4.2.4 Estimating the proportion of children who received one and two doses

For the 2010-2011 season, the proportion of children who received one and two doses was calculated in two separate analyses. The numerator for each analysis was the count of children who received one and two doses of vaccine. The denominator of each analysis was the total number of vaccinated children recorded in the databases for the 2010-2011 season.

Age-sex specific counts of children vaccinated with one and two doses of influenza vaccine from the ImmaRI, the physicians' claims' database and the Alberta Blue Cross Registry were used for the numerators. Denominators were counts of all children of the corresponding age group who were eligible for an influenza vaccine. Denominators were estimated using mid-year population estimates from the Central

Stakeholder Registry. All children aged one year were included as were half of the population counts for children aged less than one year to represent the population of children aged six months to less than one year.

Estimates of influenza vaccination coverage for two doses are presented by sex, rural or urban area of residence, and in relation to being non-immigrants or immigrants.

4.2.4.1Description of study population

Table 4.6 shows the distribution of demographic characteristics of children in the study sample. As there were no data on second dose (i.e. zero second doses for children aged 5-8) in the dataset , the final study population comprised 16,634 children < 49 months of age who received two doses of influenza vaccine in Alberta for the 2010-2011 vaccination.

The majority of children vaccinated were male (52%), 27 months of age (range: 6-48 months) and all resided in urban areas. Children between the ages of 6 months and 23 months made up 78.6% of the population. Non-immigrants and immigrants comprised 97.5% and 2.5% of the study population respectively.

4.2.4.2 Estimating influenza vaccination coverage with two doses

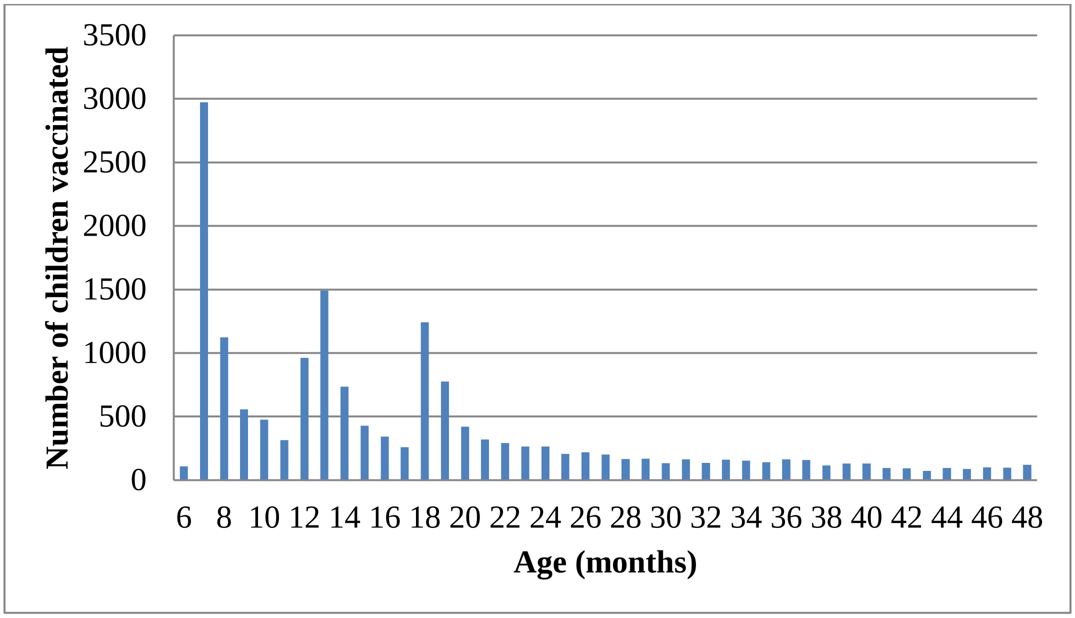
The number of children aged < 49 months of age who received two doses of influenza vaccine varied greatly by age, age group, sex and in relation to being non-immigrant and immigrant. Figure 4.10 shows that the number of children vaccinated varies by age and it is clear that there are peaks in the 7-9 and 12-14 month age groups.

Table 4.6 Demographic characteristics of children < 49 months† who received two doses of influenza vaccine, Alberta, 2010-2011 vaccination season

Characteristics	N= 16,634
Age at vaccination (months)	
Mean (SD)	27.1 (12.4)
Median	27
Range	6 ,48
Age group (months)	
6-23	78.6%
12-48	21.4%
Sex	
Male	51.7%
Female	48.3%
Residence	
Urban	100.0%
Rural	0.0% §
Non-immigrants and immigrants	
Non-immigrants	97.5%
Immigrants	2.5%

† There were no data on second dose (i.e. zero second doses for children aged 5-8) in the dataset. *SD Standard Deviation § Zero second doses were administered to all rural residents according to the dataset.

Figure 4.10 Frequency distribution of children < 49 months of age who received two doses of influenza vaccine, Alberta, 2010-2011 vaccination season by age in months



For the 2010-2011 vaccination season in Alberta, the overall influenza vaccination coverage among children aged< 49 months who received two doses of influenza vaccine was estimated to be 4.1%. Table 4.7 depicts the vaccine coverage rates by demographic characteristics.Coverage rates were similar in both sexes (males: 4.1% & females: 4.0%).Because there were zero second doses in rural residents, the rate remains the same as the overall rate. Rates were also higher for non-immigrants than immigrants.

4.2.4.3 Comparison of influenza vaccination coverage among children < 49 months by number of doses

Table 4.8 shows the distribution of demographic characteristics in the study groups. The total number of children who received one dose and two doses of influenza vaccine were 93,497 and 16,634 respectively. Overall, both groups had similar proportions of males (51.7% in the two dose vaccination group and 51.2% in the one dose vaccination group (p=0.173).

Table 4.7 Influenza vaccination coverage (percent) and corresponding 95% confidence intervals among children < 49 months who received two doses of influenza vaccine in Alberta, 2010-2011 vaccination season , by sex, rural and urban residence, and non-immigrants vs. immigrants

Characteristics	% (95%CI)
Overall coverage	4.1 (4.0-4.2)
Sex	
Male	4.1 (4.0-4.2)
Female	4.0 (3.9-4.1)
Residence	
Urban	4.1 (4.0-4.2)
Rural	Unable to calculate §
Non-immigrants and immigrants	
Non-immigrants	3.9 (3.9-4.1)
Immigrants	0.1(0.09-0.11)

§ Zero second doses were administered to all rural residents according to the dataset

Table 4.8 Demographic characteristics of children < 49 months who received one versus two doses, Alberta, 2010-2011 vaccination season

Characteristics	Two doses	One dose
Number of children Total children N=110,131	16,634	93,497
Age group (years)		
0.5 - < 2	78.6%	43.6%
2 – 4	21.4%	29.6%
5 - 8	0.0%§	26.8%
Sex		
Male	51.7%	51.2%
Female	48.3%	48.8%
Residence		
Urban	100.0%	86.6%
Rural	0.0%*	13.4%
Non-immigrants and Immigrants		
Non-immigrants	97.5%	94.9%
Immigrants	2.5%	5.1%

§There were no data on second dose (i.e. zero second doses for children aged 5-8) in the dataset. * Zero second doses were administered to all rural residents according to the dataset

The two groups differed significantly in the frequency distribution of children in the 6-23 month age group and in non-immigrants and immigrants. Children vaccinated with one dose had statistically significantly smaller proportion of children between the ages of 6-23 months than children vaccinated with two doses did (one- dose coverage 43.6% versus two-dose coverage 78.6%, p<0.0001). In addition, children vaccinated with two doses had statistically significant smaller proportion of children identified as immigrants compared to children vaccinated with one dose did (two-dose coverage 2.5% versus one-dose coverage 5.1%, p<0.0001).

The influenza vaccination coverage estimates for the receipt of one and two doses are presented in Table 4.9. The coverage rate for two doses was 4.1%, while the rate for one dose was 23%. The coverage rate for the receipt of one or more doses of influenza vaccine among children < 49 months was 27.1%. Of the 93,497 children aged < 9 years who received the first dose of influenza, only 16,634 received the second dose. The first dose compliance rate was 17.8%.

4.2.4.4 Comparison of influenza vaccination coverage among children < 49 months by sex

Sex-specific estimates for children vaccinated with one and two doses are presented Table 4.9 Confidence intervals for sex-specific estimates overlapped in both sexes.

4.2.4.5 Comparison of influenza vaccination coverage among children < 49 months by age

Age-specific estimates for children vaccinated with one and two doses are presented in Table 4.10. Confidence intervals for age-specific estimates did not overlap in all age groups.

Table 4.9 Influenza vaccination coverage (percent) and corresponding 95% confidence intervals among children < 49 months in Alberta, 2010-2011 vaccination season, by the number of doses received and sex

Number of doses of influenza vaccine and sex	Influenza vaccination coverage % (95%CI)
Two doses	4.1 (4.0-4.2)
Male	4.1(4.0-4.2)
Female	4.0 (3.9-4.1)
One dose	23.0 (22.9-23.1)
Male	23.0 (22.8-23.1)
Female	23.0 (22.8-23.1)
One or more (≥ 1) doses	27.1 (26.9-27.2)

Table 4.10 Influenza vaccination coverage (percent) and corresponding 95% confidence intervals among children < 49 months in Alberta, 2010-2011 vaccination season, by the number of doses received and age group

Age group (years)	Two doses (95% CI)	One dose (95% CI)
0.5 - < 2	16.9 (16.7-17.1)	52.6 (52.3-53.0)
2 – 4	2.4 (2.3-2.5)	18.6 (18.4-18.8)
5 – 8	Unable to calculate§	13.9 (13.7-14.0)

§There were no data on second dose (i.e. zero second doses for children aged 5-8) in the dataset.

