Validating & Measuring Influenza Vaccine Effectiveness Among and Against Cardiovascular Hospitalization

by

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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

Razan Amoud was the sole author for Chapters 1, 2, 5, and 6, which were written under the supervision of Dr. Wasem Alsabbagh and were not written for publication.

This thesis consists in part of two manuscripts written for publication. Exceptions to sole authorship of material are as follows:

Research presented in Chapter 3:

This research was conducted at the University of Waterloo by Razan Amoud under the supervision of Dr. Mhd. Wasem Alsabbagh. Razan Amoud, Dr. Jeffery C. Kwong, and Dr. Mhd. Wasem Alsabbagh conceived the research idea and designed the study. Razan Amoud and Alejandro Hernandez collected and organized the data. Razan Amoud performed the statistical analyses, and interpreted the results. Dr. Mhd. Wasem Alsabbagh, Dr. Colleen Maxwell, and Jeffery C. Kwong supervised the study. Razan Amoud drafted the manuscript, and Dr. Jeffery C. Kwong, Dr. Colleen Maxwell, Dr. Suzanne L. Tyas, Alejandro Hernandez, Dr. Martin Cooke, Dr. Mhd. Wasem Alsabbagh revised it.

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Abstract

Background: Influenza is a viral respiratory infection that causes serious health outcomes such as hospitalization and death and represents an important public health burden globally.

Vaccination is one of the most effective interventions to prevent influenza and its complications. Although administrative databases such as pharmacy billing claims are used to measure influenza vaccination status, little is known of the validity of these databases in Ontario. Patients with cardiovascular disease (CVD) may have an altered immune response, despite being at a higher risk of influenza complications. It is not known if the Vaccine Effectiveness (VE) in this population is comparable to the general population. Further, there is a lack of research in Canada evaluating influenza vaccine effectiveness against cardiovascular outcomes, particularly using robust study designs such as the test-negative design. Three interrelated studies were carried out. First, a validation study was completed to examine the accuracy of the combination of Ontario's administrative data from pharmacy and physician billing claims in identifying an individual's vaccination status. The second study assessed the influenza VE against laboratory-confirmed influenza among older adults hospitalized with CVD conditions in Ontario and examined sex and age group as potential effect modifiers in the association between influenza vaccination and laboratory-confirmed influenza. The third study measured influenza VE against acute CVD outcomes using the Test-Negative Design (TND) for the first time among older adults in Ontario who were hospitalized within three days of their influenza testing.

Methods: In the first study, I validated the combined physician and pharmacy billing

claims within administrative databases using the linked reference standard of self-report data from the Canadian Community Health Survey (CCHS). This study estimated sensitivity, specificity,

Positive Predictive Value (PPV), and Negative Predictive Value (NPV), with 95% Confidence Intervals (CI) of the estimates. In the second study, I used the TND to measure influenza VE against laboratory-confirmed influenza. The analysis included both crude and adjusted estimates accounting for potential confounders (sex, age group, neighbourhood income quintile, rurality, number of outpatient visits, beta-blocker medication use, statin medication use, receiving home care services, and influenza testing relative to the peak month of the season, and year of influenza season). In addition, I assessed effect modification of sex and age group on influenza VE by using two different methods: introducing interaction terms into the model and stratification. In the third study, I examined influenza VE against acute CVD outcomes, also using the TND. The exposure of interest was vaccination status, cases were those hospitalized for myocardial infarction, unstable angina, or stroke and testing positive for influenza, and controls were those hospitalized for a non-cardiovascular event and testing negative for influenza. Both crude and adjusted VE were estimated. Sensitivity analyses were performed to test the robustness of the findings by varying inclusion criteria, outcome definitions, and statistical adjustments.

Results: In the first study, the CCHS identified 43% as vaccinated across the two survey cycles of 2013 and 2014. The sensitivity for the combined pharmacy and physician billing codes was 60.1% (95% CI 59.3%–61.0%), specificity was 98.5% (95% CI 98.3%–98.7%), PPV was 96.7%

(95% CI 96.3%–97.1%) and NPV was 76.9% (95% CI 76.4%–77.5%). The second study

included 1,159 patients, and almost half were vaccinated. Among vaccinated patients, 14% tested positive for influenza compared to 20% of unvaccinated patients.. Crude and adjusted VE were 32% [95% CI, 8–50%] and 43% [95% CI 20%–60%], respectively. Neither inclusion of interaction terms separately in the full model, nor stratification by sex or age group, revealed any evidence of effect modification. The third study included 33,710 hospitalized individuals who tested positive for influenza and had a CVD event (cases) or tested negative and did not have a CVD event (controls). There were 18,519 vaccinated individuals (55%). Among vaccinated patients, 0.4% tested positive for influenza and were hospitalized for a cardiovascular event, compared to 0.8% of unvaccinated patients. The adjusted influenza VE against cardiovascular outcomes was 43% [95% CI 25%–58%; *p*-value =0.0001].

Conclusion: Compared to past studies with only physician billing claims, the validation study provided improved performance measures of sensitivity, specificity, PPV and NPV values in the combined physician and pharmacy billing claims in identifying individual vaccination status in Ontario. The second study estimated influenza VE against laboratory confirmed infection and supports that influenza VE among older adults with CVD hospitalization is comparable to the general population. Also, no significant effect modification in VE was observed by the patient's sex, or age. These findings suggest that the protective effect of the influenza vaccine against laboratory-confirmed influenza is consistent across key demographic and clinical subgroups within this high-risk population. The third study found that the influenza vaccine provides a significant protective effect against CVD outcomes.

The global findings of this thesis emphasize the validity of administrative databases at

estimating population-level vaccination rates and show the importance of influenza vaccination as an effective strategy to reduce both influenza hospitalization and CVD events. This unique research equips healthcare providers and policy makers with relevant findings to support their campaigns and recommendations on influenza VE, particularly in relation to CVD outcomes.

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List of Abbreviations

AMI	Acute Myocardial Infarction
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIHI	Canadian Institute for Health Information
DAD	Discharge Abstract Data
FOREVER	The Flu and Other Respiratory Viruses Research
HCD	Home Care services Data
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICES	Institute for Clinical Evaluative Sciences
IDSA	Infectious Diseases Society of America
IIV-HD	High-dose inactivated influenza vaccine
IIV-SD	Standard-dose inactivated influenza vaccine
IR	Incidence Ratio
LTC	Long Term Care
NACI	National Advisory Committee of Canada on Immunization
NACRS	National Ambulatory Care Reporting System
ODB	Ontario Drug Benefit
OHIP	Ontario Health Insurance Plan
OR	Odds Ratio
ORGD	Ontario Registrar General Deaths
RCTs	Randomized Controlled Trials
RPDB	Registered Persons Database
RR	Risk-Ratio/ Relative Risk
TND	Test-negative design
VE	Vaccine Effectiveness
WHO	World Health Organization

Thesis Organization

This thesis is organized into six chapters, each building upon the previous to address the overarching objective of evaluating influenza vaccine effectiveness among and against cardiovascular outcomes in older adults

- **Chapter 1** provides a comprehensive literature review, outlining the burden of influenza in older adults, the interplay between influenza and cardiovascular health, and current evidence on vaccine effectiveness in this population.
- **Chapter 2** describes the data sources used across all studies, including details on health administrative databases, data linkage processes, and key variables.
- **Chapter 3** presents the first study, which validates influenza vaccination status in Ontario health administrative databases following the policy implementation that authorized pharmacists to administer influenza vaccines in pharmacies.
- **Chapter 4** evaluates the effectiveness of the influenza vaccine against laboratory-confirmed influenza infection among older adults hospitalized for cardiovascular events, using a test- negative design. The study also explores potential effect measure modification by sex and age.
- **Chapter 5** examines influenza vaccine effectiveness against acute cardiovascular outcomes among older adults using a test-negative design.
- **Chapter 6** concludes the thesis with an integrated discussion of findings, implications for public health and clinical practice, and directions for future research.

Chapter 1: Introduction

1.1 Preamble

This chapter begins with an overview of the burden of the influenza infection, followed by a discussion of its viral structure and the complications it can cause in the human body. Laboratory diagnostic testing for influenza is then discussed. The chapter then addresses the influenza vaccine and the methods used for measuring the influenza vaccine's efficacy or effectiveness. The chapter ends with the rationale for carrying out the three studies and states the research objectives and hypotheses. For the purpose of this thesis and according to the World Health Organization (WHO), cardiovascular disease (CVD) includes coronary heart disease, cerebrovascular disease, rheumatic heart disease and other conditions.[1] Also, for the purpose of this thesis, the term "influenza vaccine" (or "the influenza vaccine") is used broadly to refer to all types of influenza vaccines available during the study period, rather than a specific formulation.

1.2 Influenza infection and its burden

Influenza is a communicable disease caused by the influenza virus and spread by direct or indirect contact with respiratory droplets carrying the virus. Infected people release these droplets via coughing or sneezing. People infected with influenza may experience high fever, cough, muscle aches, and fatigue. Other common symptoms include chills, headache, and loss of appetite.[2] Some, particularly children, may also experience sore throat, and even nausea, vomiting, and diarrhea, while others infected with the virus experience no symptoms at all (i.e., are asymptomatic).[2–4]

The World Health Organization, in its most recent update on influenza, reported 1

billion cases of seasonal influenza worldwide, resulting in around 290,000 - 650,000 respiratory-illness-related deaths annually.[5] The high number of case counts highlight the virus's infectious burden. In addition, Canada's National Advisory Committee for Immunization (NACI) states that about 12,200 Canadians are hospitalized and 3,500 deaths occur due to influenza each year.[3] According to FluWatch (Canada's national influenza surveillance program), Canada reported 130,548 cases during the 2024-25 influenza season, including 23,896 influenza-associated hospitalizations. There were 727 ICU admissions and 697 deaths across participating provinces and territories since August 25, 2024.[6] The integrated Public Health Information System (iPHIS), an information system for the reporting and surveillance of Diseases of Public Health Significance (DOPHS) in Ontario, reported 40,448 cases for season 2024-25.[7] It is important to note that surveillance-based case counts substantially underestimate the true incidence of influenza, as many infections are not laboratory confirmed or reported, particularly those with mild or asymptomatic illness or among individuals who do not seek medical care.

1.3 The structure of the influenza virus

The influenza virus is an orthomyxovirus (orthós being Greek for "straight"; while mýxa is Greek for "mucus")[8] composed of RNA (1%), protein (73%), lipid (20%), and carbohydrate (6%).[9] The virus invades the epithelial cell lining of the upper and lower respiratory tracts, hijacks the nucleus, and shuts off normal cell protein synthesis within three hours of infection.[9] The influenza virus is unique in being one of the few viruses that needs active host cell DNA to replicate. In the nucleus, the virus snatches cap sequences of mRNA produced by the host's DNA during transcription and attaches it to

its own.[10] The cap facilitates the ability of the viral mRNA to travel back to the cytoplasm for the host cell's ribosomes to translate the viral mRNA and begin replication.[10,11] Within about 8-10 hours, new viruses are produced.[9] After replication, the viruses bud out and are cleaved by neuraminidase, facilitating release and re-infection of other viable host cells.[12] This repeated process accounts for the localized edema and respiratory symptoms of the infection.[13–17] These viruses are spherically shaped virions which hold helical single-stranded RNA. Based on the RNA viral core composition structure, the influenza virus is categorized into three types: A, B and C. For types A and B, their RNA consists of eight separate segments and are enveloped in lipoprotein that contains both hemagglutinin and neuraminidase —two proteins on the surface of this envelope that are responsible for cell entry and infection.[18] Type C is not well studied, however, what is known about its structure is that the RNA is segmented into seven separate strands and does not contain the neuraminidase gene.[10,19]

In Type A, hemagglutinin is further divided into subtypes, for example H1, H2, H3, etc. Hemagglutinin protein facilitates infection by binding to the host's cell[9] and it is evenly distributed on the surface capsule of the virus. Neuraminidase, the second main protein that identifies the influenza virus within Type A, has a hydrophobic chain which is embedded in the viral membrane.[10] Neuraminidase is mainly responsible for releasing the newly formed viruses by cleaving off the sialic acid residue of hemagglutinin's receptors after encapsulation (progeny influenza virions); this promotes the spread of infection.[20] To date, within Type A, there are 19 different hemagglutinin subtypes identified as well as nine different neuraminidase subtypes.[21] The numbers assigned for hemagglutinin and neuraminidase proteins are based on antibody responses to those proteins; that is,

immunological entities that the virus provokes due to its special genetic composition.[22] The specific combination of hemagglutinin and neuraminidase determine the influenza subtypes, with common subtypes among humans including H1, H2, and H3 and N1 and N2, primarily subtypes H3N2 and H1N1.[23]

In Canada, influenza A is the most virulent among influenza types and at certain times is capable of causing pandemics.[24] For example, during the 2018/19 influenza season, A-H1N1pdm09 (causing a pandemic in 2009) dominated approximately 93% of all positive specimens while A-H3N2 constituted the remaining 7%. Influenza B hardly contributed to circulating influenza virus during that season.[25] Thereafter, influenza A of subtype H3N2 was the major contributing type in an unusual second wave which peaked in March 2019.[26] Influenza is named based on type, host origin, geographic origin, strain number, and year of isolation. The host origin is only indicated when it is discovered in non-humans. For example, type A discovered in Hong Kong and isolated in 1968 from human host strain, was named A/Hong Kong/03/68(H3N2). In 2015, aiming to minimize unnecessary negative impact on societies, the WHO generated new rules for scientists to avoid the use of offensive names for newly discovered infectious diseases.[27,28] This included avoiding people's names, cultural references and especially geographic locations, as this could cause harm to people and generate racism and xenophobia.[29]

1.4 Influenza-related complications

Complications from influenza are mainly due to the virus replicating in the human body, and in return, the severity of the human immunological defence system's response to influenza.

Stimulated by the virus, the human immune system can sometimes overreact, causing a 'cytokine storm'.[30] The immunopathological inflammatory response towards influenza involves macrophages, neutrophils, dendritic cells, toll-like receptors, and cytokines.[30] This suggests that the immune system's overreaction is in part responsible for lung injury when infected with influenza.

Autopsies of deceased persons due to influenza revealed significant pathological changes in their lungs. These include epithelial destruction and desquamation in the trachea and bronchia, submucosal edema, mixed inflammatory cell infiltration around the airways and throughout the lung parenchyma, hyaline membrane formation (making gas exchange nearly impossible), and even vascular thrombosis.[13–17] Indeed, pneumonia is the most common influenza-related complication; about 40% of adults hospitalized due to influenza in the US were later diagnosed with pneumonia.[31]

Patients infected with influenza can develop complications beyond the pulmonary system. The second most common complication is precipitation or exacerbation of underlying cardiovascular conditions.[32–34] Cardiovascular events such as myocardial infarction or stroke can occur due to apoptosis (programmed cell death) of endothelial cells leading to the rupture of the endothelial wall and the dislodging of unstable plaque.[35] It is hypothesized that cardiovascular complications begin when the immune system is triggered by influenza, and as a result signals a cascade of inflammatory immune responses resembling a 'cytokine storm' to combat the virus.[30] Tumour Necrosis Factor alpha (TNF-α) is overproduced, resulting in increased apoptosis of pulmonary artery endothelial cells.[36,37] Since apoptosis of the endothelium dislodges the plaque, the

dislodged plaque can lead to a cardiovascular event.[38] Acute infection can also directly promote thrombi (clot) formation through various ways:[35] (i) inflammatory-mediated activation of platelet aggregation leading to the formation of thrombi at the surface of already developed coronary plaques;[39–42] and (ii) coronary narrowing due to impairment in the response to endothelium dependent dilators, such as nitric oxide [43,44] (that limits blood flow in the lumen and increases shear-induced platelet activity).[45–47]

Complications raise concern over influenza's capability for predisposing infected patients to cardiovascular events, which in turn requires hospitalization and acute care. A systematic review investigating influenza as a trigger for acute myocardial infarction (AMI) found 14 observational studies published between 1977 and 2008 examining this association.[48] These studies used

different methods including; 12 case-control, one case-crossover, and one self-controlled case series and concluded that there was a consistent association between influenza and acute myocardial infarction.[48] Another meta-analysis looked at 16 case–control studies that measured the association between influenza and AMI as the primary outcome, including first or recurrent AMI events, during influenza seasons of up to year 2010.[49] The findings showed those with recent influenza, influenza-like illness, or respiratory infection were twice as likely to suffer an AMI.[49] In a self-controlled case series analysis, studies found that the risk for AMI admission is highest in the first 3-7 days after testing positive for influenza,[50] compared to the rest of the days of the year before and after the risk interval as their self-controls without influenza (Incidence Ratio (IR) 6.05 [95% Confidence Interval [CI], 3.86–9.50]).[51] The risk then tends to decline after day seven.[51–53]

Older adults are at high risk for developing influenza-related complications because of age- related physiological changes, comorbidity, and a weakened immune response (immunosenescence) to influenza which can cause further complications.[54–56] Studies show that older adults (≥65 years) with influenza, compared to younger adults (<65 years) are at higher risk for hospital admission (Odds Ratio (OR) 4.65, 95% CI, 1.74 – 12.41) and mortality (OR 2.95, 95% CI, 1.53 – 5.70) due to influenza illness.[55] In Canada, older adults continue to record the highest rate of influenza-related hospitalizations and the highest proportion of deaths.[57] For instance, during the first influenza season since the COVID-19 pandemic (2022-23), adults aged ≥65 years experienced 131 hospitalizations per 100,000, at least 98 more hospitalizations per 100,000 than any other age group over 4 years of age.[57] Also, 76% of deaths due to influenza were among adults aged ≥65 years.[57] These reported findings underscore and justify older age as an important risk factor for influenza-related complications.