4.3 Objective 2: Describing the occurrence of adverse events related to influenza vaccination

Findings for this objective will be presented in two sections. In the first section, the counts and proportions of AEFI are presented by attributes of age, sex, geographical indicators (urban or rural), and non-immigrants versus immigrants and severity of adverse events after influenza vaccination. The second section focuses on rates of adverse events.

One person (approximately 0.4%) for whom data was missing on sex (unknown) was excluded from all analyses. Data for the 272 individuals, who incurred one or more adverse events following influenza vaccination in 2010-2011 influenza season and for whom there was no missing data for sex, age, place of residence, and country of birth, was analyzed.

4.3.1 Description of study population

Table 4.11 shows the distribution of demographic characteristics of the individuals in the study sample.The final study population is comprised of 272 individuals who incurred one or more adverse events following influenza vaccination in Alberta. The majority of individuals were female (74%), median age 43 years (range: < 1-84 years) and 84% resided in urban areas. Non-immigrants and immigrants made up 88% and 12% of the study population respectively.

4.3.2 Frequency distribution of adverse events by age group and sex

Figures 4.11 and 4.12 depict the frequency distribution of adverse events in terms of numbers and proportions by age and age groups respectively. In Figure 4.11, it is clear that there are peaks in the age groups 0.5-<5 years and 28-65 years representing the age groups that incurred the highest number of reports of adverse events. The proportions of AE reports in the age groups <1 year, 1-<2 years, 2-<7 years, 7- < 18 years, 18- <65 years and 65+ years were 2.9%, 11.0%,14.0%, 3.7%, 57.7% and 10.7%, respectively (Figure 4.12).

The highest number of AE reports was observed in persons in the 18-<65 age group, the age group that received the highest number of influenza vaccines (323,315 vaccinations). The lowest number was among infants aged less than 1 year, the age group that received the lowest number of influenza vaccines (17729 vaccinations).

Of 272 reported AE, 74% occurred in females. Overall, predominance among the number of women reporting AE was observed. AE reporting also varied by sex and age group.Among persons older than 17 years (18- 65+ years), a predominance among women reporting AE was observed, while in all of the children age groups, a predominance among males reporting was observed (Figure 4.13).

Overall, a predominance among urban residents reporting AE was observed but the difference in sex was not statistically significant (p=0.643) (Figure 4.14). Among the non-immigrants, AE reporting was observed in all of the age groups, while persons in the 2-<7, 7- < 18 and 18- <65 age groups reported AE among the immigrants. The difference in sex was not statistically significant (p=0.126) (Figure 4.15).

Figure 4.16 shows the number and severity of AE reports by age group. While reporting of AE that were defined as ‘not serious’ was observed in all of the age groups, AE defined as ‘serious’ were only reported in persons in the 2-<7, 7- < 18 and 18- <65 age groups. There was no statistically significant difference in sex by severity of AE reports after influenza vaccination (p=0.560).

Table 4.11 Demographic characteristics of individuals 6 months of age and older who incurred one or more adverse events following vaccination against influenza, Alberta, 2010-2011 vaccination season

Characteristics	N= 272
Age (years)	
Mean (SD)	40.3 (22.9)
Median	43
Range	< 1 , 84
Sex	
Male	26.1%
Female	73.9%
Residence	
Urban	84.2%
Rural	15.8%
Non-immigrants and immigrants	
Non-immigrants	87.9%
Immigrants	12.1%
AEFI severity	
Serious	4.4%
Not serious	95.6%

*SD Standard Deviation

Figure 4.11 Frequency distribution of adverse events reported among those 6 months of age and older vaccinated against influenza in Alberta for the 2010-2011 vaccination season by age in years

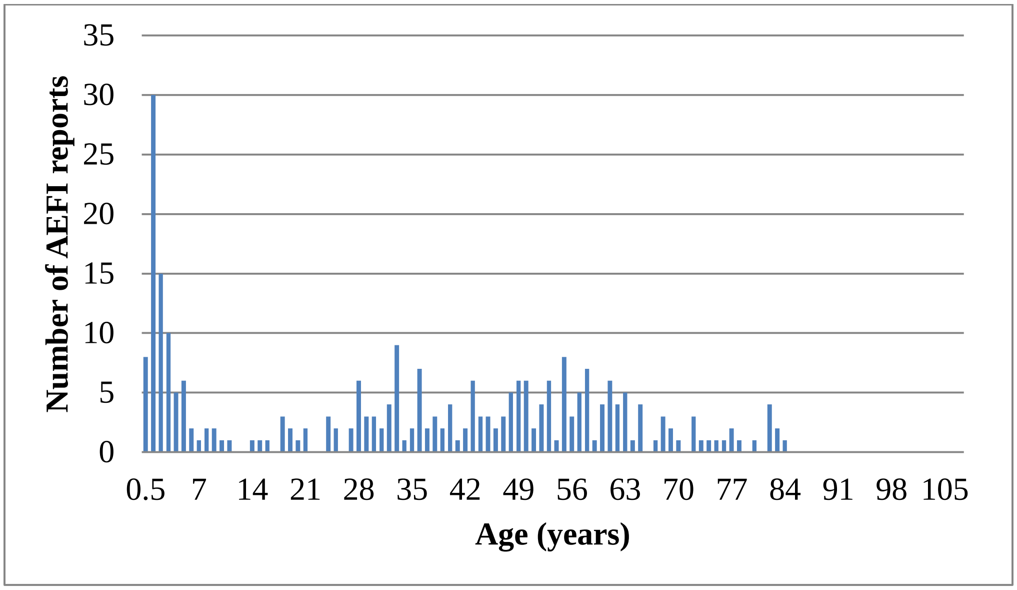


Figure 4.12 Proportions of influenza vaccinations and adverse events among those 6 months of age and older vaccinated against influenza in Alberta for the 2010-2011 vaccination season, by age group

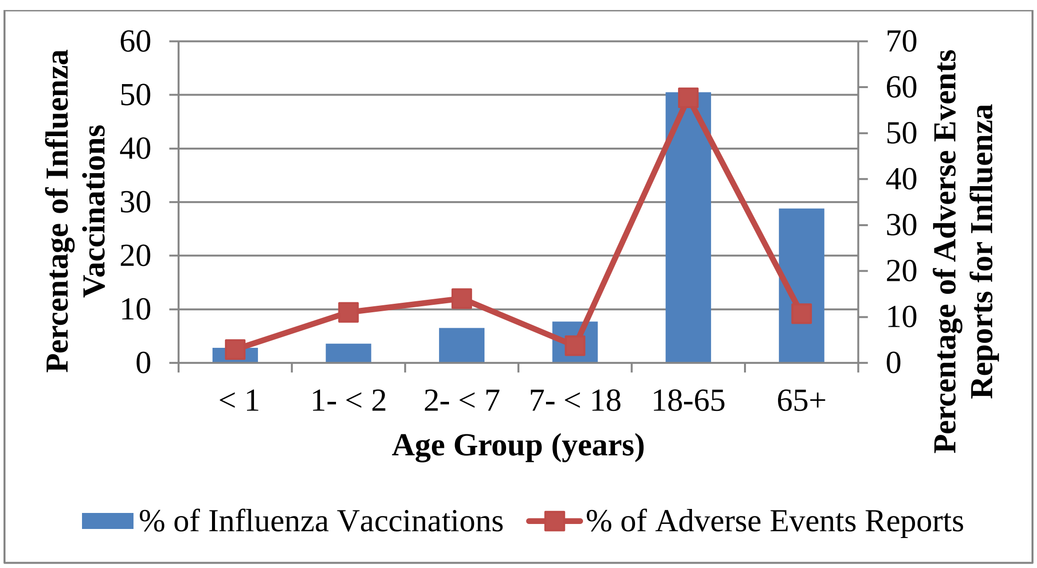


Figure 4.13 Proportions of adverse events among those 6 months of age and older vaccinated against influenza in Alberta for the 2010-2011 vaccination season, by sex and age group

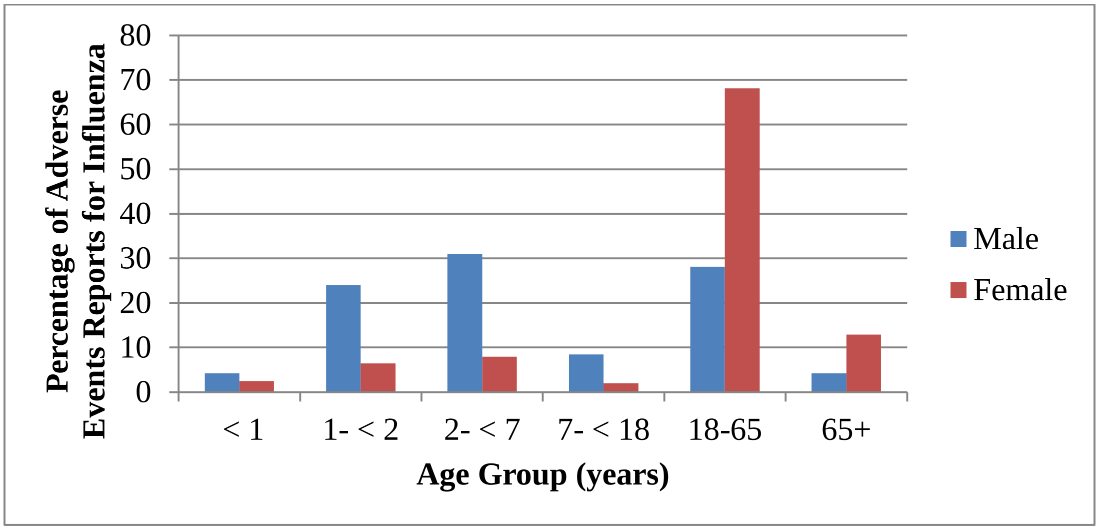


Figure 4.14 Proportions of adverse events among those 6 months of age and older vaccinated against influenza in Alberta for the 2010-2011 vaccination season, by urban and rural residence and age group

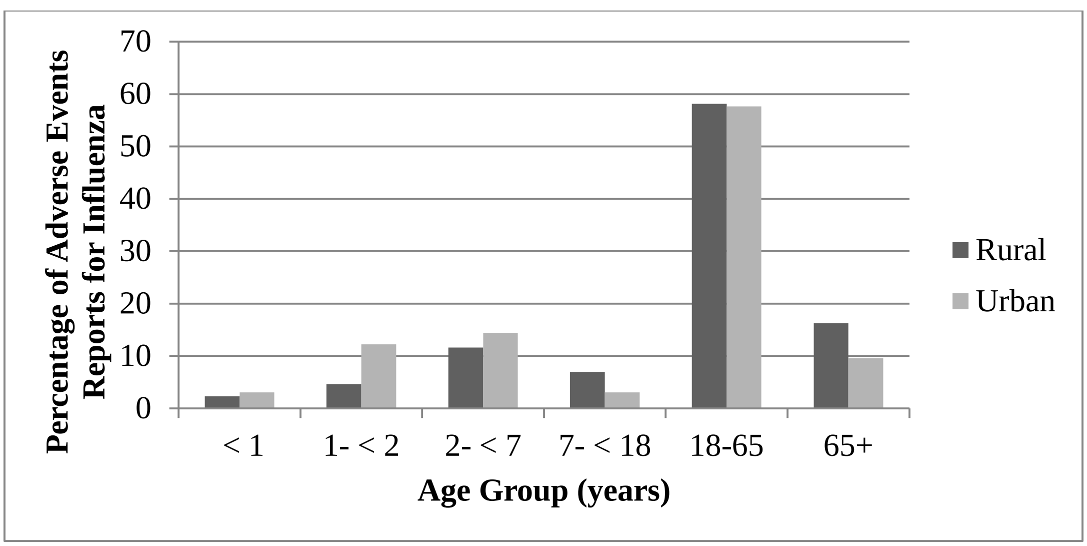


Figure 4.15 Proportions of adverse events among those 6 months of age and older vaccinated against influenza in Alberta for the 2010-2011 vaccination season, by non-immigrants and immigrants and age group

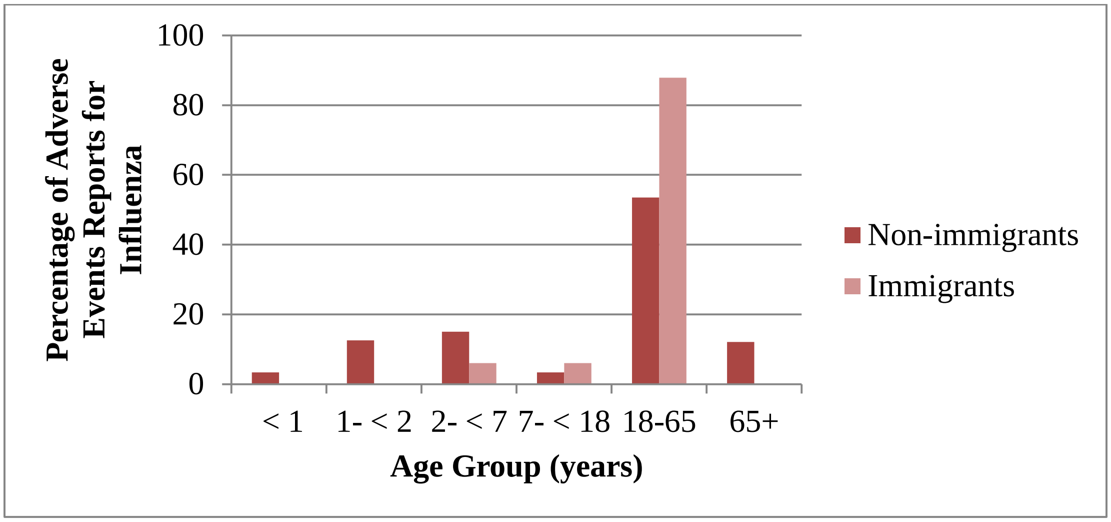
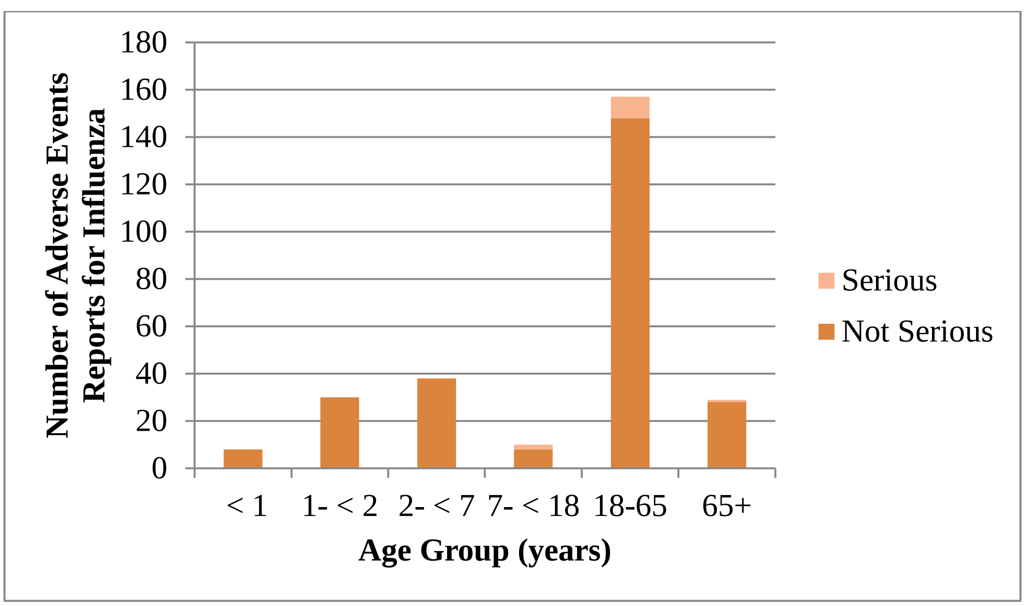


Figure 4.16 Number and severity of adverse events among those 6 months of age and older vaccinated against influenza in Alberta for the 2010-2011 vaccination season, by age group



4.3.3 Estimating the rates of adverse events for influenza vaccination

Among 640,260 persons who received at least one dose of influenza vaccine, a total of 272 reports were received for the 2010-2011 vaccination season related to the influenza vaccine.This gives an overall AE rate of 42.3 per 100,000 persons for Alberta. Table 4.12 depicts the variation in AE reporting by demographic characteristics.

Table 4.12 Rates of adverse events (per 100,000 persons vaccinated) and corresponding 95% confidence intervals among persons 6 months of age and older vaccinated against influenza for 2010-2011 vaccination season, by sex, rural and urban residence, non-immigrants and immigrants and severity of adverse events

Variable	Adverse events N	Vaccinations N	Rate per 100,000 persons vaccinated (95% CI)
Overall rate (all age groups combined)	272	640,268	42.3 (37.7-47.8)
Sex			
Male	71	281,042	25.3 (20.0-31.8)
Female	201	359,226	56.0 (48.7-64.2)
Residence			
Urban	229	543,456	42.1(37.0-47.9)
Rural	43	96,812	44.4 (32.9-59.8)

Table 4.12 Rates of adverse events (per 100,000 persons vaccinated) and corresponding 95% confidence intervals among persons 6 months of age and older vaccinated against influenza for 2010-2011 vaccination season, by sex, rural and urban residence, non-immigrants and immigrants and severity of adverse events, continued