1.5 Laboratory diagnostic testing for influenza

Testing for influenza is an important part in confirming the presence of infection. The specimen is collected by either nasopharyngeal swab (most common), throat swab, bronchial alveolar lavage, pleural fluid, or respiratory tract tissue.[58] There are three main types of influenza virus diagnostic tests: viral culture, molecular assays, and antigen detection tests. Viral culture methods include both rapid cell culture techniques, such as shell vial assays using cell mixtures, and conventional viral culture in tissue cells. Molecular assays are a group of nucleic acid amplification tests (NAATs) that detect viral RNA; these include real-time reverse transcription polymerase chain reaction (RT-PCR), rapid molecular assays, and multiplex assays capable of identifying multiple

respiratory pathogens simultaneously. Antigen detection tests include rapid influenza diagnostic tests (RIDTs) and direct or indirect immunofluorescence assays (also known as immunoassays). [58] Among these, molecular assays—particularly real-time RT-PCR—are considered the gold standard due to their superior sensitivity and specificity for detecting influenza virus. The influenza diagnostic tests are illustrated in the following table (Table 1.1).

Table 1.1: Influenza diagnostic test types with corresponding sensitivity and specificity

Diagnostic Test Type	Sensitivity	Specificity
Viral Culture		
1. Rapid cell culture in shell vials and cell mixtures 2. Viral cultures in tissue cells	Gold Standard	
Molecular Assays (nucleic acid amplification)		
1. Rapid molecular assay 2. Real-time reverse transcription polymerase chain reaction (RT-PCR) 3. Multiplex molecular assays 4. Rapid nucleic acid amplification tests (a modified RT-PCR)	73%	99%
Antigen Detection Tests		
1. Rapid influenza diagnostic tests 2. Direct and indirect immunofluorescence assays (also known as immunoassays)	54% (Influenza A) 53% (Influenza B)	99%

The RT-PCR is now the method of choice for testing for influenza A and B as it produces relatively faster results compared to viral cultures (the previous gold standard), with high specificity (99%) and sensitivity (73%) compared to the gold standard of viral cultures.[58–61]

The rapid influenza detection tests can qualitatively assess, within 10-15 minutes, the respiratory specimen, by confirming whether it is positive or negative for influenza.[62] Antigen detection tests have high specificity (99%)[62] but low to moderate sensitivities (54% for influenza A and 53% for influenza B detection).[63] Although some kits can distinguish between type A or type B, diagnostic detection tests cannot specify the influenza A virus subtype.[62]

All types of influenza testing are available in Public Health Ontario laboratories.[64] Hospitals mostly use molecular assays and viral cultures, whereas clinics or outpatient settings usually use the rapid influenza diagnostic detection tests.[51,59] The selection of the type of diagnostic influenza testing is up to the clinician's discretion and is supported by algorithms and guidelines provided by the health regions or the hospital's internal protocols.[65,66]

According to the Clinical Practice Guidelines of the Infectious Diseases Society of America (IDSA), patients recommended for influenza testing are those at high risk of developing complications because of the influenza infection.[62] People at high risk include those aged 65 years and older, people who are pregnant, young children and patients with various health conditions including asthma, heart disease, stroke, diabetes, obesity, anemia, chronic kidney disease, dementia, developmental disability, immunocompromised disease like HIV/AIDS, neurological conditions, or cancer, as well as residents of long-term care homes.[56,67] Testing high risk individuals for influenza who are presenting with influenza-like illness is recommended regardless of community influenza activity or clinical setting location (outpatient or inpatient).[3,62]

Healthcare practitioners are encouraged to use guides and algorithms provided by Public Health to help in the decision making for testing patients for influenza.[64]

In Canada, there is a paucity of studies measuring the degree to which healthcare practitioners adhere to guidelines for influenza testing.[64] In the US, a study measuring testing patients using rapid influenza tests in emergency departments with the aim to treat with antiviral medication found a gap in following the Centers for Disease Control and Prevention (CDC) guideline recommendations.[65] This study noted that the frequency of rapid test ordering did not differ between those experiencing influenza-like symptoms for as long as two days compared to those experiencing symptoms for more than two days.[65] It was noted that clinical practice in emergency departments often differed from CDC recommendations regarding the prescribing of antivirals for high-risk patients.[65]

1.6 The influenza vaccine

Vaccination is one of the most effective interventions to prevent influenza and its complications.[68] There are a number of different compositions of influenza vaccines available in Canada.[69] The two main types of influenza vaccine are live attenuated influenza virus vaccine - administered by an intranasal spray -[70] and inactivated virus vaccines which are administered by intramuscular injection.[3,70] Influenza vaccines consist of either three or four viral components and are called trivalent or quadrivalent, respectively.[3] While both types contain two type A

viruses and one type B virus, the quadrivalent vaccine also contains an additional B virus.[71] In addition, high-dose, adjuvanted, recombinant, and microemulsion-based vaccines have been developed to enhance immune responses, particularly in older adults and other high-risk populations. Due to mutations occurring in the Type A and Type B

surface protein genetic compositions, antigenic drift occurs.[72] Antigenic drift happens during viral replication, when some point mutations change in the structure of type A and B's surface proteins (HA and NA), thus host antibody-binding sites no longer recognize and effectively inhibit the virus.[73] On average, antigenic drift occurs every 2-8 years and can lead to epidemics because the population lacks immunity and the vaccine used during the current season does not match the newly drifted virus.[74–76] This makes formulating a vaccine against influenza quite challenging. Although we were able to nearly eradicate polio - through formulating a vaccine against poliovirus - formulating a vaccine with a perfect match against the mutating influenza virus has proven impossible.[77]

As such, in order to control the spread of infection, the composition of the influenza vaccine is formulated each year to best match the expected circulating virus. This means that annual vaccination is required because of this antigenic drift and also because the body's immune response is transient to influenza vaccination and unlikely to last beyond a year.[3] NACI recommends influenza vaccination to everyone aged six months and older, given they have no contraindications to receiving the vaccine.[3] Because influenza affects more high risk groups like adults ≥65 years, to reduce the burden and complications of the illness, these groups are urged to obtain the influenza vaccine every season. [3,56]

Influenza vaccines differ in antigen content and immune response, particularly for older adults who experience age-related immune decline. Standard-dose inactivated influenza vaccines (IIV-SD) have long been the primary option, whereas high-dose formulations (IIV-HD) were developed to enhance protection in this high-risk population, or at least

to stimulate an immune response comparable to that achieved by standard-dose vaccines in the general population.[78] Clinical trials and observational studies have demonstrated that IIV-HD offers similar (or improved) effectiveness compared with IIV-SD, including reductions in influenza-related complications.[79,80]

Enhanced influenza vaccines—including IIV-HD, adjuvanted (aIIV, MF59), and recombinant (RIV) formulations—have consistently demonstrated superior protection compared with standard-dose vaccines in older adults.[81–84] Across multiple studies and seasons, aIIV and RIV perform comparably to IIV-HD, with some evidence suggesting modest advantages in certain high-risk groups. [85–88] Current Canadian and U.S. guidelines therefore recommend preferential use of any enhanced vaccine (IIV-HD, aIIV, or RIV) for adults aged ≥65 years, recognizing that while all offer improved effectiveness over standard-dose products, no single enhanced formulation is consistently superior across all seasons.[3,89]

1.6.1 Influenza vaccine efficacy and effectiveness

Influenza vaccine efficacy and effectiveness, although sometimes used interchangeably, represent two distinct terms. They both measure the extent of protection the vaccine provides against influenza infection. For example, if a vaccine's efficacy/effectiveness is reported to be

60%, it means that compared to those unvaccinated, the vaccine was able to protect 6 of 10 vaccinees against the outcome of interest (e.g., symptomatic influenza infection or influenza-associated hospitalization).[90] Vaccine efficacy is usually determined in intervention studies, under highly controlled settings (i.e., Randomized Clinical Trials or

RCTs) where participants are usually healthy.[91] Vaccine effectiveness (VE), on the other hand, is determined in observational studies (i.e., in the real-world) among large populations for a wide range of outcomes. The WHO defines VE as: "Reduced risk of disease among vaccinated persons attributed to vaccination in real-world conditions; estimated from observational (non-randomized) studies".[92]

Laboratory influenza testing is needed to determine the outcome and vaccination status is needed for exposure in order to measure vaccine efficacy and effectiveness. For efficacy, vaccine status is determined by the RCT study records. On the other hand, to measure influenza VE in observational population-based studies, researchers should assess vaccination status of individuals using a validated measure.

1.6.2 Validity of Influenza vaccination status

Validation is "the process of compiling evidence that supports the interpretations and uses of the data and information collected using one or more of several instruments and procedures".[93] Typically, validation studies of assessment (or diagnostic) approaches assess sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).[94] In essence, validation studies examine if "what was intended to be measured was measured".[95]

Vaccination status in observational studies can be obtained through using vaccination registries, self-reported questionnaires, patient medical records, or administrative databases for receiving the influenza vaccine.[96] Previous studies have found self-reported vaccination status to have higher validity than patient medical records when compared to vaccination registries.[97–101] A study comparing self-reported vaccination

status of 2,907 individuals against the clinic's immunization registry found self-report to be 95% sensitive and 98% specific in identifying the individual's true vaccination status.[97] Self-reported vaccination also had PPV of 89% and NPV of 96%.[97] Other studies have also confirmed similar findings in highlighting that if registries are unavailable, self-report should be considered the reference standard for identifying influenza vaccination status.[98–101]

However, self-reported survey data might not be available for large and representative samples of the population of interest. As such, other data sources may be needed to perform effectiveness studies in large populations. Administrative health data is another important source for retrieving vaccination status. *Administrative health data* are mainly collected for administrative purposes like paying doctors or hospitals and not for research purposes.[102]

In Ontario, the cost of influenza vaccine is covered by the public health care system, hence it is offered free of charge to patients, and vaccination campaigns are carried out prior to and during every influenza season. Individuals can choose to receive the vaccine at their physician's office, regional public health clinic, school, workplace, or pop-up clinics (such as at malls). In October 2012, pharmacists started administering the influenza vaccine in pharmacies.[103] This was implemented to improve access to the influenza vaccine and increase uptake by the public.[104,105] If an individual receives an influenza vaccine at a physician's office, the vaccination is recorded into their medical file and the Ontario Health Insurance Plan (OHIP) is billed for the service. On the other hand, vaccines received in public health, school, or workplace clinics are not recorded

in the OHIP database. Consequently, in using administrative databases of physician billing claims, we only capture individuals receiving influenza vaccines at physician offices.

Identifying vaccination status from physician visits records has been previously validated.[106] A validation study looked at OHIP physician billing claims between 2007 and 2009 and compared the claims against self-reported vaccination status in the Canadian Community Health Survey (CCHS).[106] The OHIP billing claims were moderately sensitive (49.8% [95% Confidence Interval (CI) 49.0%–50.5%]), and highly specific (95.7% [95% CI, 95.5%–96.0%]) in correctly identifying vaccination status.[106] The PPV and NPV were 88.4% (95% CI, 87.8%–89.0%) and 74.5% (95% CI, 74.0%–74.9%), respectively.[106] The sensitivity was higher for certain subgroups such as those aged 65 years and older and those with comorbidities, perhaps because older adults are more likely to receive the vaccine in physician offices.[107]

Assessing the validity of administrative data for measuring influenza vaccination status in more recent years can be useful since pharmacists in Ontario were approved to administer the influenza vaccine in pharmacies starting in 2012. When an influenza vaccine is obtained at a community pharmacy in Ontario, the cost of administration is billed through the patient's public health system coverage, but this time the administrative database that captures this billing is the Ontario Drug Benefit (ODB) billing system. Although pharmacy billing data in Ontario have been validated for dispensing prescriptions,[108] to date no validation study has measured the validity of the ODB billing system in capturing influenza vaccination status, nor have both databases combined been validated (i.e.; the ODB data together with the OHIP data in capturing

the vaccination status of individuals).

Modernizing our knowledge on the validity of administrative billing claims sourced from both physician offices and pharmacies is especially important since increased awareness of the availability of a more convenient and accessible place for influenza vaccine (i.e., community pharmacies) would increase the proportion of individuals who receive it at pharmacies.[109,110] In fact, a report by Health Canada on seasonal influenza vaccine coverage in Canada in recent years, showed that the most common place for receiving influenza vaccination was at pharmacies. It is estimated that 57.4% (95% CI, 54.9%–59.9%) of Canadians who received an influenza vaccine during 2023-2024 received it at a community pharmacy versus any other place like the doctor's office (15.2%, [95% CI, 13.4%–17.1%]), vaccination centres (7.5%, [95% CI, 6.3%–8.7%]), workplace (5.0%, [95% CI, 3.7%–6.2%]), temporary vaccine clinics (4.6%, [95% CI, 3.6%–5.7%]), community health centres (3.3%, [95% CI, 2.3%–4.3%]), hospitals (2.8, [95% CI, 1.8%–3.8%]), or other locations.[111] Further, measuring the validity of administrative databases by including both pharmacy and physician billing claims, in capturing influenza vaccination status will cast clarity upon possible misclassification that may be present in using these billing systems.

1.6.3 Calculating vaccine efficacy and effectiveness

Vaccine efficacy in RCTs is calculated by comparing the proportion of infection rate (attack rate) in the unvaccinated group to that of the vaccinated group.[112]

The equation is as follows,

$$VE_{fficacy}(\%) = \left(\frac{ARU-ARV}{ARU}\right) \times 100$$

Where ARU is the attack rate of infection in the unvaccinated group and ARV is the attack rate of infection in the vaccinated group.

In observational studies, VE is also calculated by comparing attack rate in the unvaccinated group to that of the vaccinated group. The table below illustrates hypothetical data from an observational study which differentiates subjects by the outcome (laboratory-confirmed influenza infection) as cases or controls and by exposure (vaccination) as vaccinated or unvaccinated.

Table 1.2: Calculating vaccine effectiveness according to influenza results and vaccination status.