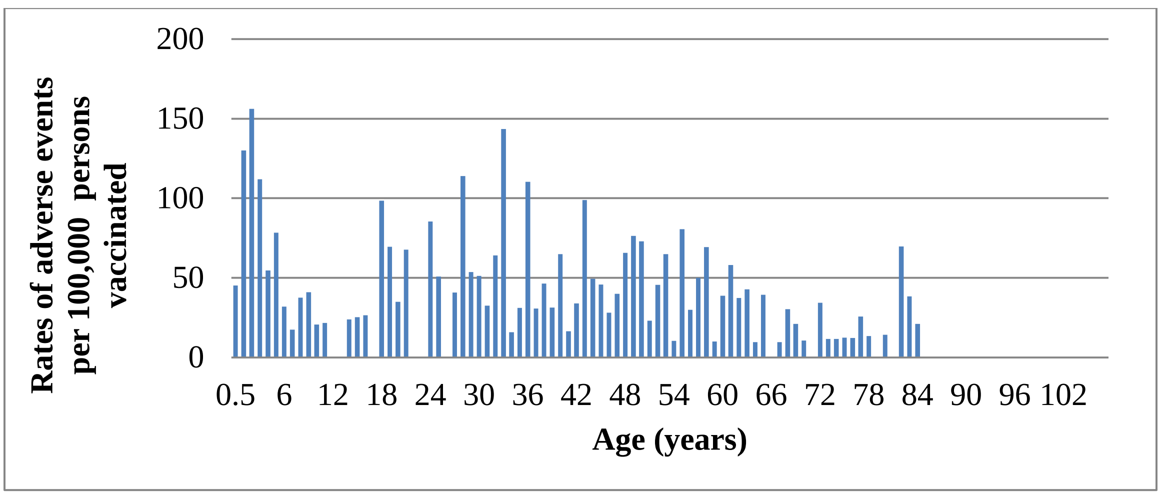
Variable	Adverse events N	Vaccinations N	Rate per 100,000 persons vaccinated (95% CI)
Non-immigrants and Immigrants			
Non-immigrants	239	556,834	42.9 (37.8-48.7)
Male	66	246,085	26.8 (21.1-34.1)
Female	173	310,749	55.7 (47.9-64.6)
Immigrants	33	83,434	39.6 (28.1-55.5)
Male	5	34,957	14.3 (6.1-33.4)
Female	28	48,477	57.8 (35.9-45.8)
Severity of adverse events for influenza			
Serious	12	640,268	1.8 (1.1-3.3)
Not serious	260	640,268	40.6 (35.9-45.8)

Females had a higher AE rate than males.AE rates were higher in rural than in urban areas but the difference was not statistically significant. Rates were also higher for non-immigrants than for immigrants but the difference was not statistically significant. In addition, the rate for AE that were defined as 'non-serious' was higher than that for AE defined as 'serious'.

4.3.3.1 Age- specific rates of adverse events

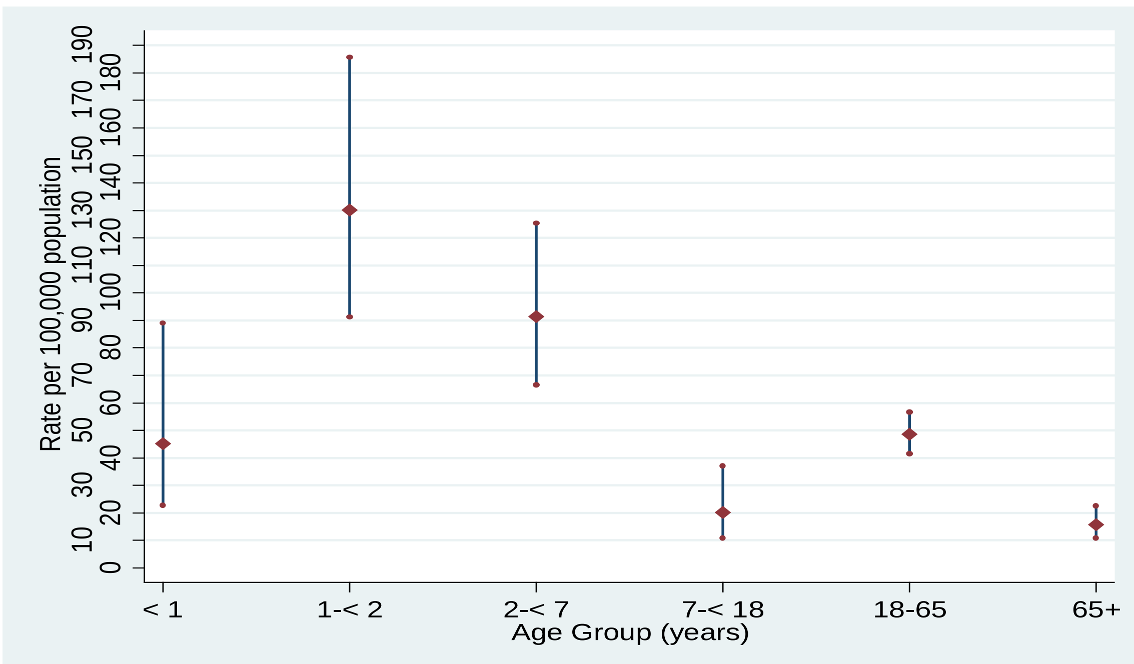
Figure 4.17 shows the rate for adverse events by age and it is clear that there are peaks in the ages 1-6 and 18-65 corresponding to the age groups that received the highest number of reports of adverse events. By age group, the highest rate (93.1 per 100,000 persons vaccinated) was among the youngest age group (children 6-23 months), while the lowest rate was among the oldest age group, those aged 65 years and older (15.7 per 100,000 persons vaccinated).

Figure 4.17 Rates of adverse events (per 100,000 persons vaccinated) among those 6 months of age and older vaccinated against influenza in Alberta for the 2010-2011 vaccination season, by age in years



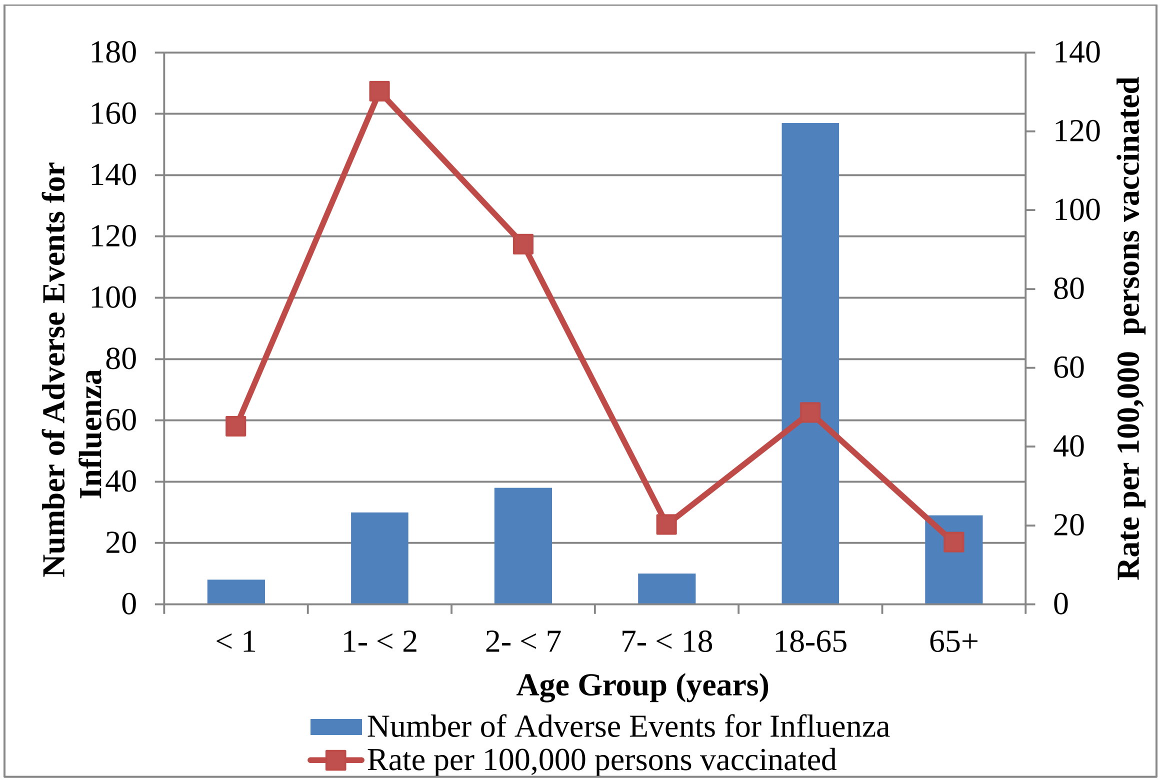
By age group, children < 9 years had a rate of 84.4 per 100,000 persons vaccinated. Age–specific estimates for adverse events are presented in Figure 4.18. Confidence intervals for age-specific estimates overlapped in all of age groups so that the difference in rates by age group was not statistically significant. Figure 4.19 depicts the relationship between the number of adverse events and rate by age.

Figure 4.18 Rates of adverse events (per 100,000 persons vaccinated) and corresponding 95% confidence intervals among those 6 months of age and older vaccinated against influenza in Alberta for the 2010-2011 vaccination season, by age group



It can be seen from Figures 4.11 and 4.12 that children aged 6-23 months (age groups <1 and 1- <2) reported the largest number of adverse events even though they received the smallest number of vaccinations.However, when rates per 100,000 persons vaccinated were considered, although the rate peaked first among children aged 6-23 months, it then declined among older children (Figures 4.17, 4.18, and 4.19).