		Outcome	
		Positive with influenza	Negative with influenza
Exposure	Vaccinated	a	b
	Not Vaccinated	c	d

Observational studies measure VE using the same formula but with the difference in the target population where the ARU and ARV were taken from:[113]

$$VE_{ffectiveness}(\%) = \left(\frac{(ARU-ARV)}{ARU}\right) \times 100,$$

By rearranging the above equation, cohort studies measure VE by measuring the Relative Risk (RR = ARV/ARU). The equation for measuring VE in cohort studies looks like this:

$$VE_{ffectiveness}(\%) = \left(1 - \left(\frac{ARV}{ARU}\right)\right) \times 100$$

Where ARV= $\frac{a}{a+b}$ (Table 1.2)

And ARU= $\frac{c}{c+d}$ (Table 1.2)

Therefore,

Equation 1.1: $VE_{effectiveness}\ (\%) = (1 - RR) \times 100$

The equation to calculate VE in case-control studies replaces RR with the Odds Ratio (OR) since it can be considered (under specific conditions like low prevalence counts) as an approximation of the relative risk (RR) measure of effects:[112]

$$\text{Relative Risk (RR)} \cong \text{Odds Ratio (OR)} = \frac{a/c}{b/d} = \frac{ad}{bc}$$

$$VE\%_{\text{influenza}} = (1\text{-}RR) \times \mathbf{100}$$

Can be approximated

Equation 1.2: $VEffectiveness\%_{\text{influenza}} = (1 - \boldsymbol{OR}) \times \mathbf{100}$

1.6.4 Impact of COVID-19 pandemic on vaccine delivery, public perception, and health system

The COVID-19 pandemic caused substantial disruptions in vaccine delivery infrastructure in Canada. Routine childhood immunization programs were particularly affected; between 19% and 25% of Canadian parents reported that their children's immunizations were missed or delayed because of lockdowns, clinic closures, or reallocation of healthcare resources toward pandemic response efforts.[114] Vaccine delivery models also shifted, with expanded roles for pharmacies, mobile units, and mass vaccination clinics, though these changes sometimes created new barriers to access for vulnerable populations.[115] Several studies show that during and after the pandemic,

people perceive influenza infection as more dangerous and vaccines (including influenza vaccines) as safer or more beneficial compared to pre-pandemic. For example, a longitudinal study in Finland found that more people wanted to get influenza vaccines, and perceived benefits and safety of influenza vaccination increased during the pandemic.[116] In Canada, influenza vaccination coverage among adults dropped during the initial COVID-19 years but has since rebounded to levels similar to before the pandemic.[117] Also, there's been a marked shift in where people receive influenza vaccines: pharmacies have become much more prominent vaccination sites.[117]

Despite overall improvements, a substantial proportion of people remain hesitant or uncertain about getting influenza vaccines. In a U.S. survey (NFID, 2024), while many agree annual influenza vaccination is important, almost half either do not plan to get vaccinated or are unsure.[118] Some studies also suggest that younger age groups, those without chronic health conditions, or people who do not regularly receive influenza vaccines are more likely to be hesitant.[117] The evidence suggests that vaccine hesitancy toward influenza has decreased or softened for many people post-COVID-19, with increases in perceived safety, benefit, and a return of coverage to pre-pandemic levels in some settings. However, hesitancy has not disappeared, particularly among certain demographics, and intent to vaccinate remains only moderate in many surveys.

In addition to hesitancy, vaccine fatigue has emerged as a relevant factor in the post-pandemic landscape. Defined as a sense of weariness or demotivation toward receiving repeated vaccinations, vaccine fatigue may stem from the intensive focus on COVID-19 vaccination campaigns, mixed messaging about booster doses, and perceived vaccination overload.[119] This fatigue can lead to reduced engagement with other immunization

programs, including seasonal influenza vaccination, especially among individuals who feel "over-vaccinated" or believe they have achieved sufficient immunity. Addressing both vaccine hesitancy and vaccine fatigue is therefore critical to maintaining long-term vaccine confidence and uptake across populations.

1.7 Strengths and limitations of RCTs and observational studies in measuring influenza vaccine's efficacy and effectiveness

While RCTs are the gold standard for measuring the efficacy of an intervention like the influenza vaccine, they have their limitations.[92,120,121] First, they are limited to measuring only common outcomes occurring among their recruited study participants and are often limited to one or two seasons.[90] Older adults and particularly those with chronic conditions and/or who are frail are the least likely to be included in RCTs, thus the results of RCTs are often non-generalizable to these high-risk populations.[122] Placebo controlled trials for research on interventions known to be beneficial, like the influenza vaccine, are considered unethical, especially in high-risk groups such as older adults.[3,123] Further, because of high costs, RCTs cannot realistically measure vaccine efficacy each year given feasibility and cost concerns.[92] As such, using observational studies is a better option in assessing VE in the real-world;[124] however, unmeasured confounding factors represent an important source of bias in these studies.[124–128]

Observational study designs like cohort studies estimate the influenza VE against all-cause mortality during the winter season, among community-dwelling older adults (≥65 years), to be 50%.[127] This finding suggests overestimation of the effects of the vaccine, because when seasonal all-cause mortality rates were analyzed nationally from 1980−2001, the average excess mortality attributed to influenza was merely 5% and never more than 10%.[129]

Therefore, the vaccine could not possibly offer protection more than the proportion of mortality it was causing.

A general approach in detecting unmeasured confounding is testing VE outside the influenza season.[126,130] Unmeasured confounding is suspected when the vaccine shows protection ***outside*** the influenza season, since the influenza virus is a seasonal virus circulating more frequently in the fall with incidence of influenza peaks during the winter.[9,124] To test this claim, there should be no risk difference between those who were vaccinated versus unvaccinated during the summer. Thus, outside the season, the vaccine should not play a role in protection from influenza. For example, a cohort study measuring influenza VE *outside* the influenza season compared with individuals with no previous influenza vaccination was estimated to be significant (OR 0.67, 95% CI, 0.57 – 0.80).[126] The protection outside the season indicates residual confounding that was not identified or controlled for. This residual confounding suggests that there remain factors not controlled for which resulted in the vaccinated group being different from the unvaccinated group due to other unknown characteristics beyond vaccination status. This residual confounding remains, even after adjusting for age, sex, and chronic diseases such as heart failure, coronary artery disease, diabetes mellitus, and chronic obstructive pulmonary disease (COPD).[126]

Case-control studies have two main limitations: selection bias and misclassification bias.[131] Selection bias occurs when the study sample selection introduces different probabilities in selecting cases vs. controls because of differences in exposure. Berkson's bias is a specific example of selection bias associated with hospital-based case-control studies.[132] Berkson's bias occurs when the probability of patients being hospitalized are

based on their exposure (e.g. influenza vaccination) and differs between cases and controls, that is cases and controls are systematically different because of the combination of their "exposure to risk and occurrence of disease increases the likelihood of being admitted to the hospital".[133–135] Selection bias can also occur if vaccinated patients are more likely to seek hospital care and become hospitalized versus their unvaccinated comparison group. This is also known as the healthy behaviour effect bias.[136]

Misclassification bias can manifest in two different forms: differential or non-differential, the former being a more serious concern. Looking back at the odds ratio in Equation 1.2, non- differential misclassification can indiscriminately classify cases as controls, or controls as cases because of inaccurate sensitivities and specificities in classifying the outcome. In VE studies, where classification of outcome depends on laboratory-based results, this would entail controls and cases being misclassified independent of the exposure (i.e., vaccination status). Non-differential misclassification is more likely to occur when knowledge of the exposure, such as being vaccinated, does not influence the reporting or coding of the outcome like the laboratory results for influenza testing. VE calculation in false-negatives will treat the cases as controls; and in false-positives will treat controls as cases. The effect of this non- differential misclassification is generally an underestimation of influenza VE, as the resulting VE estimates would be biased towards the null, hence reducing or diluting the true effectiveness of the vaccine.[137]

On the other hand, differential misclassification can occur when classifying exposure (vaccinated vs. unvaccinated) is influenced in some manner by knowledge/awareness of

the outcome (influenza positive vs. influenza negative) or vice versa.[131] As an example, if unvaccinated patients are more likely to be tested for influenza than their vaccinated peers, this results in more influenza positives being captured in the unvaccinated group. This would cause the denominator in the control (c) to increase, and increasing the denominator causes the overall OR to decrease and VE to increase; hence overinflating VE and overestimating it (Equation 1.1 and Equation 1.2).[131]

1.8 Test-Negative Design (TND) as a solution for limitations of cohort and case-control studies

Given the potential limitations of cohort and case-control study designs for estimating VE, an alternative, more robust design has been proposed. The Test-Negative Design (TND) has become the preferred research design for estimating VE in observational studies.[137] This is mainly due to limiting the study sample to those who have been tested for influenza during the specified influenza season, mitigating both differential misclassification and selection bias in the case- control design.[138] In the TND, the study population is restricted to only those who have laboratory-confirmed test results.[139] Those testing negative for influenza are treated as controls, while those testing positive are treated as cases, and the exposure is vaccination status (i.e. vaccinated or unvaccinated).[138,139] These restrictions eliminate the uncertainty of being influenza positive or negative (i.e., reducing misclassification bias) by limiting the influenza infection status to only laboratory test results which confirm the presence or absence of influenza infection. Laboratory testing provides the highest possible specificity and sensitivity in confirming influenza infection. And in retrospect, because everyone sought care and was tested, this also excludes the disproportionate probability of including more people

seeking medical care than not, thus overcoming the healthy behaviour effect bias.[140]

Calculation of the relative risk using the TND case-control design is similar to the calculation of VE in case-control studies covered previously. However, performing influenza testing is usually a procedure taken for severe cases or high-risk groups or at least those seeking medical care. Therefore, inferences made from this design cannot be generalized to the broader public and is limited to influenza cases that were severe enough to be tested.[138,141] Many primary care providers, for instance, may not test for influenza in community-dwelling patients who are not candidates for antiviral treatment, as test results would not alter clinical management. This can be viewed as both an advantage and a disadvantage,[142] as this design reduces bias from the healthy behaviour effect, but limits inferences to only those for whom the illness was severe enough to seek medical care and to be tested for influneza.[143]

There are three main concerns with using the Test-Negative design.[144] *First,* restricting the study population to those being tested for the influenza virus may promote collider bias, a type of selection bias, in the VE estimate, because people with health-seeking behaviour and people presenting with influenza infection are more likely to be tested. This induces a correlation among those being tested between their health-seeking behaviour and influenza positivity. In this regard, collider bias may be playing a role, because we are conditioning the analysis on testing, when there is a correlation between seeking testing (health-seeking behaviour) and being tested.[144] *Second,* VE measures the direct effect of influenza vaccine against the influenza infection.[145] Therefore, the influenza vaccine "must not affect probability of conditions that lead to testing negative

(e.g. other infections) either directly or indirectly".[144] For example, if testing patients for influenza is the common practice during a season where the common circulating virus is NOT influenza, the results for testing are more likely going to be negative thus contributing to a higher VE estimate not because of the influenza vaccine, but because of another circulating virus, such as SARS-CoV-2, thus overestimating influenza VE.[146]

Conversely, because the circulating influenza virus is an immunizing infection, the influenza VE can be underestimated due to bias introduced by the influenza infection itself.[147] That is, a person infected with influenza (regardless of vaccination status) is less likely to become infected again by the same virus during the same influenza season; this is also known as "infection-induced immunity".[148] Thus, unvaccinated persons at high risk who are infected will be leaving the study cohort more rapidly than the infected individuals who were vaccinated.[149] In other words, those unvaccinated would gradually become immunized because of contracting the infection, and while the vaccine will show high effectiveness in the beginning, the VE will gradually decrease because towards the end of the season, more vaccinated individuals rather than unvaccinated will likely be captured. During an effective influenza vaccine season this would be observed as a decline in effectiveness over the course of the season.[149] Additionally, these characteristics could also be playing an effect modification role and must be explored further for confirmation. *Lastly,* controls and cases are ascertained based on laboratory influenza testing. These tests are subject to false-positives and false-negatives, introducing non-differential misclassification.

1.9 Influenza vaccine effectiveness among and against concurrent cardiovascular hospitalizations

It is important to examine influenza VE among high-risk patient populations to identify the degree of protection the vaccine is providing for those most at risk of suffering from influenza- related complications. Previous systematic reviews of observational studies examined influenza VE among high risk individuals with existing conditions such as stroke,[150] heart failure,[151,152] or diabetes mellitus.[153] However, these observational studies were hindered by their inability to overcome issues with unmeasured confounding due to the lack of robust methods used.[153] This is evident when the influenza vaccine was found to be effective both ***during*** and ***outside*** the influenza season.[151] For example, one systematic review looked at the association between influenza vaccine with all-cause mortality, all-cause hospitalization and heart failure-related hospitalization among patients with heart failure.[151]The meta-analysis included two cohort studies and found an association of reduced risk of all-cause mortality ***outside*** the influenza season (pooled HR 0.79, [95% CI, 0.68–0.89]) and ***during*** the influenza season (pooled HR 0.49, [95% CI, 0.30–0.69]).[151] A similar meta-analysis found that influenza vaccination was associated with a reduced risk of all-cause mortality (HR 0.83; [95% CI, 0.76 – 0.9].[152] Among all studies included in the meta-analysis for measuring VE against all-cause mortality, only one study (of six) was conservative in carrying out the analysis ***only during*** the influenza seasons. [152,154]

1.10 Important effect modifiers of influenza VE among patients overall and for patients with concurrent cardiovascular-related hospitalizations

Data from several studies have identified key factors that may serve as effect modifiers in the

association between the influenza vaccine exposure and influenza-related outcomes.[155–157] An effect modifier is a third variable that modifies the association between an exposure and an outcome such that the association under study varies in meaningful ways across one or more levels of the effect modifier.[158] Every study should test for suspected effect modifiers and, if present, any effect modification should be reported.[131] Effect modifiers may have specific clinical implications for specific populations. These implications could help in the development of clinical interventions and guidelines for special populations.[131] For example, in identifying specific populations most at risk of influenza-related complications, influenza vaccines can provide the highest possible prevention of infection with or complications from the influenza virus.[33] Findings regarding these potential effect modifiers are summarized in the following section. These variables were found to have an effect modifying role in the degree of vaccine immunogenicity (i.e., the vaccine's ability to provoke an immune response in the human body). Some potential modifiers of interest include sex and frailty.

Biological sex has been shown to be an effect modifier in influenza VE. Specifically, VE has been observed to be higher in females vs. males. In a study considering sex as an effect modifier in the evaluation of influenza VE, the overall VE for females was 49% (95% CI, 43% – 55%) whereas for males it was 38% (95% CI, 28% – 46%) (Absolute difference, 11%; *p*- value=0.03).[159] Further supporting studies measuring sex as an effect modifier in influenza VE are scarce. However, sex is theoretically suggested to be playing a modifying role because of the differences in hormones affecting differences in morbidity and mortality following an influenza infection, consequently contributing to observed differences in rates of hospitalization due to influenza across both sexes.[160]

Male patients who test positive for influenza consistently demonstrate higher risk for hospitalization in comparison to female patients.[161–163] For example, a study found that their risk for all-cause hospital admission during influenza season was higher (OR 1.26, 95% CI, 1.07 – 1.47) compared to female patients.[55] Sex in the above example conveys those most at risk not only for becoming infected with influenza but also for developing severe illness requiring hospitalization. This suggests that sex should be investigated as an effect modifier in all influenza VE studies, as VE may differ between males and females across both infection and severe outcomes.

Frailty is "a state of increased vulnerability to poor resolution of homoeostasis after a stressor event, which increases the risk of adverse outcomes, including falls, delirium, and disability".[164] Frailty is an important measure that should be addressed when estimating influenza VE. This is especially important given frail individuals comprise 25% of Canadians aged ≥65 years and 50% of those aged ≥85 years.[165] In comparison to frail seniors, healthy seniors are more likely to receive the vaccine.[124] As such, in measuring VE against mortality, frail patients are more likely to pass away irrespective of vaccination status. In a study sample, if frail patients were more likely unvaccinated, the VE against mortality would be overestimated. If perhaps frail patients were more likely vaccinated, the overall VE would be underestimated. Identifying people at highest risk for mortality and removing them before calculating VE may handle some of the overestimated or underestimated VE.[166] On the other hand, addressing frailty by measuring VE across strata defined by frailty status may be preferred, as it not only accounts for the presence of frailty among the population, but can also allow one to examine variation in the degree of VE among frail compared with non-frail

individuals.[167] Older age (≥65 years) is one of the factors measured in assessing frailty.[168] The frailty index is found to show an age-dependent exponential increase relationship with mortality.[168] The degree of influenza VE varies across age groups. Because of natural aging, the immune response in older adults (≥65 years) is weakened and the influenza vaccines provide weaker protection due to immunosenescence.[128] This emphasizes the importance of measuring VE with a focus on older adults to convey the true effectiveness in this population. Further, age may be an approximate proxy predictor of frailty and, thus, emphasizes the need for VE comparisons between younger and older age groups.[169]

1.11 Chapter Summary

In summary, since the start of 2012-13 influenza season (October 2012), pharmacists in Ontario were approved to administer influenza vaccines in pharmacies. This policy change offered a new administrative database resource for measuring vaccination status using pharmacy billing claims. However, these administrative billing sources have never been validated in detecting an individual's vaccination status. There is a need for validation as research studies utilize these administrative billing resources in extracting individuals' vaccination status and, subsequently, to calculate influenza VE.

To derive accurate conclusions about VE against influenza among patients with concurrent cardiovascular event hospitalizations, robust methodology must be used. Previous studies were limited due to their non-robust methodologies.[49,170,171] Although the TND is the suggested approach to measure VE, to date no TND design has measured VE against influenza in patients with cardiovascular-related hospitalizations or VE

against cardiovascular outcomes - a severe complication related to influenza.

Previous research has established that some variables are effect modifiers of concern with regard to the relationship of influenza VE among population subgroups. Although extensive research has been carried out on influenza VE and hospitalization/mortality, no single observational study exists which specifically investigated effect modifiers in relation to the association between influenza VE in patients hospitalized with cardiovascular conditions with the focus on sex or age as potential effect modifiers.

The data used in this study were collected prior to the COVID-19 pandemic, providing a stable baseline for evaluating influenza vaccine effectiveness in the absence of pandemic-related disruptions. These pre-pandemic data remain valuable because they reflect routine patterns of healthcare use, vaccination behavior, and disease circulation unaffected by COVID-19 mitigation measures, testing changes, or shifts in health system priorities. As such, they offer a clear context for understanding vaccine performance under typical seasonal conditions, serving as an essential reference point for interpreting post-pandemic trends.

1.12 Research objectives

1. To validate Ontario's administrative pharmacy and physician billing claims for identifying an individual's vaccination status against the reference standard of self-report.

2. To measure influenza VE against laboratory-confirmed influenza infection among older adults with CVD event hospitalizations in Ontario and examine sex or age group as potential effect modifiers of influenza VE.

3. To measure influenza VE against CVD hospitalization in older adults in Ontario.

1.13 Research hypotheses

1. Pharmacy (ODB) and physician (OHIP) billing claims considered together will result in a more valid estimate of an individual's vaccination status as reflected by relatively high estimates of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) compared to OHIP billing claims alone.

2. The influenza vaccine is effective against laboratory-confirmed influenza infection among older adults hospitalized with CVD conditions. Given the use of the robust TND study design the influenza VE results will only be effective during the influenza season vs. outside the season. Sex or age group will have a modifying effect on influenza VE against influenza among older adults hospitalized with cardiovascular conditions. Specifically;

- **i)** Females compared to males will be more likely to have higher VE against influenza.

- **ii)** Older age groups, compared to younger age groups, will be more likely to have lower VE against influenza.

3. The influenza vaccine is effective against CVD hospitalization in older adults. Specifically, the influenza VE among older adults with laboratory-confirmed influenza and hospitalized due to an acute myocardial infarction, unstable angina, or stroke is more than 0%, (VE > 0%).

Chapter 2: Data sources

2.1 Preamble

The purpose of this chapter is to provide an overview of the common data sources used across all three studies. Further specific details pertaining to each study's methods will be discussed in their designated chapters.

The studies included survey and administrative health databases held at ICES (formerly known as the Institute for Clinical Evaluative Sciences). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, ***without consent***, for health system evaluation and improvement.[172] All data sources at ICES are stored under highly secure measures to maintain the privacy and confidentiality of information. The data were accessed remotely through a secure connection. All databases were linked at the individual level by ICES using unique encoded identifiers and analyzed via the ICES secure environment. This deterministic and partially probabilistic linkage was achieved using personal identifiers which included individual's Health Identification Number, name, sex, date of birth, and postal code.[173,174] Appendix A illustrates the measures examined and the corresponding database(s) used.

2.2 Survey data: Canadian Community Health Survey (CCHS)

CCHS is a cross-sectional survey of a representative sample of persons aged 12 years and older in all Canadian provinces and territories.[175] This survey targets the Canadian population at a sub- provincial level (by health region or combined health regions) and collects information related to respondents' health status, health determinants such as

education status and income, and health

care utilization.[176] The survey excludes populations living on reserves and other Aboriginal settlements in the provinces, full-time members of the Canadian Armed Forces, people that reside in institutions, persons living in the Inuit and Cree regions of Quebec (namely, Québec health regions of Région du Nunavik and Région des Terres-Cries-de-la-Baie-James) and children aged 12-17 living in foster care. Altogether, these exclusions account for about less than 3% of the representative Canadian population aged ≥12 years.[176]

The CCHS collects data on an ongoing basis over a one-year collection cycle (during the months of January to December). Every year, a "multi-stage sample allocation strategy" of 65,000 respondents is required and selected across all Canadian provinces and territories.[176] The sample collected comes from three different sample frames: 58.5% of the sample is selected from a list frame of telephone numbers, 40.5% is from an area frame, and 1% is from the Random Digit Dialing sampling frame. These respondents provide reliable estimates of the 110 health regions. [176] The multi-stage sample allocation strategy carried out by CCHS treats all health regions and provinces with relatively equal importance. There are three question content types in the CCHS questionnaire: core, optional, and rapid response. Core content questions target all provinces during every collection period. Optional content includes questions that are selectively chosen by some provinces to be provided to their residents included in the survey.

Rapid response content questions are asked during a single three-month collection period. For the purpose of this thesis, the only type of questions of interest were core content type questions.

Multiple steps are taken to perform data validation in CCHS.[176] First, the CCHS team uses a validation program that compares estimates of the common content health indicators with that of the previous year. These estimates are examined at various geographic levels in addition to

using age and sex as estimates of comparison. Non-Statistics Canada surveys that collect information on variables contained in the CCHS are compared with CCHS results. The CCHS team searches for important differences between the surveys to check if there are any anomalies in the data. If the differences are significant, the CCHS team investigates and documents the possible causes. Second, CCHS analysts look at many variables in-depth and publish analytical articles on specific themes carried out in the survey. In doing this, the analysts effectively identify errors in the data. This practice increases the possibility of error detection and adds to the validation of the CCHS. Lastly, as an external validation measure, prior to release of the collected data, shared files are sent for a two-week review period to provincial and federal partners.[176] These partners examine, scrutinize, and advise Statistics Canada on any concerns or abnormalities related to data quality. [176]

Linking individuals' survey responses to their health administrative data requires consent by the respondents. A previous study, carried out at ICES, reported that the linkage rate between administrative databases and the CCHS was 83%.[106] The deterministic linkage is carried out using an individual's Health Number.[176] The most recent CCHS data cycles linked with administrative data that I had access to at ICES, during my PhD candidacy, were from 2013 and 2014. Everyone who consented to the linkage were linked to their available administrative health data.

2.3 Administrative databases:

Ontario health administrative databases are suitable for VE studies and are frequently used in health services research. Research exploring the validity and reliability of these databases has found them to be robust for real-world studies.[177] The following sections summarize the health administrative databases specific to the studies carried out in this thesis.

2.3.1 Ontario Health Insurance Plan (OHIP) database

In Ontario, OHIP is a publicly funded health plan provided to Ontario residents. OHIP covers the cost of medically necessary physician, diagnostic, and hospital services for all Ontarians with provincial health coverage.[178] Other services such as podiatry, optometry, dental, and travel service depend on certain eligibility criteria for coverage by OHIP.[178] Medically necessary services are defined by the province and recorded in the Schedule of Benefits for physician services under the Health Insurance act.[179] This database contains physician services captured using OHIP codes for diagnoses or procedures such as laboratory testing and vaccination.[180] The key variables provided in this database are: patient ID, physician ID, date of service, diagnoses, and procedures.[180] Diagnoses are captured using diagnostic codes provided by the Ministry of Health in Ontario for physician services.[179] Researchers at ICES report that the extent of missing demographic information of age, sex, and residence code from physician billing claims is less than 1%.[181]

2.3.2 Ontario Drug Benefit (ODB) database

The ODB Program is a publicly funded program in Ontario that covers some prescription medication costs mainly for older adults in Ontario. Other groups of the population aged

less than 65 years may be eligible for ODB, including residents receiving social assistance, people with disability, those living in long-term care homes or receiving professional home care services and, starting January 2018, residents who are 24 years and younger without a private insurance plan for prescription drug cost coverage.[182,183] The majority of all beneficiaries are represented by those aged ≥65 years (over 70% of filled prescriptions in 2016/17 fiscal year were for those aged ≥65 years).[184] When an eligible resident for ODB fills a prescription at an Ontario pharmacy, a claim is sent to the public payer and is captured in the ODB database. On the other hand, pharmacists' clinical services, including administering influenza vaccination, are covered for ***all*** Ontario residents and are also captured in the ODB database. As such, the ODB database includes vaccination status of all residents and medication-use of covered individuals. A study found the overall error rate in dispensed prescriptions in ODB to be 0.7%.[108] Potential misclassification was found among days of supply and quantity.[185]

Information on each individual's medication use for treatment of chronic conditions was extracted using the ODB database. For the purpose of this thesis, only certain medications reflecting specific chronic conditions of interest were examined. These chronic conditions were selected based on NACI's list of high risk chronic conditions for influenza-related complications.[33] The medications related to these chronic conditions were extracted from the Compendium of Therapeutic Choices for treating the chronic conditions of interest.[186] To avoid repetition, the conditions will be listed in this chapter. The following conditions were considered: Anemia, Asthma, Cancer, Cardiovascular Disease (Arrhythmia/ Congestive Heart Failure/ Hypertension/ Ischemic heart disease/ Myocardial Infarction/ Stroke), Chronic Kidney Disease, Chronic Obstructive Pulmonary

Disease, Dementia, Diabetes, and immunocompromised conditions (for example using HIV medications). Although other databases were used to capture chronic disease status, the aim for capturing types of medications used was another approach to investigate the possible confounding effects of certain medications used.[187,188] Details concerning the medications of interest for treating each condition are available in Appendix B.

2.3.3 Registered Persons Database (RPDB) and Postal Code Conversion File (PCCF+)

The RPDB contains demographic data on registered persons under OHIP.[189] Data include residents' age, sex (male/female), and date of death (if applicable). The PCCF dataset, available at ICES, links postal codes to census data to derive the characteristics of areas of residence such as rurality and income quintile. The binary rurality variable is measured by the relative number of residents in the community, where rural areas are defined as areas with <= 10,000 residents using most recent census data.[190] The household income quintile is assessed by neighbourhood at census Dissemination Area-level and is used as a proxy to reflect an individual's socioeconomic status.

2.3.4 The Flu and Other Respiratory Viruses Research dataset

The Flu and Other Respiratory Viruses Research (FOREVER) Cohort dataset includes information on all patients seeking care and being tested for respiratory viruses within the 11 Public Health Ontario laboratories and eight academic hospital-based laboratories.[173] Patients' test results are linked using their unique Health Identification Number. Influenza A and B are part of the respiratory viruses tested for in test kits provided by Public Health Ontario, other viruses tested include Respiratory Syncytial Virus (RSV), adenovirus, coronavirus, enterovirus (including rhinovirus), parainfluenza virus, human metapneumovirus, and bocavirus. The list of kits and source of testing

reagents for influenza testing available during the time span of the dataset used for this thesis (2010-2016) are illustrated in Appendix C. Details on the kits used for testing are available at Public Health Ontario.[64]

The FOREVER Cohort dataset spans from the 2010-11 to 2015-16 influenza seasons, providing six influenza seasons in total. The signal of the influenza season is generally identified during all weeks when the positivity rate of laboratory influenza tests are reported to be 5% and a minimum of 15 positive tests are observed.[191] The peak month of influenza activity is defined by the CDC as "the month with the highest percentage of respiratory specimens testing positive for influenza virus infection during that influenza season".[192] The peak month is a comparative measure usually announced once the positivity rate of laboratory influenza testing starts to decline during the influenza season. Details on the exact dates of the beginning, peak and end of each influenza season are illustrated in Appendix D. The validity of the FOREVER Cohort dataset, in calculating influenza VE in community-dwelling older adults, has been shown to be comparable to VE estimates of other studies, especially when measuring VE for older adults in inpatient hospital settings.[173]

2.3.5 Canadian Institute for Health Information (CIHI) Databases

The Canadian Institute for Health Information (CIHI) collects data pertaining to hospitalization and emergency department visits from all provinces (except Quebec) using a standardized procedure.[193] CIHI databases were the source for three important datasets used in this thesis: the Discharge Abstract Database (CIHI-DAD), the National Ambulatory Care Reporting System (CIHI-NACRS), and the Same Day Surgery

database (CIHI-SDS). CIHI-DAD provides patient- level data about all inpatient hospital stays in Ontario and discharges including demographic, administrative, and clinical information.[193] The CIHI-NACRS provides information about all patient visits to hospital and community-based ambulatory care in Ontario including day surgeries, outpatient and community-based clinics, and emergency departments.[194] Finally, the CIHI-SDS offers patient-level data for all day surgery institutions in Ontario. The common key variables available across the three databases are study ID, physician ID, hospital (facility) ID, diagnoses, and procedures.[180] CIHI-NACRS and CIHI-SDS provide date of service while CIHI- DAD provides key variables of date of admission, date of discharge, and length of stay.[180]

The coding standards used for classifying diseases in hospital healthcare settings is the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10-CA) and the Canadian Classification of Health Interventions (CCI), both adopted in 2002.[181,195] Prior to 2001, the Canadian coding standards followed the Coding Sourcebook.[196] The Coding Sourcebook included the International Classification of Disease, 1975 Revision (ICD-9) and the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) and some information associated with the American clinical modification of ICD-9, the ICD-9-CM.[196] Data quality documentation of CIHI-DAD is reported every year.[197]

Diagnostic accuracy of administrative databases used in research is vital. Accurately coded diagnoses mitigate overestimation or underestimation of the outcome being measured such as cardiovascular-related hospitalization.[198–200] Researchers at ICES routinely estimate the extent of missing information from CIHI databases and report that

it is less than 1%.[181] In re-abstraction studies comparing agreement of hospital discharge data in Ontario, the agreement rate on demographics was found to be 93% or higher.[181] Cardiovascular hospitalization events were also found to have very high validity in ICD coding in CIHI-DAD (ICD-10; 92% [95 % CI 88 – 95]).[181,201]

2.3.6 Measures of chronic disease conditions in administrative databases.

Chronic disease conditions that increase the risk of influenza-related complications include hypertension, asthma, diabetes, cancer, chronic obstructive pulmonary disease (COPD), congestive heart failure, myocardial infarction, chronic kidney disease, morbid obesity, stroke,

immunosuppression disease like HIV, and dementia.[3] At ICES, medical conditions are identified using various administrative databases such as the OHIP, ODB, CIHI-DAD, CIHI-NACRS, in addition to the Canadian Organ Replacement Register (CORR), the Ontario Renal Reporting System (ORRS), the Ontario Diabetes Database (ODD), the Ontario Cancer Registry (OCR), the Ontario Congestive Heart Failure Database (CHF), and the Ontario HIV database (HIV). Further details about the databases used to capture the comorbidities for the purpose of the three studies are provided in Appendix A. ICES uses algorithms to derive cohorts of certain medical conditions (Appendix E).[202–209] The algorithms were previously validated using a vast number of registries and specialized databases.[202,203,206,210–216] In general, these validated algorithms have high sensitivity in measuring the disease of interest. The validated algorithms range in performance measures to as high as 96.2% in sensitivity and 99.6% in specificity for identifying patients with HIV to as low as 72% in sensitivity and 95% in specificity in identifying patients with hypertension.[214,215] Discussing validated performance measures for each

database / registry is beyond the scope of this thesis. The references used for measuring each medical condition are provided in Appendix E.

Frailty also increases the risk of influenza-related complications.[164]At ICES, frailty is captured using set criteria as a binary measure or an index measure (Appendix F). In this thesis, only the binary measure was used. The criteria for using the binary measure was inspired from the Edmonton Frail Scale[217] and Urquhart et al.'s "Rules to Identify Persons with Frailty",[218] and uses CIHI-DAD data, Home Care Database (HCD) data, and/or OHIP physician billing claims. To date, this measure which solely depends on administrative data, has not been validated.[219] The HCD provides details on whether an individual received home care services. Home care

visits is one domain that can convey the type of healthcare utilization usually required by patients who are frail but are community dwellers.