Figure 4.19 Number and Rates of adverse events (per 100,000 population) among those 6 months of age and older vaccinated against influenza in Alberta for the 2010-2011 vaccination season, by age group



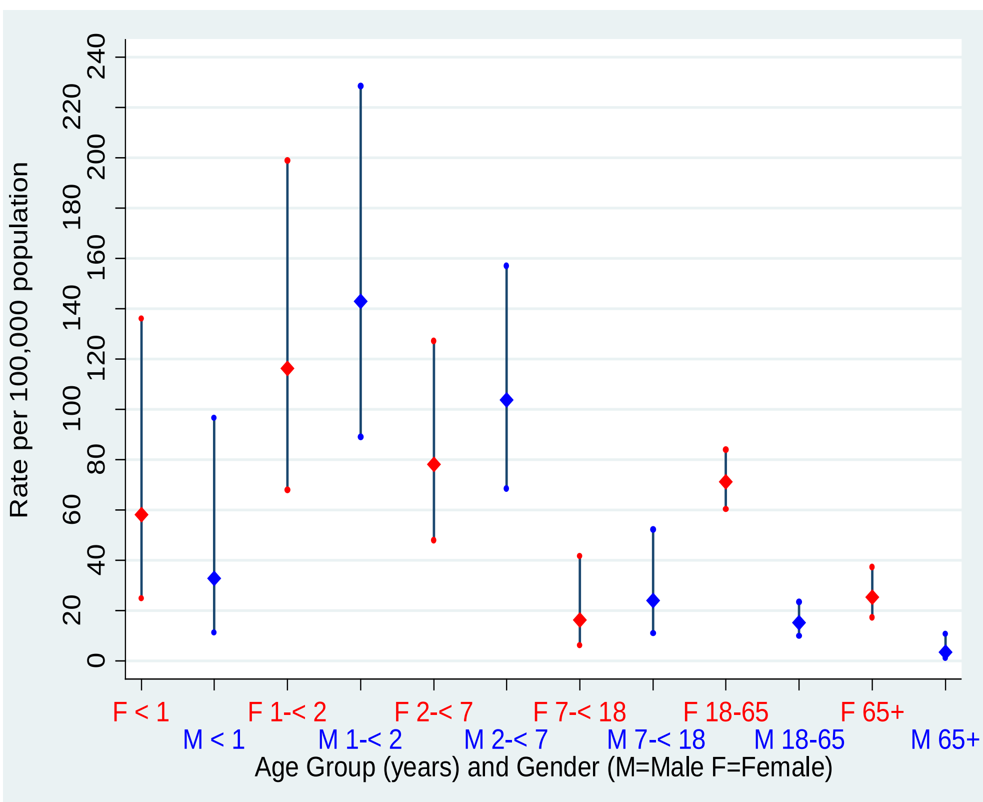
4.3.3.2 Age- specific rates of adverse events by sex

The distribution of rates of adverse events by sex and age groups shows that in the adult age groups, predominance in female rate was observed, but the difference in male rate was highest among children (Figure 4.20).

Overall, females (55.9 per 100,000 persons vaccinated) had a higher rate than males (25.3 per 100,000 persons vaccinated). The rates for females varied from 25.5 (65 years and older) to 116.4 (1-<2 years old) per 100,000 persons vaccinated.

In contrast, the rates for males varied from 3.6 (65 years and older) to 142.9 (1-<2 years old) per 100,000 persons vaccinated. Confidence intervals for age-specific estimates overlapped in the adult age groups (18-65 years & 65 years and older) showing no statistically significant difference in rates by sex.

Figure 4.20 Rates of adverse event (per 100,000 persons vaccinated) among those 6 months of age and older vaccinated against influenza in Alberta for the 2010-2011 vaccination season, by sex and age groups

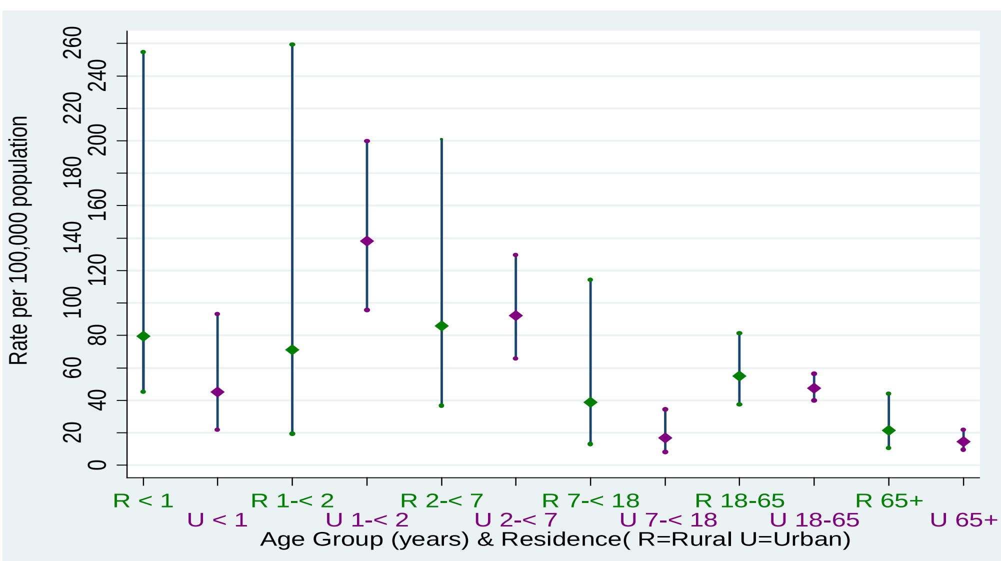


4.3.3.3 Age- specific rates of adverse events by location of residence

Estimates for rates of adverse events incurred by urban and rural residents are presented by age group in Figure 4.21. Although overall rural residents had a slightly higher rate than urban residents, the patterns in rates are different among the age groups. By age group, higher rates were observed among rural residents in the older age groups than their urban counterparts of the same age.

In contrast, higher rates were observed among urban residents in the younger age groups than their rural counterparts of the same age. Confidence intervals for age-specific estimates overlapped in all of age groups so that the difference in rates by age group was not statistically significant.

Figure 4.21 Rates of adverse events (per 100,000 persons vaccinated) among those 6 months of age and older vaccinated against influenza in Alberta for the 2010-2011 vaccination season, by urban and rural residence and age groups

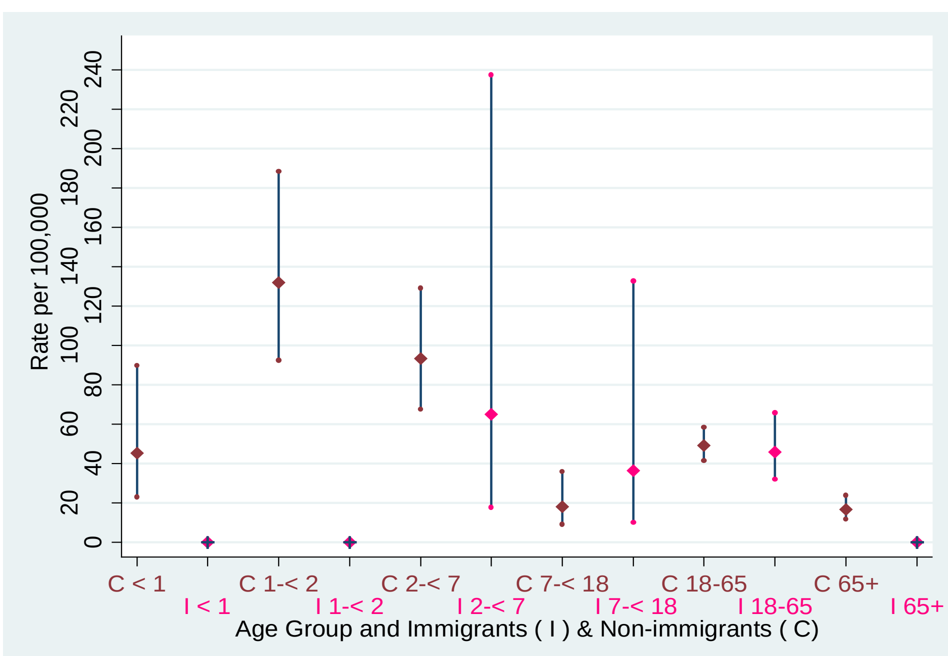


4.3.3.4 Age-specific rates of adverse events by non-immigrants and immigrants

Rates for adverse events incurred by non-immigrants and immigrants are presented by age groups in Figure 4.22.

Overall, non-immigrants had a slightly higher reporting rate than the immigrants. There were no reports of adverse events for immigrants in the youngest age group and oldest age groups so that rates for these groups could not be estimated. In general, rates for non-immigrants decreased as the age group increased. Confidence intervals for age-specific estimates overlapped in all of age groups so that the difference in rates by age group was not statistically significant.

Figure 4.22 Rates of adverse events (per 100,000 persons vaccinated) among those 6 months of age and older vaccinated against influenza in Alberta for the 2010-2011 vaccination season, by non-immigrants and immigrants and age group



4.3.3.5 Rate*s of adverse events by severity*

The 272 AEFI reports described 12 (4.4%) serious reports and 260 (95.6%) non-serious reports (Table 4.13). There were no reports of serious adverse events for immigrants in all of the children age groups so that the rates for these groups could not be estimated. Reports of serious adverse events were observed predominantly among the adult age groups (83.3%). The proportions of reports of non-serious adverse events varied from 3.1% (<1 & 7-<18 age groups) to 56.9% (65 years and older).

The highest proportions of both serious (75%) and non-serious (56.9%) AE were observed among the oldest age group (65+), the age group that received the highest number of influenza vaccines (323,315 vaccination counts). There was no statistically significant difference in severity by sex (p= 0.560).

Table 4.13 Description of adverse events following vaccination with the influenza vaccine by severity, 2010/2011 season, Alberta

Characteristic	Serious reports		Non-serious reports		Total
	N	%	N	%	
Total number	12	4.4	260	95.6	272
Age group (years)					
< 1*	0	0	8	3.1	8
1 - < 2*	0	0	30	11.5	30
2 - < 7*	0	0	38	14.6	38
7 - < 18	2	16.7	8	3.1	10
18 – 65	9	75.0	148	56.9	157
65+	1	8.3	28	10.8	29
Sex					
Male	4	33.3	67	26.0	71
Female	8	66.7	193	74.0	201
Rate/ 100,000 persons vaccinated	1.9		40.6		

* There were missing values for adverse events in these age groups

Chapter Five: Discussion

5.1. Introduction

This present study was unique in its analysis of the AH's largest population-based dataset for influenza vaccination to provide province-wide estimates of vaccination coverage and adverse event of influenza vaccination. The current study examined the pattern of influenza coverage and adverse events rates in the 2010-2011 vaccination season by sex, age groups, geographical indicators (rural versus urban), immigrant versus non-immigrant, provider type (coverage rates only) and provides explanations and hypotheses for the variability in rates.