2.4 Ethics and Statistical Software.

Ethics clearance for all three studies were received through a Clinical Research Ethics Board at the University of Waterloo (CREB: IRB00007409). SAS® Enterprise Guide software versions 7.1 and 8.4 (SAS Institute Inc., Cary, NC) were used to carry out all statistical analyses.

Chapter 3: Validation of influenza vaccination status using health administrative databases by integrating pharmacy claims and medical billing databases in Ontario, Canada

A version of this chapter is published as follows:

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3.1 Overview

Background: Determining vaccination status among the population is key for vaccine research and surveillance. This study aimed to validate the combined use of Ontario Health Insurance Program (OHIP) physician billing claims and Ontario Drug Benefit program (ODB) pharmacist billing claims against data from the Canadian Community Health Survey (CCHS).

Methods: OHIP and ODB billing claims databases were linked to 2013-2014 CCHS data, which contain self-reported seasonal influenza vaccination status of respondents (the reference standard). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), and their associated 95% confidence intervals (CIs) were estimated. Subgroup analyses were performed based on key respondent characteristics, including having a regular medical doctor and the presence of risk factors for influenza complications.

Results: There were 31,390 eligible CCHS respondents aged ≥12 years in Ontario who responded to the influenza vaccination questions and agreed to have their responses linked to health administrative databases. More than half (55%) were female, 29% were aged ≥65 years, 93% had a regular medical doctor, and 54% had one or more risk factors for influenza complications. The sensitivity for the combined administrative databases was 60.1% (95% CI, 59.3%–61.0%), specificity was 98.5% (95% CI, 98.3%–98.7%), PPV was 96.7% (95% CI,
96.3%–97.1%), and NPV was 76.9% (95% CI, 76.4%–77.5%). Sensitivity was higher among those aged ≥65 years (72.7%; 95% CI, 71.6%–73.7%), with a regular medical

doctor (61.1%; 95% CI, 60.3%–62.0%), and those with at least one risk factor for influenza complications (65.8%; 95% CI, 64.9%–66.8%).

Conclusion: Combining administrative physician and pharmacy claims data in Ontario results in moderate sensitivity but very high specificity and PPV, demonstrating that they can be a valid measure of influenza vaccination status.

Keywords

Influenza Vaccination, Administrative Health Data, Validation, Pharmacist, Immunization

3.2 Introduction

Influenza remains a significant public health challenge in Canada, contributing to approximately 12,200 hospitalizations and 3,500 deaths annually.[220,221] This high burden of illness underscores the critical need for effective prevention strategies. Vaccination plays a vital role in reducing the spread and severity of influenza.[222,223] Consequently, the Canadian province of Ontario offers influenza vaccines free of charge to all residents aged ≥6 months.

Accurately determining vaccination status within the population is essential for advancing vaccine research, monitoring public health activities, and evaluating the effectiveness and impact of immunization programs. To assess the impact of vaccination efforts, it is essential to accurately measure vaccine effectiveness. Studies on vaccine effectiveness rely on valid data about individuals' vaccination status and their subsequent health outcomes.[224] These data allow researchers to evaluate how well the vaccine prevents illness, hospitalizations, and severe complications across diverse population groups. Valid measures of vaccination status are needed for vaccine effectiveness studies to produce accurate estimates, which in turn are necessary for guiding public health policies and resource allocation.[225] Moreover, understanding the effectiveness of the vaccine helps to refine future vaccination campaigns so that they continue to provide optimal protection to the population.

Vaccination status can be determined using vaccination registries, self-report questionnaires, patient medical records, or administrative databases.[100] Previous studies suggest self-report should be the reference standard for determining influenza vaccination

status in the absence of registries.[97–101] However, due to the absence of influenza vaccine registries in Ontario, and challenges obtaining timely self-reported vaccination status, administrative databases become an essential resource to measure influenza vaccination status.

Until recently, physician billing claims for administering influenza vaccines, which are captured in the Ontario Health Insurance Plan (OHIP) database, were the main source for ascertaining influenza vaccination status. A previous validation study by Schwartz et al., which compared OHIP claims between 2007 and 2009 against self-reported vaccination status from the Canadian Community Health Survey (CCHS), showed that the claims data were moderately sensitive (49.8% [95% Confidence Interval (CI), 49.0%–50.5%]) and highly specific (95.7% [95% CI, 95.5%–96.0%]) in correctly identifying vaccination status.[106] The positive and negative predictive values were 88.4% (95% CI, 87.8%–89.0%) and 74.5% (95% CI, 74.0%–74.9%), respectively.

In 2012, Ontario authorized pharmacists to administer influenza vaccines in community pharmacies, which facilitated access and increased vaccine coverage in the population.[103,104] As a result, pharmacies became the most common place for influenza vaccination in Ontario.[226] These claims are recorded in the Ontario Drug Benefit (ODB) database. Despite the growing role of pharmacies in vaccination efforts, the approach of including pharmacy claims along with OHIP physician billing claims to assess influenza vaccination status has yet to be validated in Ontario.

The objective of this study was to validate the measure of vaccination status derived from combining OHIP and ODB data in Ontario against the reference standard of self-

report in the CCHS.

3.3 Methods

3.3.1 Study Design & Data Sources

We conducted a validation study using CCHS survey data linked to OHIP, ODB, and other health administrative databases (described below). These databases were linked using unique encoded identifiers and analyzed at ICES. ICES is an independent, non-profit research institute whose status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement.[172]

CCHS is a cross-sectional survey targeting a representative sample of Canadians aged ≥12 years across all provinces and territories, excluding those living on First Nations reserves or other Indigenous settlements, full-time members of the Canadian Armed Forces, institutionalized individuals, and children in foster care.[176,227] Excluded individuals represent less than 3% of the population aged ≥12 years.[228] The annual survey cycles sample 65,000 respondents recruited by a multi-stage sampling strategy and weighted to provide valid estimates of the Canadian population.[176] The CCHS has the capability to combine two consecutive annual samples using appropriate weighting techniques, enabling researchers to increase sample size and improve the precision of estimates.[176] The CCHS uses a sampling method designed to produce representative samples at both provincial and national levels. Thus, the survey's respondents reflect the demographic and health characteristics of the broader populations in each province and across Canada.

The OHIP database captures physician billing claims for the reimbursement of clinical services provided in physician offices, including influenza vaccination.[179] Information on pharmacist billing claims for influenza vaccinations administered in community pharmacies, including the vaccine's unique product number and service date, are recorded in the ODB database. Clinical services including the vaccine and administration fees are covered by the ODB program for all Ontario residents aged six months or older.[229] As such, all vaccinations of Ontario residents by pharmacists are captured in this database.

Demographic characteristics of respondents (age, sex) and postal code were extracted from Ontario's Registered Persons Database (RPDB). The Postal Code Conversion File (PCCF+) dataset was used to link postal codes to Census data to derive area-based relative measures of residence for each individual (urban vs rural, with the latter defined as a community with
≤10,000 residents).[190] Further, the PCCF+ was also used to link each respondent's residential postal code to Census dissemination area (population of between 400 and 700 people) median household income quintiles as a proxy for individual socioeconomic status.

Respondents' clinical characteristics related to the risk for serious influenza infection complications (i.e., risk factors) were identified using previously validated algorithms involving diagnostic codes recorded in the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), the National Ambulatory Care Reporting System (NACRS), the Same Day Surgery (SDS) database, and the OHIP database (details in Appendix E).[202,204,206,210–213]

Ethics approval for this study was obtained from the University of Waterloo, Office of Research Ethics (CREB# IRB00007409, HREB# IRB00002419) in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2), Canada.

3.3.2 Study Sample

All CCHS respondents interviewed during the 2013 and 2014 cycles were included if they had agreed to having their data linked to administrative databases, answered the "flu shot" theme questions, and were Ontario residents with OHIP coverage for at least one year prior to the CCHS interview date. At the time this study was conducted, the most recent CCHS cycles linked and accessible at ICES were the 2013 and 2014 cycles. Respondents interviewed for both cycles were only included once during the earliest cycle (i.e., 2013). Respondents whose physician claims data for influenza vaccination indicated only an "incentive fee" billing code (Q130), used by physicians to indicate that a patient has received an influenza vaccine elsewhere, without a corresponding pharmacy or physician claim, were excluded as this was considered an ambiguous vaccination status. In a sensitivity analysis, these respondents were included as vaccinated.

3.3.3 Measures

Demographic variables examined included sex, age group, rurality, and neighbourhood-level median household income quintile. Data on year of survey and having a regular medical doctor were extracted from the CCHS. A "regular medical doctor" generally refers to a family doctor or general practitioner who offers ongoing primary care and serves as the main point of contact for various health concerns, including specialist referrals. The risk groups for influenza-related complications were selected based on

recommendation statements from Canada's National Advisory Committee on Immunization (NACI). The following risk factors were identified: anemia, asthma, cancer, cardiovascular disease (including arrhythmia, hypertension, ischemic heart disease, myocardial infarction, and stroke), chronic obstructive pulmonary disease (COPD), dementia, and being immunocompromised. These risk factors guided the selection of the groups included in the analysis (Appendix E).

Influenza vaccination status

The CCHS included a set of flu shot-themed questions that were asked of every respondent. We developed the following algorithm to determine the vaccination status of respondents (Appendix G). Respondents were asked "Have you ever had a seasonal flu shot, excluding the H1N1 flu shot?". If the response was "NO", respondents were considered unvaccinated. If they said "YES", they were prompted to indicate the timing of this vaccination relative to the interview date (less than 1 year ago, 1 year to less than 2 years ago, or 2 years ago or more). Only those choosing "less than 1 year ago" for their most recent influenza vaccination were considered vaccinated. Individuals who provided ambiguous responses to either of the two questions such as "Don't Know/Refuse [to answer]" were removed from the study sample. Previous validation studies have used a similar approach for ascertaining influenza vaccination status.[106,230,231]

In the administrative databases, respondents' vaccination status was determined by the presence of a billing code for influenza vaccination in OHIP or ODB (codes available in Appendix H).[179,232] The timing of billing codes relative to the CCHS interview date was used to determine influenza vaccination status. The vaccination lookback window extended from the interview date to 365 days prior. Individuals vaccinated on the

interview day were considered vaccinated. If multiple vaccination dates were recorded in OHIP or ODB, the closest date to the interview was used.

3.3.4 Data analysis

We presented the distribution of respondents' demographic and clinical characteristics by their CCHS vaccination status. Chi-square (χ^2) tests for each categorical variable by exposure (vaccination status) were performed to check for bivariate statistical significance. The *p*-value

for statistical significance was <0.05. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated (with 95% CIs), assessing the validity of the combined administrative databases (OHIP and ODB) compared with the reference (CCHS).[233,234] Sensitivity was defined as the proportion of individuals vaccinated according to the reference standard (CCHS) who were also identified as vaccinated in the administrative data source (pharmacy claims or physician billing databases), among all individuals vaccinated in CCHS. Specificity was defined as the proportion of individuals unvaccinated in CCHS who were also classified as unvaccinated in the administrative data source, among all individuals unvaccinated in CCHS. PPV was calculated as the proportion of individuals identified as vaccinated in the administrative data source who were confirmed as vaccinated in the reference standard. NPV was the proportion of individuals classified as unvaccinated in the administrative data source who were also unvaccinated in the reference standard. The 95% confidence intervals were calculated using the Clopper-Pearson exact method.

3.3.4 a Subgroup analysis

Subgroup analyses were conducted by CCHS cycle year (2013 and 2014), sex, age

group, rural/urban residence, presence of a regular medical doctor, and risk factors for influenza-related complications (one or more as well as individual risk factors, including arrhythmia/hypertension/ischemic heart disease/myocardial infarction/stroke), COPD, dementia, and being immunocompromised.

3.3.4 b Sensitivity analysis

Three sensitivity analyses were carried out. First, to determine if excluding respondents with ambiguous vaccination status—identified by the presence of the "incentive fee" code (Q130)

without a corresponding ODB or OHIP claim—affected the results, we re-ran the analyses including these respondents as vaccinated. Second, since participants were asked about the 365 days before the interview, there is a risk of misclassification of the immunization year (whether it was during the most recent influenza vaccination campaign or the previous one).[106] To minimize this risk, we conducted a sensitivity analysis by only including respondents interviewed outside influenza vaccination campaigns (between February 1 and August 31, in both 2013 and 2014), so that their answers specifically reflected the most proximal season to the date of interview. This sensitivity analysis aimed to include individuals vaccinated after the peak influenza vaccination campaign period, which typically occurs in the fall and early winter. It is important to distinguish between the timing of influenza vaccination campaigns and the influenza season, when virus circulation is highest. As this study focused on the accuracy of vaccination records rather than influenza infection risk, the relevant time period was the vaccination campaign period, when vaccines were administered, rather than the influenza season itself. Finally, since billing timestamps in administrative databases might not always match vaccine

administration dates due to potential delays in billing, we conducted a sensitivity analysis allowing an extra 30 days of billing delay. Thus, we only considered vaccinations billed in 335 days before the interview date.

3.4 Results

There were 42,553 respondents aged ≥12 years interviewed in Ontario during CCHS cycles 2013 and 2014.[176,227] The number of respondents who agreed to data linkage was 33,047 (77.5%).

After applying the inclusion and exclusion criteria, the final study sample included 31,390 CCHS

respondents (Figure 3.1).

A total of 13,358 (42.6%) of these CCHS respondents reported receiving an influenza vaccination in the past 12 months (Table 3.1). This was higher for those surveyed in 2014 than in 2013 (44.4% versus 40.8%, *p*-value<0.0001), for females than for males (45.3% versus 39.2%, *p*-value<0.0001), and for those aged ≥65 years than those younger than 65 (71.4% versus 30.7%, *p*-value<0.0001). There was a similar proportion reporting having received the influenza vaccination across urban and rural settings (~43%, *p*-value=0.65) and across neighbourhood income quintiles (~41-–43%, *p*-value=0.1973). However, a larger proportion of individuals with a regular medical doctor had been vaccinated compared to those without one (44.2% versus 20.4%, *p*-value<0.0001). The proportion of respondents with any risk factors for influenza- related complications who were vaccinated was 55.4%, but this percentage ranged from 78.4%, among respondents with dementia to 45.2% among respondents with asthma.

There were 8,308 individuals ascertained as having received influenza vaccination in the

combined (OHIP and ODB) administrative data (Table 3.2). Of these, 6,238 (75.1%) individuals were captured by OHIP only, 1,994 (24.0%) were captured by ODB only, and 76 (0.9%) had both physician and pharmacy billing claims. There were 274 respondents (0.87% of the total study population) identified as being vaccinated based on OHIP/ODB data who reported in the CCHS that they had not been vaccinated.

3.4.1 Performance Measures (sensitivity, specificity, PPV, NPV)

The sensitivity of the administrative databases in capturing individual vaccination status was 60.1% (95% CI, 59.3%–61.0%), whereas the specificity was 98.5% (95% CI, 98.3%–98.7%)

(Table 3.2). The PPV and NPV were 96.7% (95% CI, 96.3%–97.1%) and 76.9% (95% CI, 76.4%–77.5%), respectively.

3.4.2 Subgroup Analyses

Performance measures varied by several respondent characteristics (Table 3.2). Sensitivity was higher in the 2014 CCHS interview year (63.0%, 95% CI, 61.8%–64.1%) compared with the 2013 interview year (57.3%, 95% CI, 56.1%–58.5%). It was also higher for respondents aged ≥65 years (72.7%, 95% CI, 71.6%–73.7%) relative to those younger than 65 years (48.3%, 95% CI, 47.1%–49.4%), and for those with a regular medical doctor (61.1%, 95% CI, 60.3%–62.0%) compared to those without (31.9%, 95% CI, 27.5%–36.6%). Sensitivity was also higher among respondents with any medical risk factors (65.8%, 95% CI, 64.9%–66.8%) compared to those with no risk factors (46.7%, 95% CI, 45.1%–48.2%). The specificity was consistently higher than 95% across all subgroups. The only subgroup showing relatively lower specificity was that for respondents with dementia where the specificity was 82.5% (95% CI,

70.1%–91.3%).

3.4.3 Sensitivity Analysis

None of the three sensitivity analyses showed substantial differences compared to the original analysis. Including the 304 respondents with only the Q130 "incentive fee" code as vaccinated produced results consistent with the main analyses (Appendix I). Restricting the CCHS data to only those interviewed between February and August of each survey cycle did not substantially alter the results (Appendix I). Lastly, excluding billings in month 12 resulted in similar performance measures, with the largest change being a 3.4% decline in sensitivity (Appendix I).