In this chapter, findings will be contextualized, the strengths and limitations of the research will be discussed, and recommendations made for practice and for research.

5.2 Contextualization of Study Findings

This section contextualizes the study findings in the Alberta context and in relation to prior research beginning with the first objective and then focuses on the second objective of the study.

5.2.1 Objective1: Estimating influenza vaccination coverage

Using secondary analysis of administrative data from Alberta's publicly funded and administered health-care system, two measures of influenza vaccination coverage were estimated among people 6 months of age and older during the 2010-2011 influenza season.

The key findings were as follows:

1) Influenza vaccination coverage rates varied by age, sex, place of residence, vaccination provider and in relation to being immigrant and non-immigrant; and

2) The coverage estimates for the overall population (for all age groups combined) (17.2%) and across all age groups were low (range 5.7-52.6%).

Prior AHS reports did not give any overall coverage estimate for the receipt of one dose of influenza vaccine.The overall estimate obtained for influenza vaccination coverage in this study is consistent with 14-27% influenza vaccine coverage in the general Canadian population.[15,63]

There are limited data to assess vaccination coverage in Canada and for the most part estimations of seasonal vaccination coverage are primarily available from CCHS which assesses immunization status for seasonal influenza vaccination only for people aged 12 years or older.[14] Previous studies using the CCHS data and other studies suggest that influenza vaccination coverage rates are low in Canada. [14,15,63,67,79] There are two limitations of the CCHS data which make comparisons with this study challenging due to differences in methodology. First CCHS does not include data from those under the age of 12 years, and secondly, CCHS is survey data based upon respondent self-reports.

When the findings for this study for the age groups 6-23 months and 65 years and older were compared with those for the AHS reports, the coverage rates for both age groups were lower than the target (75%). This study, for the same period of time, showed coverage rate for children aged 6-23 months to be 53% while the AHS reports showed it to be 27%.[20] Among people 65 years and older , for the same period of time, this study showed coverage rate to be 46% % while the AHS reports showed it to be 59%.[20]

The differences in the coverage estimates between this study and AHS reports [20] may be attributable to the differences in the methods used to estimate the numerator for coverage. While this study defines the numerator as the receipt of 1 dose of influenza vaccine for all age groups, the AHS report defines the numerator as "% Immunized' represent the 1-dose immunization rate (need only one dose of vaccine to be complete)" for the age group 65 years and older and '% Complete' represent the 'dose 2 of 2 + Annual' immunization rate (need two doses or one annual dose to be complete) for the age group 6-23 months. "[20] The latter could be translated into receipt of 1 or more doses which would mean fewer vaccination counts than receipt of one dose, resulting in lower coverage for children aged children 6-23 months in the AHS report.This indicator of coverage for receipt of one or more doses of influenza has also been referred to in the literature as the combined rate.[67]The lack of consistencies in the definitions of reporting and methodology make comparison within and across age groups very challenging, as others have previously suggested.[67]

However, caution should be used to compare results because of changes in the methodology used to estimate coverage for this age group for the 2010-2011 and results for prior years.[23] The 2010-2011 annual report states that "rates for children aged 6 – 23 months in 2009/2010 and 2010/2011 are calculated as "dose 2 of 2 + Annual."[23] Prior to 2009/2010 this rate was calculated as "Doses 1 of 1 + Annual .[23]

The low two-dose influenza vaccination coverage among children under 9 years for which two influenza vaccine doses were recommended according to the NACI statement for the 2010-2011 vaccination season[47]may be attributed to two reasons. First, there were no data on second dose (i.e. zero second doses for children aged 5-8) in the dataset. Second, this study did not link to the influenza vaccination data of prior years for each individual child to see if children had received a dose in the prior year. Thus such children, which would really have received the equivalent of 2 doses (met the NACI criterion)[47]would be misclassified as not being 'adequately' vaccinated (i.e. have not received 2 doses).These factors may have contributed to the low vaccination rate for the receipt of two doses observed here.

This study was not able to estimate the vaccination coverage for the receipt of a second dose of influenza vaccine for all rural residents < 9 years as zero second doses were administered according to the dataset. The urban data for the receipt of the second dose were available for children aged under 49 months. Possible reasons for zero second doses in rural children include the following: 1) the finding may be true in which case that raises the possibility that all the rural children got a dose in prior year. This could lead to misclassification of some children as earlier explained; 2) the finding may be true because rural children did not receive a dose in the prior year and also did not receive the 2 doses they should therefore have received in the current year; and 3) the finding may not be true in which case vaccination records might not have been made or data were not entered or coded wrongly. This results in bias.

Previous studies have shown that provider immunization delivery practices, parent, and systems-based factors (e.g. missed opportunities for influenza vaccination) [73,78,79,82,98] are key determinants of vaccination levels, which may contribute to the incomplete and delayed influenza vaccination.[80] Unlike the routine immunization which is administered all year round, the administration of influenza vaccine is influenced by several challenges that may contribute to low coverage rates. These include delivering two doses of vaccines to all previously unvaccinated children within a short period of time[30,81-83], the need to vaccinate each year,[75] limited awareness of the magnitude of influenza burden in young children [82,98] and the need for two doses in all previously unvaccinated children.[80]

One study of timeliness and vaccination coverage among children under nine years requiring 2 doses in a season reported that most children who required two doses failed to receive both doses; and receipt of the second dose was often delayed among children who received both doses.[80] This finding is consistent with other studies which identified that the majority of children who received their first dose did not complete the 2-dose series.[78,125]

The present study showed that among children aged under nine years, the proportion of first-vaccinated children who received a second vaccination was 18% in the 2010-2011 season. I propose that there are three reasons for this under -vaccination. First, because of the closeness of the study season to the pandemic HIN1 season, parents might have incorrectly interpreted the study year's dose to be the second dose and the H1N1 dose to the first dose. Second, parents may just have had enough of the influenza vaccination campaigns that they did not bother to bring their children for the second vaccination hoping that one dose will provide protection for the season. Third, children were misclassified because they got a dose in the prior year. To some extent, this under-vaccination may be a reflection of the NACI's implementation of 2 dose-series among children under 9 years of age. This finding is particularly concerning since studies have shown that receipt of two doses offered better protection against influenza than receipt of one dose. [29,30,68,69]

5.2.1.1 Variations in coverage rates by age

Children under the age of two years (6 months to 23 months of age) had the highest influenza vaccination coverage rate for receipt of at least one dose (52.7%) and two doses (16.9%) of influenza vaccine respectively, while people aged 65 years and older had the second highest coverage rate (46.2%) for receipt of at least one dose of influenza vaccine.

I propose that there are two reasons for this finding. First, this is not a surprise finding since these age groups have been two of the three priority groups (the third being residents of long term care facilities) targeted for Alberta's publicly funded influenza vaccination program [20,21,38, 126] (see methods section 2.3.2.1for details) and second, because children under the age of two years have frequent contact and access to health services for childhood routine immunization.

Moran *et al.* (2009) [67] estimated much higher influenza coverage for receipt of at least one dose of influenza vaccine (52.2%) in Alberta among children aged 6-23 months than for Ontario (24%). This was similar to the coverage rate (52.7%) that was attained among children aged 6-23 months for the 2010-2011 influenza season.For the 2010-2011influenza season, Nova Scotia[127] attained a much higher coverage rate for receipt of at least one dose of influenza vaccine (72.7%) among children aged 6-23 months than did Alberta (52.7%). Is Alberta's coverage rate of 52.7% statistically different from the Nova Scotia's of 72.7%? Are the differences real? Could the variation in coverage rates be caused by differences in measurement methods?

I propose that much of the difference was caused by differences in measurement methods. One source of the difference was the fact that different denominators were used to estimate coverage rates. The Alberta 52.7% figure was based on 2010 mid-year population from AHCIP Central Stakeholder Registry [121], whereas the Nova Scotia 72.7% figure was based on a single year of age projection data from 2006 census data for children 6-23 months.[127] Alberta and Nova Scotia also used different databases and data collection methods for the number of vaccine doses administered. These methodological differences can produce a profound difference in coverage rates.[76]

Comparisons across studies are challenging due to a lack of standardization in data collection methodology, reporting definitions [67] and changes in the methodology used to calculate the coverage rate.[23] For example, the AH report states that "caution should be used in comparing the Alberta 2010-2011 and 2011-2012 result for children aged 6-23 months with the results from prior years due to changes in the methodology used to calculate coverage among children aged 6-23 months who have received the recommended seasonal influenza vaccination."[38] For example, the present study found that 16.9% of children aged 6-23 months had received two doses of influenza vaccine, compared to 27.2% stated in the surveillance report for the 2010-2011 influenza season.[20] The latter estimate represents the receipt of 'dose 2 of 2 plus Annual' immunization rate (need two doses or one annual dose to complete). The correct estimate for the AHS report would have been 14.2% coverage rate for receipt of two doses of influenza vaccine among children aged 6-23 months during this study period.[20] This compares to the 16.9% coverage rate estimate for this study. In order to meet the timelines for reporting, results for persons aged 65 years and older and children aged 6 to 23 months were submitted to AH and current as of March 31, 2011, which was earlier than the end of the seasonal influenza immunization season.[20]

The present study used all the data available to April 30, 2011 so that the missing data in the report could have slightly underestimated the coverage rate. Alberta attained a much higher coverage rate for receipt of two doses of influenza vaccine among children aged 6-23 months than did Ontario (<10%) during 2002-2009.[79] Santibanez *et al.* (2006)[30] using the data from the 2003 and 2004 National Immunization Survey in the United States reported coverage rates for receipt of two doses of influenza vaccine to be 4.4% and 8.4% for the 2002-2003 and 2003-2004 respectively.