3.5 Discussion

In this validation study that used CCHS responses as the reference standard, the combination of physician and pharmacist billing claims had moderate sensitivity (60.1%) and high specificity (98.5%) for correctly classifying respondents' vaccination status in Ontario. These data correctly identified vaccinated respondents an estimated 96.7% of the time (PPV) and unvaccinated respondents 76.9% of the time (NPV). Sensitivity increased from the 2013 survey to the 2014 survey and was highest among older respondents and those who reported having a regular medical doctor.

The administrative databases did not capture all vaccinated Ontario residents, resulting in a sensitivity estimate of 60.1%. This could be because many residents had received influenza vaccines in settings outside of physician offices or pharmacies, such as universities, workplaces, or public health clinics, which do not report vaccination data to administrative databases as they do not bill the Ministry of Health directly for

vaccinations. In some cases, a billing claim may not have been submitted by a physician or pharmacist (e.g., forgetting to bill) or received by the Ministry of Health (e.g., technical issues). Nonetheless, most Ontario respondents were likely captured in our sample, as pharmacies and physician offices are the most common locations for receiving influenza vaccines in the province.[226] As such, our findings suggest that administrative databases can still provide a valuable measure of influenza vaccination in Ontario.

Combining physician and pharmacy billing claims appears to have increased the validity of measured influenza vaccination status. In addition to the increased sensitivity from 2013 to 2014 observed in this study, sensitivity improved by 10.3 percentage points compared to Schwartz et al.'s study.[106] Specificity increased by 2.8 percentage points, while PPV and NPV improved by 8.3 and 2.4 percentage points, respectively.[106] This improvement in validity might reflect the increased utilization of pharmacies as preferred places for influenza vaccination, a pattern that has likely become even more common in recent years. Canada's Seasonal Influenza Vaccination Coverage Survey suggests that the increased utilization of pharmacies as a vaccination site was not merely at the expense of physician offices; rather, it mainly came at the expense of other places like workplaces, temporary vaccine clinics, community health centres, hospitals, or retirement residences.[226] In fact, the majority of respondents to the Seasonal Influenza Vaccination Coverage Survey reported that they received their vaccine in pharmacies (52%) or doctor's offices (17%), other places such as; temporary vaccine clinics, community health centres, workplace, hospitals, retirement residence, or other places (13%).[226] This could be due in part to the policy change and also the accessibility of pharmacies.[105] As

such, combining physician and pharmacy claims improved the accuracy of administrative databases in capturing influenza vaccination status within the Ontario population, enhancing their utility for vaccine effectiveness studies.

In the absence of vaccination registries, administrative data offer a valid alternative for tracking immunization status, making them valuable for epidemiological studies. These datasets, derived from physician and pharmacy billing claims, are directly tied to healthcare encounters, providing objective evidence of vaccinations received within formal healthcare settings.[107] Although administrative data may miss vaccinations administered outside of physician offices or pharmacies, they cover large populations comprehensively and enable researchers to conduct population-level analyses. This makes administrative data a critical tool for understanding vaccination trends, evaluating coverage rates, measuring vaccine effectiveness, and informing public health policies when centralized vaccination registries are unavailable.

The relatively higher sensitivity among certain groups within our sample, including older respondents, those with a regular medical doctor, and those with comorbidities, implies that these groups are more likely to receive influenza vaccines from their physicians and pharmacists than from other providers.[107,226] Researchers assessing vaccine effectiveness should be aware of this variation in validity estimates when evaluating vaccine effectiveness among different population subgroups. Younger respondents and those without a regular medical doctor may be more likely to receive their vaccination from other places not captured by administrative databases such as workplaces or public health clinics. Further, these findings have important implications for studies using administrative data to measure

influenza vaccination coverage or vaccine effectiveness. Specifically, relying solely on claims data may underestimate true vaccine coverage, and misclassification of vaccinated individuals as unvaccinated could bias vaccine effectiveness estimates towards the null in the absence of other biases. Integrating multiple data sources may help mitigate these limitations and improve the accuracy of vaccination status ascertainment.

3.5.1 Strengths and Limitations

This study is the first to rigorously assess the validity of using administrative databases that combine both physician and pharmacy claims to determine individual vaccination status in Ontario. Still, several limitations should be noted. First, while 77.5% of CCHS respondents consented to data linkage, it is uncertain if there are differences between those who consented and those who refused to have their data linked.[235] However, the proportion vaccinated for all CCHS respondents was comparable to that of respondents who consented to linkage in our sample (42.6% vs. 41.4%, respectively). Additionally, 93.1% of all CCHS respondents indicated having a regular medical doctor, which was comparable with that found in this study (93.2%).

These findings, though based on only two variables, suggest minimal differences between those who consented to data linkage and those who did not. Second, the CCHS data, relying on self- report, likely also suffer from recall or social desirability bias. Only 0.87% of the total study population who reported being unvaccinated in the CCHS were identified as vaccinated in the administrative databases. On the other hand, social desirability bias might explain some instances in which vaccination is self-reported in survey data but not found in administrative databases.

Further, while many questions in the CCHS have been validated and shown to be

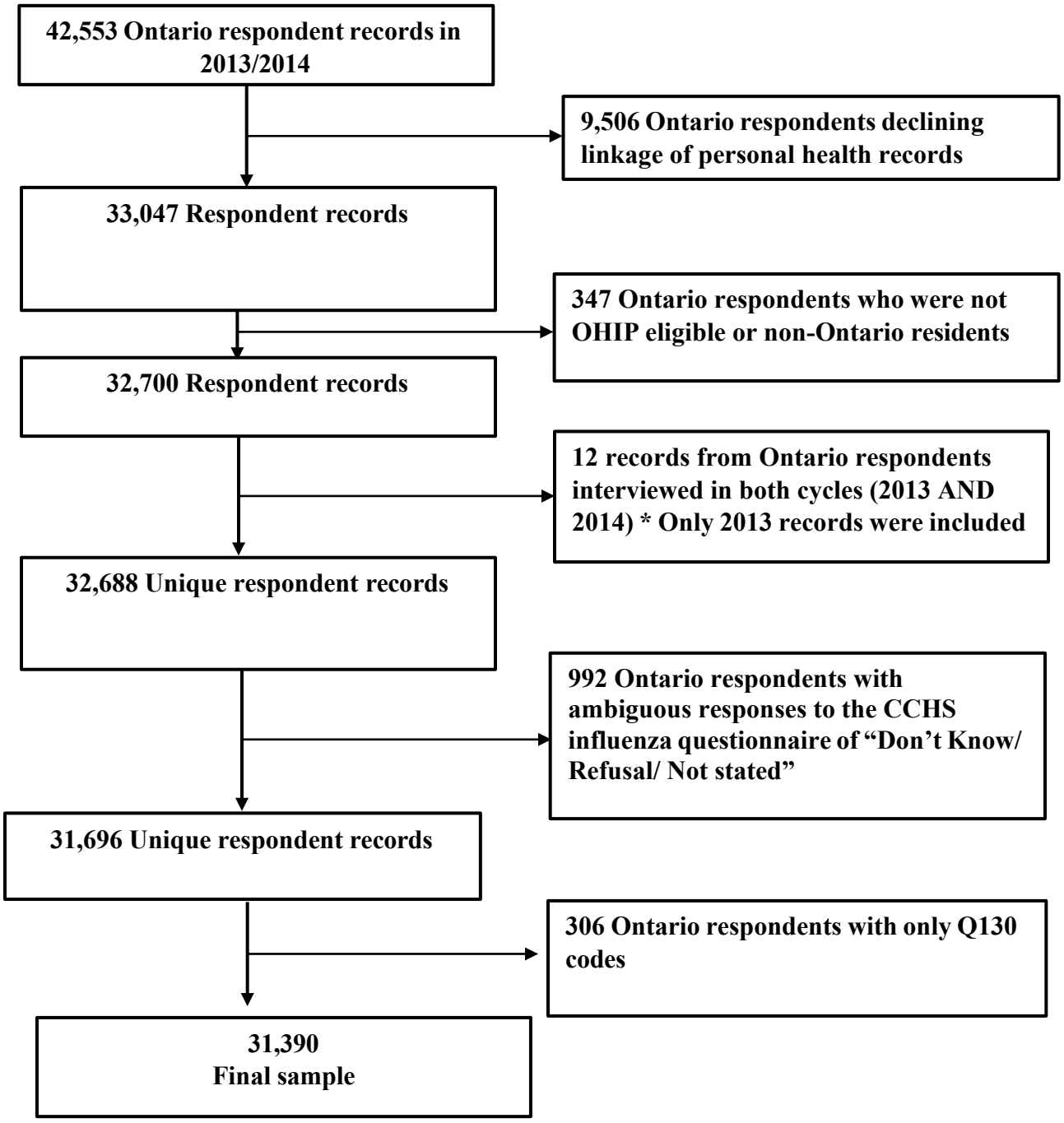
reliable, it is important to note that the question regarding vaccination status has never been validated against an official registry. This is particularly relevant because there is no centralized registry specifically for influenza vaccinations in Ontario. As such, while the CCHS data on influenza vaccination status is widely used, we acknowledge that it may not fully capture the accuracy of influenza vaccination status compared to an official registry. Finally, at the time the study was conducted, the most recent available linked CCHS interviews were cycles 2013 and 2014, just two years after pharmacist influenza vaccine administration was permitted in Ontario (October, 2012). A clear trend is not discernable from only two time points. However, the sensitivity in 2014 was observed to be higher than 2013, suggesting an improvement in performance measures for detecting influenza vaccination status in administrative databases. Further research is required for a more recent update on the validity of administrative databases in measuring influenza vaccination status.

3.6 Conclusion

This study suggests that, after Ontario's policy change to allow influenza vaccines to be administered at pharmacies, administrative billing data that combine pharmacy and physician billing records are valid for measuring influenza vaccination status. The results of this validation study offer crucial insights into the utility of health administrative physician and pharmacy billing claims for determining influenza vaccination status, underscoring the importance of having accurate estimates for a variety of purposes, including surveillance, public health interventions, and investigations of vaccine effectiveness.

3.7 Tables and Figure

Figure 3. 1 Flowchart of the study sample for Canadian Community Health Survey 2013/2014 respondents



OHIP=Ontario Health Insurance Plan, CCHS=Canadian Community Health Survey

Table 3.1 Descriptive characteristics by influenza vaccination status within the previous 12 months according to the Canadian Community Health Survey

Characteristics	Respondents who received influenza vaccine, no. (Row %)	Respondents who did not receive the influenza vaccine, no. (Row %)	*p*-value
	n= 13,358 (42.6%)	**n= 18,032 (57.4%)**	
Canadian Community Health Survey Year of Interview			
2013	6625 (40.8%)	9604 (59.2%)	<0.0001
2014	6733 (44.4%)	8428 (55.6%)	
Sex			
Female	7824 (45.3%)	9443 (54.7%)	<0.0001
Male	5534 (39.2%)	8589 (60.8%)	
Age group			
12-17	694 (27.9%)	1792 (72.1%)	<0.0001
18-49	2595 (22.8%)	8810 (77.2%)	
50-64	3559 (42.4%)	4825 (57.6%)	
≥65	6510 (71.4%)	2605 (28.6%)	
< 65	6848 (30.7%)	15427 (69.3%)	
Residence*			
Urban	10503 (42.5%)	14205 (57.5%)	0.65
Rural	2851 (42.8%)	3810 (57.2%)	
Neighbourhood income quintile§			
1 (least affluent)	2509 (43.4%)	3267 (56.6%)	0.1973
2	2745 (42.6%)	3698 (57.4%)	
3	2585 (41.4%)	3654 (58.6%)	
4	2766 (42.3%)	3773 (57.7%)	
5	2723 (43.1%)	3597 (56.9%)	
Has a Regular Doctor¥			
Yes	12919 (44.2%)	16335 (55.8%)	<0.0001
No	429 (20.4%)	1671 (79.6%)	
Influenza complication risk factors			
Any Risk Factor€	9390 (55.4%)	7554 (44.6%)	<0.0001
Anemia	1051 (62.0%)	645 (38.0%)	<0.0001
Arrhythmia	902 (73.6%)	324 (26.4%)	<0.0001
Asthma	2091 (45.2%)	2531 (54.8%)	<0.0001
Cancer	1580 (68.8%)	718 (31.2%)	<0.0001
Cardiovascular Disease (Arrhythmia/HTN/IHD/MI/ Stroke)	2520 (70.4%)	1060 (29.6%)	<0.0001
Chronic Kidney Disease	569 (75.6%)	184 (24.4%)	<0.0001
Congestive Heart Failure	658 (76.8%)	199 (23.2%)	<0.0001
COPD	2142 (65.0%)	1151 (35.0%)	<0.0001

Characteristics	Respondents who received influenza vaccine, no. (Row %)	Respondents who did not receive the influenza vaccine, no. (Row %)	*p*-value
Dementia	207 (78.4%)	57 (21.6%)	<0.0001
Diabetes	2640 (66.5%)	1327 (33.5%)	<0.0001
Frail	132 (75.4%)	43 (24.6%)	<0.0001
Hypertension	6580 (65.0%)	3542 (35.0%)	<0.0001
Immunocompromised	370 (75.5%)	120 (24.5%)	<0.0001
Ischemic heart disease	1643 (71.2%)	665 (28.8%)	<0.0001
Myocardial Infarction	722 (70.5%)	302 (29.5%)	<0.0001
Stroke	403 (69.4%)	178 (30.6%)	<0.0001

* Missing data on 21 respondents
§ Missing data on 73 respondents
¥ Missing data ('Don't Know') on 36 respondents
€ Anemia, Arrhythmia, Asthma, Cancer, Cardiovascular Disease (Arrhythmia/Hypertension/ Ischemic heart disease, Myocardial Infarction, Stroke), Chronic Kidney Disease, Congestive Heart Failure, COPD, Dementia, Diabetes, Frail, Hypertension, Immunocompromised, Ischemic heart disease, Myocardial Infarction, Stroke

Table 3.2 Performance measures of administrative data (Ontario Health Insurance Program + Ontario Drug Benefit Program) in identifying influenza vaccination status, using the Canadian Community Health Survey as reference standard, stratified by respondent characteristics

Characteristics	True Positive	False Positive	True Negative	False Negative	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Total (n=31,390) Total Vaccinated in CCHS= 13,358 (43%)	8034	274	17758	5324	60.1% (59.3%-61.0%)	98.5% (98.3%-98.7%)	96.7% (96.3%-97.1%)	76.9% (76.4%-77.5%)
Canadian Community Health Survey Year								
2013 (n=16,229) Total Vaccinated in CCHS= 6,625 (41%)	3795	146	9458	2830	57.3% (56.1%-58.5%)	98.5% (98.2%-98.7%)	96.3% (95.7%-96.9%)	77.0% (76.2%-77.7%)
2014 (n=15,161) Total Vaccinated in CCHS= 6,733(44%)	4239	128	8300	2494	63.0% (61.8%-64.1%)	98.5% (98.2%-98.7%)	97.1% (96.5%-97.6%)	76.9% (76.1%-77.7%)
Sex								
Female (n=17,267) Total Vaccinated in CCHS= 7,824 (45%)	4728	143	9300	3096	60.4% (59.3%-61.5%)	98.5% (98.2%-98.7%)	97.1% (96.6%-97.5%)	75.0% (74.3%-75.8%)
Male (n=14,123) Total Vaccinated in CCHS= 5,534 (39%)	3306	131	8458	2228	59.7% (58.4%-61.0%)	98.5% (98.2%-98.7%)	96.2% (95.5%-96.8%)	79.2% (78.4%-79.9%)
Age group								
12-17 (n=2,486)) Total Vaccinated in CCHS= 694 (28%)	224	31	1761	470	32.3% (28.8%-35.9%)	98.3% (97.6%-98.8%)	87.8% (83.2%-91.6%)	78.9% (77.2%-80.6%)

Characteristics	True Positive	False Positive	True Negative	False Negative	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
18-49 (n=11,405)) Total Vaccinated in CCHS= 2,595 (23%)	1121	78	8732	1474	43.2% (41.3%-45.1%)	99.1% (98.9%-99.3%)	93.5% (92.0%-94.8%)	85.6% (84.9%-86.2%)
50-64 (n=8,384)) Total Vaccinated in CCHS= 3,559 (42%)	1959	68	4757	1600	55.0% (53.4%-56.7%)	98.6% (98.2%-98.9%)	96.7% (95.8%-97.4%)	74.8% (73.7%-75.9%)
<65 (n=22,275) Total Vaccinated in CCHS= 6,848 (31%)	3304	177	15250	3544	48.3% (47.1%-49.4%)	98.9% (98.7%-99.0%)	94.9% (94.1%-95.6%)	81.1% (80.6%-81.7%)
≥65 (n=9,115) Total Vaccinated in CCHS= 6,510 (71%)	4730	97	2508	1780	72.7% (71.6%-73.7%)	96.3% (95.5%-97.0%)	98.0% (97.6%-98.4%)	58.5% (57.0%-60.0%)
Residence								
Urban area of residence (n=24,708) Total Vaccinated in CCHS= 10,503 (43%)	6435	236	13969	4068	61.3% (60.3%-62.2%)	98.3% (98.1%-98.5%)	96.5% (97.0%-96.9%)	77.5% (76.8%-78.1%)
Rural area of residence (n=6,661) Total Vaccinated in CCHS= 2,851(43%)	1598	38	3772	1253	56.1% (54.2%-57.9%)	99.0% (98.6%-99.3%)	97.7% (96.8%-98.4%)	75.1% (73.8%-76.3%)
Has a Regular Doctor								
Yes (n=29,254) Total Vaccinated in CCHS= 12,919 (44%)	7894	262	16073	5025	61.1% (60.3%-62.0%)	98.4% (98.2%-98.6%)	96.8% (96.4%-97.2%)	76.2% (75.6%-76.8%)
No (n=2,100) Total Vaccinated in CCHS= 429 (20%)	137	12	1659	292	31.9% (27.5%-36.6%)	99.3% (98.8%-99.6%)	92.0% (86.4%-95.8%)	85.0% (83.4%-86.6%)

Characteristics	True Positive	False Positive	True Negative	False Negative	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Risk factors (comorbidities) for influenza complication								
No Risk Factor (n=14,446) **Total Vaccinated in CCHS= 3,968 (27%)**	1852	107	10371	2116	46.7% (45.1%-48.2%)	99.0% (98.8%-99.2%)	94.5% (93.4%-95.5%)	83.1% (82.4%-83.7%)
Any Risk Factor (n=16,944) **Total Vaccinated in CCHS= 9,390 (55%)**	6182	167	7387	3208	65.8% (64.9%-66.8%)	97.8% (97.4%-98.1%)	97.4% (97.0%-97.8%)	69.7% (68.8%-70.6%)
Anemia (n=1,696) **Total Vaccinated in CCHS= 1,051 (62%)**	719	17	628	332	68.4% (65.5%-71.2%)	97.4% (95.8%-98.5%)	97.7% (96.3%-98.7%)	65.4% (62.3%-68.4%)
Arrhythmia (n=1,226) **Total Vaccinated in CCHS= 902 (74%)**	637	9	315	265	70.6% (67.5%-73.6%)	97.2% (94.8%-98.7%)	98.6% (97.4%-99.4%)	54.3% (50.2%-58.4%)
Asthma (n=4,622) **Total Vaccinated in CCHS= 2,091 (45%)**	1271	52	2479	820	60.8% (58.7%-62.9%)	98.0% (97.3%-98.5%)	96.1% (94.9%-97.1%)	75.1% (73.6%-76.6%)
Cancer (n=2,298) **Total Vaccinated in CCHS= 1,580 (69%)**	1112	21	697	468	70.4% (68.1%-72.6%)	97.1% (95.6%-98.2%)	98.2% (97.2%-98.9%)	59.8% (57.0%-62.7%)
Cardiovascular Disease: Arrhythmia/HTN/IHD/MI/Stroke (n=3,580) **Total Vaccinated in CCHS= 2,520 (70%)**	1761	30	1030	759	69.9% (68.1%-71.7%)	97.2% (96.0%-98.1%)	98.3% (97.6%-98.9%)	57.6% (55.3%-59.9%)
COPD (n=3,293) **Total Vaccinated in CCHS= 2,142 (65%)**	1470	27	1124	672	68.6% (66.6%-70.6%)	97.7% (96.6%-98.5%)	98.2% (97.4%-98.8%)	62.6% (60.3%-64.8%)

Characteristics	True Positive	False Positive	True Negative	False Negative	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Dementia (n=264) **Total Vaccinated in CCHS= 207 (78%)**	146	10	47	61	70.5% (63.8%-76.7%)	82.5% (70.1%-91.3%)	93.6% (88.5%-96.9%)	43.5% (34.0%-53.4%)
Hypertension (n=10,122) **Total Vaccinated in CCHS= 6,580 (65%)**	4566	99	3443	2014	69.4% (68.3%-70.5%)	97.2% (96.6%-97.7%)	97.9% (97.4%-98.3%)	63.1% (61.8%-64.4%)
Immuno-compromised (n=490) **Total Vaccinated in CCHS= 370 (76%)**	274	6	114	96	74.1% (69.3%-78.5%)	95.0% (89.4%-98.1%)	97.9% (95.4%-99.2%)	54.3% (47.3%-61.2%)
Ischemic heart disease (n=2,308) **Total Vaccinated in CCHS= 1,643 (71%)**	1147	19	646	496	69.8% (67.5%-72.0%)	97.1% (95.6%-98.3%)	98.37% (97.5%-99.0%)	56.6% (53.6%-59.5%)
Myocardial Infarction (n=1,024) **Total Vaccinated in CCHS= 722 (71%)**	510	8	294	212	70.6% (67.2%-73.9%)	97.4% (94.9%-98.9%)	98.5% (97.0%-99.3%)	58.1% (53.7%-62.4%)
Stroke (n=581) **Total Vaccinated in CCHS= 403 (69%)**	287	6	172	116	71.2% (66.5%-75.6%)	96.6% (92.8%-98.8%)	98.0% (95.6%-99.2%)	59.7% (53.8%-65.4%)

Chapter 4: Influenza vaccine effectiveness against laboratory-confirmed influenza infection among older patients hospitalized for cardiovascular events in Ontario: A Test-Negative Design Study

A version of this chapter was submitted for publication in July 2025 with the exclusion of the supplementary notes (Section 4.8).

4.1 Overview

Introduction

Older adults hospitalized for major cardiovascular events may experience reduced influenza vaccine effectiveness (VE) due to age-related changes in immune function and the use of chronic medications. This population also faces a high burden of cardiovascular disease—a leading cause of morbidity and hospitalization among older adults—often accompanied by multimorbidity, frailty, and other age-related vulnerabilities. Influenza VE among this population has not been examined, however. We therefore aimed to estimate the effectiveness of the influenza vaccine against laboratory-confirmed influenza infection among older adults hospitalized with cardiovascular conditions and examined if sex and age modified the effectiveness of the vaccine in this population.

Methods

Using linked health administrative datasets, we used a test-negative design (TND) to estimate influenza VE against laboratory-confirmed influenza infection among older adults (66 years and above) hospitalized, within three days, due to a cardiovascular event (acute myocardial infarction, unstable angina, or stroke) in Ontario, Canada during the 2010−11 to 2015−16 influenza seasons. Multivariable logistic regression models estimated the adjusted odds ratios (ORs) of vaccination among cases versus controls, adjusted for demographic and clinical covariates. VE was derived as (1 − OR) ×100%. Effect modification analysis by sex (male vs. female) and age (≤80 vs. >80 years) was conducted separately by introducing relevant interaction terms in the model.

Results

The study sample included 1,159 patients. Of those vaccinated (50% of total sample; p-value 0.01), 14% tested positive for influenza, while 20% of unvaccinated patients tested positive for influenza (p-value 0.013). Adjusted VE against laboratory-confirmed influenza infection was 43% (95% CI, 20%-60%). No effect modification was observed.

Conclusion

Influenza vaccination was associated with moderate VE in preventing influenza infection among patients hospitalized due to cardiovascular events regardless of age or sex, with an estimate similar to that in general population. Findings inform vaccination strategies and clinical decisions for high-risk older adults with cardiovascular conditions.

4.2 Introduction

Older adults, particularly those with chronic illnesses, are disproportionately affected by influenza infection due to age-related physiological changes, comorbidity, and weakened immune response (immunosenescence).[55] They also face a higher risk of influenza-related complications.[32] Aside from age, studies show that older adults with cardiovascular disease (CVD) are especially vulnerable to influenza-related adverse outcomes.[236] Vaccination is one of the most effective interventions to prevent influenza and its complications,[68] significantly reducing hospitalizations, deaths, and healthcare costs.[3] Randomized clinical trials (RCTs) have demonstrated the efficacy of influenza vaccines in preventing infection and reducing complications among the general population and high-risk groups, including older patients and those with CVD.[90,237] Systematic reviews of randomized controlled trials (RCTs) have estimated a pooled vaccine efficacy of 59% among adults aged 18–65 years[90] and 43% among community- dwelling older adults.[237] Among patients with CVD, a separate review of nine RCTs reported a 33% reduction in all-cause mortality.[238] At first glance, this may suggest the vaccine is less effective among patients with CVD; however, these figures reflect different outcomes and are not directly comparable. Specifically, the 59% and 43% estimates refer to reductions in the risk of laboratory-confirmed influenza or influenza-like illness, whereas the 33% estimate refers to a reduction in risk of all-cause mortality, a broader and more severe outcome.

Observational studies are crucial for evaluating influenza vaccine effectiveness (VE) against laboratory-confirmed influenza infection in real-world settings.[124] The Test-Negative Design (TND) has become the preferred method for estimating VE.[137] In TND studies, participants with laboratory-confirmed test results are considered cases if their tests were positive for influenza, or controls if their tests were negative.[138] This approach minimizes misclassification bias by relying solely on confirmed laboratory results.[139] The TND helps control for this bias by comparing test- positive and test-negative patients who sought care for similar symptoms. A meta-analysis of 30 TND studies between 2010 and 2015 reported a pooled VE of 41% across all influenza strains, with higher effectiveness in adults aged 18–64 (51%) compared to those aged 65 and older (37%).[68] Some observational studies have evaluated VE in high-risk populations such as patients with chronic conditions. One study assessed VE among patients with chronic obstructive pulmonary disease (COPD) and found the vaccine to be modestly effective, with a VE of 22%.[239] However, no studies have focused on patients with CVD, which may impact VE due to unique immunological and clinical characteristics. Patients with CVD often exhibit immune dysregulation[240] and heightened inflammation[241] which may reduce VE by impairing the initial immune response. In addition, medications commonly used by older adults with CVD, such as statins or antiplatelets, can interfere with immune response, altering VE.[242,243] These findings emphasize the complexity of immune response in older adults with CVD, highlighting the need for

evaluating influenza VE in this population using a robust method.

Age and sex are important determinants of influenza VE.[155,156,159,239,244–246] Examining VE among patients with CVD is important as they are at higher risk of severe complications and mortality from influenza, and infections can precipitate acute CVD events.[51] In addition, because several factors may modify the association between influenza vaccine exposure and outcomes, it is important to examine these factors to offer optimal protection to patients with higher risk. As such, the objectives of this study were to: (i) estimate influenza VE against laboratory-confirmed influenza infection among older patients hospitalized for cardiovascular conditions; and (ii) examine sex and age group as potential effect modifiers of influenza VE among older patients with cardiovascular event hospitalizations.

4.3 Methods

4.3.1 Study Design and Setting

This was a retrospective and population-based TND study among patients who were simultaneously tested for influenza and hospitalized for CVD in Ontario, Canada during six influenza seasons (2010–11 to 2015–16). The influenza season was identified as weeks during which 5% of specimens or more had tested positive for influenza. Appendix D includes the start and end dates of the studied seasons.

4.3.2 Data sources

Multiple health administrative databases for Ontario were used (Appendix A). Data were linked using unique encoded identifiers and analyzed at ICES

(linkage rate= 97.8%).[173] ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. The data sources examined included the following.

Hospitalization Data

Determination of hospitalization was identified using the Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD).[193] CIHI-DAD provides patient-level data about all inpatient hospital discharges including demographic, administrative, and clinical information.[181] Diagnoses are recorded in up to 25 fields using International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada (ICD-10-CA) for the main (first) diagnosis and other comorbidities.

Laboratory Data

Influenza testing results were obtained from the Flu and Other Respiratory Viruses Research (FOREVER) cohort database.[173] FOREVER includes data about all patients with respiratory virus testing results from the 11 Public Health Ontario laboratories and eight academic hospital-based laboratories. In Ontario during the study period, influenza and other upper respiratory viruses testing was publicly funded and primarily available to patients presenting to hospitals or healthcare providers with acute respiratory symptoms, as well as to those for whom testing was clinically indicated (e.g., severe illness, underlying conditions, or part of outbreak investigations).[64] Details of the

respiratory viral diagnostic assays (i.e., kits) used for the testing by laboratory, testing method, and influenza season are available in Appendix C.

Influenza Vaccination Data

Vaccination status was determined using billing claims from physicians or pharmacists. Physician billing was identified in Ontario Health Insurance Plan (OHIP) data while pharmacist billing records were identified using the Ontario Drug Benefit (ODB) database.

Other Data Sources

Demographic characteristics were obtained from Ontario's Registered Persons Database (age, sex), and the Canadian Census Area profile data and Postal Code Conversion File (PCCF+) during the corresponding year of index date (neighbourhood income quintile, rurality), while selected comorbidities (defined below) were identified using the National Ambulatory Care Reporting System (NACRS), the database covering emergency department visits, in addition to OHIP and CIHI-DAD.[181] The Home Care Dataset provides details on whether an individual received home care services. Home care visits is one domain that can convey the type of healthcare utilization usually required by patients who are frail but are community dwellers. Information on each individual's medication use for treatment of chronic conditions was extracted using the ODB database.

4.3.3 Study Population

This study included community-dwelling Ontario residents, aged 66 years or older, with at least one influenza test during a healthcare encounter between

influenza seasons 2010–11 and 2015– 16, with the test date designated as the index date. Patients who received an influenza vaccine less than 14 days before testing were excluded to ensure adequate time to develop an immune response to the vaccine.[247]

All patients included had experienced a cardiovascular event (acute myocardial infarction, unstable angina, or stroke) resulting in hospitalization within three days before or after the index date. Patients had to survive for at least four days post-index date, to confirm non-fatal hospitalization for at least one day. Patients were also excluded if they had a cardiovascular event hospitalization within 30 days preceding the index date to avoid any association of a previous cardiovascular event with the current event of interest. To maintain the independence of observations for logistic regression analysis, each patient was included only once in the study, based on the earliest season and their first influenza-positive test result requiring healthcare. This approach avoided inter- and intra-person dependence across seasons.

4.3.4 Measures

Exposure: independent variable

The exposure of interest was seasonal influenza vaccination status as determined by a physician or pharmacy billing claim. For the purpose of this study, the term “influenza vaccine” (or “the influenza vaccine”) is used broadly to refer to all types of influenza vaccines available to Ontario patients within the publicly funded vaccines during the study period, rather than a specific formulation. Fee/billing codes used are provided in Appendix H. A

previous study has shown this approach to be moderately sensitive (sensitivity 60.1%) and highly specific (98.5%) for assessing influenza vaccination status.[248]

Outcome: dependent variable

The dependent variable was the laboratory-confirmed influenza infection test result. Cases were those testing positive for influenza virus, while those who tested negative for the influenza virus were considered as controls.

Covariates

Following previous research,[249,250] the following baseline characteristics were examined as potential confounders: sociodemographic factors, healthcare utilization, comorbidity, medication use, and frailty. Sociodemographic measures at the time of index included age (categorized as 66–75, 76–85, and ≥86 years), sex (male/female), rural residence (defined as communities with <10,000 residents; yes/no), and neighbourhood median household income quintile (at the census Dissemination Area level[1]).[251] Healthcare utilization variables, relative to index date, included number of outpatient visits in the past year, number of hospitalizations in the past three years, and receipt of home care services (as a measure of disability) in the past year. Comorbidities were selected based on the National Advisory Committee for Immunization (NACI) list of high-risk chronic conditions for influenza-related complications.[3] Included comorbidities were cancer,[206] asthma,[216] ischemic

[1] A dissemination area is the smallest standard geographic area for which all census data are disseminated.

heart disease,[252] COPD,[211] anemia, chronic kidney disease,[210] and diabetes.[212] Details on the identification of comorbidities are provided in Appendix E. Based on established methods at ICES, the lookback window for comorbidities depended on the comorbidity and data source. Use of antiplatelets, β-blockers, diuretics, and statins during the year prior to the index date was also captured (Appendix B). Frailty was assessed using a binary measure criteria established by ICES, where the lookback for frailty was one year before index date (Appendix F).[126]

To control for antigenic drifts and shifts in dominant circulating influenza viruses across seasons we adjusted for year of index date and to control for within-season variation we adjusted for index date relative to the peak month of each season. Peak month was a binary variable indicating whether the index date was during or outside the peak month of the season (Appendix D).