Zimmerman *et al*. (2007)[76] using the immunization information system (IIS) in Arizona and Michigan in the United States estimated coverage rates for receipt of two doses of influenza vaccine during the 2004-2005 influenza season. Among children aged 6-23 months, coverage rates were 13% and 11% in Arizona IIS and Michigan IIS respectively.

Apart from the changes in the methodology used to calculate coverage among children aged 6-23 months, the coverage estimate for children aged 6-23 months in this study is consistent with that obtained from the AHS report. The vaccination of these young children poses a unique challenge to vaccination providers in terms of logistics of delivering two doses within a short period of time, scheduled at least 4 weeks apart. [30,67,68]

Coverage rates for receipt of at least one dose of influenza vaccine initially decreased as the age group increased, especially among children < 9 years and then increased from the age group 25-29 onwards. This pattern was consistent between sexes and across all of the age groups for the observed variations in coverage rates by place of residence, and in relation to being immigrant and non- immigrant and vaccination providers.I propose there are two reasons for this pattern. First, parents might be motivated to vaccinate younger children as vaccine becomes free of charge in addition to the recommendation by physicians or public health nurses in the context of routine visits for childhood immunization, and second because the public health messaging for influenza vaccination places a strong emphasis on vaccinating children, especially those < two years, parents may think that vaccinating older children is not a priority.[126]

The use of simple messages might not only facilitate the acceptance of the message, but also might reflect the recommendations for the older children and the benefits of vaccinating them.It will also provide effective communication to target audiences and create a sense of urgency. Among children aged 6-23 months who had received two doses of influenza vaccine, coverage rates decreased consistently with increased age in all years. This is no surprise as children are likely to have less frequent health services utilization with increasing age.

5.2.1.2 Variations in coverage rates by sex

Coverage rates for receipt of at least one dose of influenza vaccine varied also by sex. There was no observed sex difference in coverage rates until the 15-19 age group. From this age group onwards, females had significantly higher coverage rates than males in all of the age groups except the oldest age group when coverage rates were again similar for both sexes.

This pattern is consistent with studies that reported significantly higher coverage rates in women than men in the age group 20-64 and among persons aged 50 and older.[61,108] The explanation for this pattern is a matter of speculation, but I propose that the sex differences in vaccination coverage may be attributed to lower health care utilization in men than women. Men were more likely to have had more opportunities to be reminded to be vaccinated or to actually receive the vaccine.

5.2.1.3 Rural-Urban variations in coverage rates

Statistically significant differences in influenza vaccination coverage were found between urban and the rural areas. Among all of the age groups, urban residents had significantly higher influenza vaccination coverage than rural residents. Differences in coverage rates range from a low of 4.3% among the age group 20-24 to a high 39.7% among children aged 6-23 months. Among the urban residents, children aged 6 months and older had the highest influenza vaccination coverage rates for receipt of at least one dose.

In contrast, people aged 65 years and older had the highest coverage rate among rural residents. The second highest coverage rate among rural residents was observed among children aged 6-23 months.These meaningful differences suggest disparities in vaccination coverage between rural and urban area. Disparity is defined as differences in vaccination coverage rates that follow a social gradient.[128] For example, disparity exists when "each stepwise increase in education level, or total income corresponded to an incremental rise in influenza vaccination prevalence."[128]

I propose that there are two reasons for these findings. First, people living in rural areas may differ from those in urban in terms of race/ethnicity, poverty level, education, vaccination provider, and access to health care and health services utilization, health status and other sociodemographic characteristics.[100,101] Second, there may also be systematic differences in access involving financial access (indirect costs), scheduling of vaccination appointments (temporal access), and transportation/ geographic location[100,101] Health system factors such as limited access to public health influenza vaccination clinics or to other influenza vaccination providers (physicians, pharmacists) in rural compared to urban Alberta might be important.

5.2.1.4 Variations in coverage rates by immigrants versus non-immigrants

Statistically significant differences in the influenza vaccination coverage were found between non-immigrants and immigrants.This study showed that non-immigrants attained significantly higher coverage rates than did the immigrants across all of the age groups.

Among non-immigrants, children aged 6 months and older had the highest influenza vaccination coverage rates for receipt of at least one dose, while people aged 35-39 years had the highest coverage rate among immigrants. These meaningful differences suggest disparities in vaccination coverage between immigrants and non-immigrants.

Guttmann et al. (2008)[27] found that immigrant children (69%) were significantly more likely than non-immigrant children to be up-to-date (UTD) for routine childhood vaccinations at two years in Ontario. The authors noted that the origin was predictive of UTD status with Asian immigrants more likely to be UTD than those from Latin and Central America) and concluded that immigrant mothers were accessing immunizations for their children at least as effectively non-immigrant mothers.

One study using the CCHS survey data reported that immigrants attained a significantly higher coverage rate for the receipt of one dose of influenza vaccine among persons aged 12 or older than did non-immigrants.[15]The coverage estimates obtained from CHSS survey data may not be comparable to those from this study for two reasons. First, vaccinations from young children and residents of the long-term health care facilities were excluded, thus underestimating coverage.Second, CCHS data were based on self-reports, which may be prone to respondent bias.Self-reported influenza vaccination rates have been shown to have a high sensitivity (98%) and a low specificity

(38%), indicating that the actual rates may be lower than those reported by CCHS data.[16-19]

The study of influenza vaccination coverage by Quach *et al.* (2012) relates to ethnicity/ race rather than immigration and comparison of findings with this study may be difficult.[107] An important methodological issue is the difference in constructs that are measured by race/ethnicity and immigrants/non-immigrants.This may impact on the interpretations of the coverage estimates.

The reasons for lower coverage rates among immigrants in the present study are not clear. Other studies of influenza vaccination coverage in Canada have produced contradictory findings, whereby immigrants were more likely to have received the influenza vaccine. [15,103,104] I propose that there are three reasons for this finding. First, access to health care may play a role as immigrants may encounter greater linguistic barriers[129] or have lower health care comprehension and fewer contacts with health services[105, 130,131] ; second, immigrants may not receive sufficient information about vaccine [105,128,131]; and third lower motivation to get vaccinated, fears of getting influenza from the vaccine.[128]

5.2.1.5 Variations in coverage rates by vaccine providers

This study shows that there were differences in vaccine administration and coverage rates between the AHS public health provider and the community providers (physicians, pharmacists, and other providers). Of the three provider categories, AHS public health had the highest coverage rate overall and for all of the age groups. For physician administered influenza vaccinations, the highest coverage rate was among people aged 65 years and older, while the lowest coverage rate was among children 6 months and older.

The estimated coverage with influenza vaccine was over 10 percentage points lower with community providers than with AHS public health. This difference in coverage rates between AHS public health and community providers may be attributable to the variation in health service utilization for influenza and to the public health messaging that encourages parents to vaccinate their children, especially those aged < 9 years by the AHS public health.[126]

Physicians mostly see sicker older people which may account for why the present research found that the highest coverage rate for physician administered influenza vaccinations was among people aged 65 years and older.

5.2.2 Objective 2: Describing the occurrence of adverse events related to influenza vaccination

Adverse events event rates were estimated among people 6 months or older who incurred one or more adverse events following influenza vaccination in 2010-2011 influenza season, by age groups, sex, geographical indicators (rural versus urban), seriousness of adverse events and in relation to being immigrant versus non-immigrant.

The key findings were as follows:

1. Adverse events rates for influenza vaccine varied by age, sex, place of residence, seriousness of adverse events and in relation to being immigrant versus non-immigrant.

2. Children aged 6-23 months reported the largest number of adverse events even though they received the smallest number of vaccinations.

3. However, when rates per 100,000 persons vaccinated were considered, although the rate peaked first among children aged 6-23 months, it then declined among older children. The adverse event rates for influenza vaccine were compared with those reported by AH's 2010/2011 summary report.[22] This study estimated rate of 42 per 100,000 persons vaccinated was close that of the report (45events per 100,000 doses).Rates were based on slightly different counts of events and vaccinations.As this study used all the data available to April 30, 2011, this could have meant more vaccination counts resulting in a lower rate estimate than reported.

5.2.2.1 Variations in adverse event rates by age

Children under the age of two years (6 months to 23 months of age) had the highest AE rate, while children 2-<7 years old had the second highest rate following receipt of at least one dose of influenza vaccine. The lowest rate was among the oldest age group, those aged 65 years and older. The highest number of AE reports was observed in persons in the 18-<65 age group, the age group that received the highest number of influenza vaccines (323,315 vaccinations).This finding is consistent with the literature which reports that an increase in reported events may be due to an increase in the number of vaccine doses administered.[132,133]

I propose that there are two reasons for this finding.First, as the number of vaccinations increases, it is likely that the number of adverse events reports increases.

Second, the increase in the number of adverse events reports may likely be due to reporting bias especially in children aged 6-23 months and people 65 years and older in whom the highest number of vaccinations were administered.

5.2.2.2 Variations in adverse event rates by sex, immigrants/non-immigrants and severity of adverse events

There was a predominance among the number of women reporting with higher rates in females than males in age groups 1- <2 and 2- <7 years. The female rates were statistically different from the male rates in the all of the adult age groups. I propose that the following reason for this finding. Women have higher number of vaccinations administered than men in all of the adult age groups and it is likely that this difference may have resulted in reporting bias towards higher rates for women than men. Biased reporting may also explain the predominance of higher rates in males in age groups 1- <2 and 2- <7 years, although males have slightly higher vaccinations administered than females in these age groups.

Non-immigrants had a slightly higher AE rate than the immigrants but the rates decreased as the age group increased. There were no AE reports for immigrants in the youngest and the oldest age groups so that reporting is incomplete.This absence of reports for immigrants in these age groups is concerning as it is difficult to ascertain if this is due to reporting bias or problems with data collection.

Family physicians' awareness of the need to monitor and report vaccine-associated adverse events (VAAE) in Canada is low.[52] In Alberta, children under the age of 9 years are primarily vaccinated by public health nurses, as indeed are the majority of all other persons. However, people with AE may present to family physicians with the AE even in Alberta. Thus family physicians must be able to recognize and report AE even in Alberta.

5.3 Study strengths

One of the major strengths of using administrative data from Alberta's publicly funded and administered healthcare system for this research is the population coverage. Because the AHCIP Central Stakeholder Registry captures over 99% of Alberta's residents, the vaccination coverage rates estimated from this study are generalizable to the whole province of Alberta. Therefore the estimates of influenza vaccination coverage and adverse events reporting are population-based estimates.

The availability of reliable and validated numerator data sources for the number of vaccination counts and the large sample size also generated precise estimates of vaccination coverage and adverse events rates.

Appropriately designed population-based databases can facilitate adverse events research as all immunization and hospitalization events can be examined simultaneously yet ascertained independently. The use of Imm/ARI facilitates the linkage of vaccination and adverse events data as both datasets are located in Imm/ARI. Surveillance data regarding influenza coverage rates as tracked by Imm/ARI may generate essential information in evaluating the public health impact of influenza.

This study used aggregated data to estimate influenza vaccination coverage and to describe adverse events related to influenza vaccination.Aggregate data pertaining to influenza- related adverse influenza by generating rates for adverse events may provide data to reassure the public about the risk-benefit ratio of influenza vaccine. Aggregate data provide data without individual identifiers and generates a minimal dataset that is considered both ethical and efficient.

5.4 Study limitations

5.4.1 Completeness of reporting and biases

Data capture for the total number of persons who are vaccinated against influenza in Alberta is not complete.The population of Alberta includes those who are employed and those not employed.People who are employed may or may not show up in Imm/ARI. First Nations persons may also receive health services from the province and Imm/ARI may not capture vaccinations from the First Nationals who received federally funded influenza vaccine.For this reason, coverage estimates might be underestimated.

There is no accessible data source that captures information on influenza vaccine administered in the workplace, and indeed, employers may choose to not use publicly funded influenza vaccination in their occupational health programs.AHS may be able to provide counts of the number of AHS employees who are vaccinated. For people who are vaccinated but are not eligible for public funding, records of their vaccination will be missing from SESE or Alberta Blue Cross.

Thus numerator counts from the ImmaRI Registry, Supplemental Enhanced Service Event System-SESE and the Alberta Blue Cross database are not complete as there may be other potential sources of influenza vaccinations that are missing or incomplete.These missing vaccination events data would underestimate and may lead to biased estimates of influenza vaccination and coverage rates. Coverage data based on administrative data are mainly subject to numerator (number of doses administered) and denominator biases (target population).[74] Bias can occur when the data collection/reporting system excludes part of the population.[134]

Administrative data are also vulnerable to inadvertent recording, calculation and transcription errors.[74] Potential data entry errors in Imm/ARI could be related to reason coding for influenza vaccination which may result in misclassification of reasons and not underestimation of influenza vaccination. Unfortunately, the study design does not allow one to assess such data entry errors as the relevant variables are not required for this study.

This study shows that there were missing values of adverse events for immigrants in all of the children age groups and a predominance of AE among female reporting. This suggests reporting bias.It is difficult to speculate on the outcome of AEFI reporting for people who are vaccinated and not eligible for public funding and for whom AEFI develops. This suggests underreporting of AEFI.

5.4.2 Influenza vaccination coverage estimations (for all age groups combined and particularly for the elderly)

The numerator counts for the residents of LTC facilities may have underestimated the coverage rate reported by AHS [20] for this population group as most but not all LTC facilities vaccination data are captured by Imm/ARI. Because people aged 65years and older may be institutionalized or in home care, Imm/ARI may not have captured all the vaccinations in this age group. This exclusion has a moderate impact (a slight but significant decrease of 0.3%) on the estimated coverage rate in the sensitivity analysis. Because Imm/ARI does not capture vaccination counts of HCW, the exclusion of this population group had a significantly greater impact on the estimated coverage rate (a decrease of 1.1%). Thus the exclusion of the residents of LTC facilities and the HCW may bias the estimated coverage rates for all the age groups and particularly for the elderly.

5.4.3 Use of aggregate data

There is also no accessible data source that captures the aggregated vaccination counts for disease that AHS did not administer themselves or for their employees.These aggregated data may not be available for all age groups/risk groups.Such data could be generated from surveys e.g. CCHS data for the disease in which self-reports on health conditions relevant to vaccinations are elicited. The age-sex-specific proportions with one or more health conditions indicative of the need for vaccination can then be estimated.

5.4.4 Data availability

The conclusions drawn from this study are constrained by the availability of data for only one influenza season. Therefore secular trends in influenza vaccination coverage and adverse events reporting cannot be explored.

5.4.5 Passive reporting system

Imm/ARI is a passive reporting system for adverse events related to publicly funded vaccinations. Some of the limitations of passive surveillance systems in assessment of vaccine adverse events also apply to Imm/ARI. These include significant underreporting of known outcomes, and the nonspecific nature of most adverse event reports.[132]

The true incidence of an AE cannot be determined, but it is possible to estimate a rate of reporting per vaccine from passive reporting.[6]The passive surveillance system using voluntary reporting does not usually distinguish events caused by vaccination from coincidental events.[6]

It may be difficult to establish the temporal relationship between influenza vaccination and adverse events-related health service utilization. Even if a temporal association between adverse events and vaccination is suggested, it may be influenced by age[135] and causal relationships between vaccination and the events are by no means indicated.[6]

5.4.6 Denominators for immigrants and non-immigrants

As there is no single ideal source for denominator data for non-immigrants and immigrants, several potential denominator data sources were identified for generating vaccination coverage.This introduces potential biases into the study, including inaccurate denominator which may exclude immigrants before 2004, and the data may not account for all categories of immigrants.This may lead to an underestimation of the denominator which may bias coverage towards a higher level than is real.

5.5 Recommendations for practice

1) Official reports from AH continue to present influenza vaccination coverage and adverse event reporting related to influenza vaccination only for priority groups in spite

of universal publicly funded program since fall 2009.[20,36] No figures were cited for the overall population rates neither for influenza vaccination coverage nor for adverse events reporting. The universal publicly funded influenza vaccination program implies that the entire target population to which the coverage and adverse events rates applies is the estimated population of Alberta. Therefore, it is recommended that the coverage estimate for the overall population aged 6 months and older, for various subgroups defined by sociodemographic characteristics (for example rural-urban) be provided in reports, in addition to the rates for the risk groups for influenza vaccination.

These population-based indicators will allow for monitoring of trends and progress towards the coverage targets for influenza vaccination over time. Coverage indicators for priority groups are also critical for monitoring progress towards targets for influenza vaccination in high-risk populations.

2) This finding of zero second dose in rural children< 9 years and in urban children in the age group 5-9 years is particularly concerning since the present study cannot ascertain if these children got one dose in a prior year and consequently were adequately protected against influenza. The assessment of adequate protection (i.e. receipt of two doses) requires more than one vaccination season data. This finding deserves further investigation.

3) AHS should develop and pilot test educational programs directed at physicians and other community providers about the need to report, and how to report adverse events related to vaccines.

4) It is recommended that error rates in Imm/ARI be checked by comparing vaccination counts with data from SESE or the Alberta Blue Cross to ensure the accuracy of the data.

5.6 Recommendations for research

This study showed that the estimated influenza vaccination coverage for the overall population (all age groups combined), for all age groups, for rural population, for immigrant population and by physicians and pharmacists are low. Further studies are recommended to define the population groups at risk of under vaccination and to identify the risk factors for low influenza vaccination coverage. Then the development of interventions to address the risk factors at the appropriate level and to improve coverage rates for all people may follow.

Further studies are also needed to explore the pattern of influenza coverage rates season by sex, age groups, geographical indicators (rural versus urban), immigrants versus non-immigrants born, demographic and their interactions using modelling techniques. These models will adjust for the sociodemographic characteristics and other covariates so that a clear insight of the independent risk factors associated with influenza vaccination outcomes can be gained.

This study also suggests that there is underreporting and reporting bias for adverse events related to influenza vaccination. Future research should be directed at factors that influence reporting and non-reporting of adverse events by Alberta researchers and health professionals in order to identify interventions for improving rates for AEFI.

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