4.3.5 Analysis

Baseline characteristics of the sample were summarized based on exposure (vaccination status) and outcome (influenza testing results). Bivariate analyses examined patient characteristics (categorical variables) by study exposure and outcome measures with chi-square (χ^2) tests. A multivariable logistic regression model was used to evaluate the association between influenza vaccination and laboratory-confirmed influenza and estimate the odds ratios. The model was built using the forward selection method. Variables were retained in the final model if they were significant in bivariate analyses, increased the fit of the model as assessed by the Akaike Information Criterion

(AIC), or both. Age, sex, and influenza season were placed in the model regardless of statistical significance. VE was derived as (1−OR) ×100%. Multicollinearity among categorical covariates retained in the model was tested using Spearman's rank correlation coefficient, which is suitable for detecting non-linear associations among binary and multi-level ordinal variables. The cut-off for correlation was explored and set at 0.7.[253]

4.3.5a Assessment of effect modification

We checked for effect modification by patient age and sex (i.e., characteristics that could influence the degree of vaccine immunogenicity).[160,169] In this analysis, logistic regression

modeling was similar to that used for the main model but with the introduction of an interaction term between the exposure (vaccination status) and age or sex. Each interaction term was tested separately for significance in the same model to estimate the VE for males or females and for patients aged ≤80 or >80 years. Subgroup-specific estimates were obtained from interaction models using the full sample rather than stratified analyses.

4.3.5b Sensitivity analysis

Two sensitivity analyses were conducted: (i) redefining the hospitalization time window to 0–2 days from the index date; and (ii) excluding patients tested for influenza more than 48 hours after admission to rule out nosocomial infections.[254] The *p*-value for statistical significance was <0.05. Analysis was performed using SAS® 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

Ethics clearance for this study was obtained from the Office of Research Ethics at the University of Waterloo (CREB: IRB00007409).

This was a retrospective and population-based TND study among patients who were simultaneously tested for influenza and hospitalized for CVD in Ontario, Canada during six influenza seasons (2010–11 to 2015–16). The influenza season is generally identified as including all weeks when 5% or more of specimens test positive for influenza. Appendix D includes the start and end dates of the studied seasons.

4.4 Results

4.4.1 Study Sample

We included a total of 1,159 older patients tested for influenza and hospitalized for a major CVD event within three days of being tested. There were 17.1% of patients testing positive for influenza (198/1159; Table 4.1). From the whole sample, there were 579 vaccinated patients (50.0%). Of those who tested positive for influenza, 41.9% were vaccinated for influenza, compared with 51.6% among patients who tested negative (p-value=0.01). Except for certain medication use such as diuretics or beta-blockers, influenza season, and testing relative to peak month, there were no other statistically significant differences between test-positive and test- negative patients. Test positivity was relatively higher during seasons 2012–13 and 2014–15 (p-value = 0.0003).

Table 4.2 illustrates the characteristics of the study sample according to their

exposure (vaccination status). The influenza test positivity differed significantly between vaccinated (14.3%, 83/579) and unvaccinated patients (19.8%, 115/580) (p-value=0.01). There were no significant differences between vaccinated and unvaccinated patients in relation to sex, age group, rural residence, number of previous hospitalizations, home care use in the past year, or influenza complication risk factors. However, relative to vaccinated patients, unvaccinated patients were more likely to have 0–6 outpatient visits in the previous year (p-value < 0.01), belong to the lowest neighbourhood income quintile (p-value = 0.02), and have lower use of all studied cardiovascular medications (p-values < 0.05).

4.4.2 Measurement of VE

Ten covariates were retained in the final logistic regression model: neighbourhood income quintile, rurality, number of outpatient visits, beta-blocker use, statin use, receiving home care services, and influenza testing relative to the peak month of the season, in addition to sex, age group, and year of influenza season. Diuretic use was highly correlated with beta-blocker use, and thus only the latter was retained in the model. Although sex, age group, rurality, peak, season, home care services use, neighbourhood income quintile, and number of outpatient visits were not statistically significant confounders in bivariate analyses, they were retained in the multivariable models as their inclusion improved overall fit of the model. No significant correlations were observed among the covariates.

The crude model showed that the influenza VE was 32% (95% CI, 8–50%).

After adjusting for the aforementioned confounders, the adjusted VE increased to 43% (95% CI, 20–60%). Table 4.3 illustrates the estimated odds ratios (OR) of vaccination among cases (tested positive for influenza) vs. controls (tested negative).

4.4.3 Effect Modification Assessment

The interaction terms for sex and age showed no statistically significant interaction for either variable (p-values 0.33 and 0.42; Table 4.4), indicating that neither sex nor age alone significantly altered VE in this model. However, the point estimates suggested a trend toward higher VE among females and individuals older than 80 years, warranting further exploration.

4.4.4 Sensitivity Analysis

When the time window for hospitalization was changed to hospitalization within zero, one and two days of index date, the VE did not substantially change (Appendix J). The VEs ranged from 40% for those hospitalized on the same day of testing (Day 0) to 47% for those tested within one day of hospitalization. The VE was 45% after excluding influenza tests carried out after 48 hours of hospitalization.

4.5 Discussion

This retrospective, population-based study employed the TND design to estimate influenza VE against laboratory-confirmed influenza infection among 1,159 older adults with CVD hospitalizations during six influenza seasons (2010–11 to 2015–16). Approximately half of the study cohort was vaccinated.

Among them, only 14% of those vaccinated tested positive for influenza compared to 20% among unvaccinated patients. The estimated crude and adjusted influenza VE against laboratory-confirmed influenza infection over the study period was 32% (95% CI, 8–50%) and 43% (95% CI, 20–60%), respectively. Neither sex nor age significantly modified of VE estimates. Sensitivity analyses supported the robustness of these findings.

We believe this is the first study estimating VE among patients hospitalized with a CVD event using the TND design. Our results indicate that being hospitalized for CVD while undergoing influenza testing during a medical encounter neither potentiates nor attenuates VE, as the vaccine still provides comparable protection to these patients. Our study followed robust methods and should reassure clinicians and policy makers about influenza VE among patients with CVD hospitalization.

It is concerning that our study found the vaccination rate among patients hospitalized for CVD events was only around 50%. A previous study estimated the vaccination annual uptake among people with a history of CVD in Canada to be 58.9%.[250] This is noticeably lower than the recommendation of 80% by NACI.[255] Vaccination, in spite of being a relatively low-cost and effective intervention, is still underutilized. In Ontario, influenza vaccines are publicly funded and available at no cost to eligible individuals, suggesting that factors beyond affordability—such as trust, awareness, and accessibility—may be contributing to low uptake. Lessons from vaccination campaigns during the COVID-19 pandemic era should provide insights about enhancing influenza

vaccine uptake among high-risk patients including patients with a history of cardiovascular events.[256] Strategies should focus on building a trusting and constructive relationship with patients through tailored communication and the multifaceted implementation of vaccination campaigns. This is expected to contribute significantly to the reduction of cardiovascular disease burden in Canada.[257]

The findings regarding sex as a potential effect modifier, although statistically non-significant in this study, may be considered consistent with the results of previous studies, at least in terms of the point estimate.[159,258] Chambers et al. found higher influenza VE among 7,319 females compared with 4,959 males, with an absolute difference of 11% (49% for females vs. 38% for males, *p*-value=0.03), when examining the same influenza seasons (2010–11 to 2015–16) as our study.[159] While the observed differences were not statistically significant, some patterns warrant cautious interpretation. Males testing positive for influenza may have been at higher baseline risk for cardiovascular hospitalization, potentially attenuating observed VE. Conversely, females, who were older in our cohort, may have experienced greater immunogenicity in response to the vaccine, possibly due to sex-related hormonal differences that modulate immune response.[258]

Similarly, we observed a trend toward higher VE among patients aged >80 years compared to those ≤80 years, despite the expected pattern of lower VE in older adults. This may reflect healthy user or survival bias, where older vaccinated individuals hospitalized with CVD may be healthier overall.[259]

While speculative, these findings may help inform strategies to reduce clinical inertia around influenza vaccination, particularly in older adults under 80 years of age.

We studied influenza VE among the older population hospitalized for a CVD event in Ontario (the most populous province in Canada) using a robust design over several influenza seasons. However, several limitations should be noted. First, assumptions of the TND method such as equal exposure to influenza virus,[139] equal healthcare access, uniform vaccine accessibility, and similar specificity and sensitivity results of the test cannot be confirmed. However, it is reasonable to make such assumptions in the context of Ontario's universal health care system.

Second, we restricted the sample to patients tested within three days of hospital admission for a major CVD event as the most responsible diagnosis, excluding chronic cardiopulmonary conditions. However, when this time window was changed, VE did not change substantially and ranged between 40% and 47%. A third limitation of the TND is the variability in physicians' decisions regarding influenza testing and its timing, coupled with uncertainties in the onset of symptoms and the timing of cardiovascular events. Lastly, vaccination uptake rates were likely an underestimation as people vaccinated outside physician offices and pharmacies were not captured and were thus classified as unvaccinated. However, 70% of adults in Canada report receiving influenza vaccines at pharmacies or physician offices.[111] The impact of this misclassification is likely non-differential.

4.6 Conclusion

In this study we estimated VE of influenza vaccines against laboratory-confirmed influenza infection among older adults with CVD hospitalizations, using a robust design. The results showed that VE in this high-risk population is comparable to the general population, reassuring clinicians and policymakers of the benefits of influenza vaccination in this population. Our study also demonstrates the feasibility of using a TND method for measuring other influenza-related outcomes among high-risk populations.

4.7 Tables and Figure

Table 4.1. Descriptive characteristics of influenza test-positive and influenza test-negative patients with cardiovascular-related hospitalization, 2010–2016

Characteristics	Test-Positive Patients, n=198 (Column %)	Test-Negative Patients, n=961 (Column %)	Total (% of 1159)	*P* value
Vaccinated	83 (41.9%)	496 (51.6%)	579 (50.0%)	0.01
Sex (M)	112 (56.6%)	524 (54.5%)	636 (54.9%)	0.60
Age group				
66–75 y	66 (33.3%)	326 (33.9%)	392 (33.8%)	0.39
76–85 y	71 (35.9%)	382 (39.8%)	453 (39.1%)	
86+ y	61 (30.8%)	253 (26.3%)	314 (27.1%)	
Rural residence	17 (8.6%)	84 (8.7%)	101 (8.7%)	0.94
Neighbourhood income quintile				
1 (least affluent)	50 (25.3%)	246 (25.6%)	296 (25.5%)	0.76
2	44 (22.2%)	218 (22.7%)	262 (22.6%)	
3	41 (20.7%)	196 (20.4%)	237 (20.4%)	
4	33 (16.7%)	130 (13.5%)	163 (14.1%)	
5	30 (15.2%)	171 (17.8%)	201 (17.3%)	
Number of outpatient visits in the past year				
0–6	61 (30.8%)	310 (32.3%)	371 (32.0%)	0.85
7–14	67 (33.8%)	331 (34.4%)	398 (34.3%)	
15+	70 (35.4%)	320 (33.3%)	390 (33.6%)	
Number of hospitalizations in the past 3 years				
Never	92 (46.5%)	452 (47.0%)	544 (46.9%)	0.95
Once	51 (25.8%)	237 (24.7%)	288 (24.8%)	
More than once	55 (27.8%)	272 (28.3%)	327 (28.2%)	
Received homecare in past year	83 (41.9%)	371 (38.6%)	454 (39.2%)	0.38
Influenza complication risk factors				
Cancer	42 (21.2%)	220 (22.9%)	262 (22.6%)	0.61
Asthma	51 (25.8%)	204 (21.2%)	255 (22.0%)	0.16
Ischemic Heart Disease	92 (46.5%)	423 (44.0%)	515 (44.4%)	0.53
COPD	88 (44.4%)	425 (44.2%)	513 (44.3%)	0.95
Anemia	37 (18.7%)	198 (20.6%)	235 (20.3%)	0.54
Chronic Kidney Disease	49 (24.7%)	206 (21.4%)	255 (22.0%)	0.31
Diabetes	99 (50.0%)	482 (50.2%)	581 (50.1%)	0.97
Medication use				

Characteristics	Test-Positive Patients, n=198 (Column %)	Test-Negative Patients, n=961 (Column %)	Total (% of 1159)	*P* value
Antiplatelet medication use	55 (27.8%)	215 (22.4%)	270 (23.3%)	0.10
β-Blocker medication use	116 (58.6%)	453 (47.1%)	569 (49.1%)	0.003
Diuretic medication use	106 (53.5%)	430 (44.7%)	536 (46.2%)	0.024
Statin medication use	140 (70.7%)	619 (64.4%)	759 (65.5%)	0.09
Influenza season				
2010–11	20 (10.1%)	133 (13.8%)	153 (13.2%)	0.0003
2011–12	9 (4.6%)	68 (7.1%)	77 (6.6%)	
2012–13	46 (23.2%)	183 (19.0%)	229 (19.8%)	
2013–14	22 (11.1%)	211 (22.0%)	233 (20.1%)	
2014–15	72 (36.4%)	235 (24.5%)	307 (26.5%)	
2015–16	29 (14.7%)	131 (13.6%)	160 (13.8%)	
Influenza testing relative to peak month				
During Peak	82 (41.4%)	206 (21.4%)	288 (24.9%)	<.0001

Table 4.2. Descriptive characteristics of vaccinated and unvaccinated patients with cardiovascular-related hospitalization, 2010-2016

Characteristics	Vaccinated n=579 (Column %)	Unvaccinated n=580 (Column %)	Total (% of 1159)	*P* value
Tested positive for influenza	83 (14.3%)	115 (19.8%)	198 (17.1%)	0.013
Sex (M)	327 (56.5%)	309 (53.3%)	636 (54.9%)	0.27
Age group				
66-75 y	180 (31.1%)	212 (36.6%)	392 (33.8%)	0.11
76-85 y	241 (41.6%)	212 (36.6%)	453 (39.1%)	
86+ y	158 (27.3%)	156 (26.9%)	314 (27.1%)	
Rural residence	51 (8.8%)	50 (8.6%)	101 (8.7%)	0.91
Neighbourhood income quintile				
1 (least affluent)	140 (24.2%)	156 (26.9%)	296 (25.5%)	0.02
2	145 (25.0%)	117 (20.2%)	262 (22.6%)	
3	114 (19.7%)	123 (21.2%)	237 (20.4%)	
4	68 (11.7%)	95 (16.4%)	163 (14.1%)	
5	112 (19.3%)	89 (15.3%)	201 (17.3%)	
Number of outpatient visits in the past year				
0–6	117 (20.2%)	254 (43.8%)	371 (32.0%)	<.0001
7–14	237 (40.9%)	161 (27.8%)	398 (34.3%)	
15+	225 (38.9%)	165 (28.4%)	390 (33.6%)	
Number of hospitalizations in the past 3 years				
Never	286 (49.4%)	258 (44.5%)	544 (46.9%)	0.24
Once	136 (23.5%)	152 (26.2%)	288 (24.8%)	
More than once	157 (27.1%)	170 (29.3%)	327 (28.2%)	
Received homecare in past year	217 (37.5%)	237 (40.9%)	454 (39.2%)	0.24
Influenza complication risk factors				
Cancer	134 (23.1%)	128 (22.1%)	262 (22.6%)	0.66
Asthma	129 (22.3%)	126 (21.7%)	255 (22.0%)	0.82
Ischemic Heart Disease	266 (45.9%)	249 (42.9%)	515 (44.4%)	0.30
COPD	246 (42.5%)	267 (46.0%)	513 (44.3%)	0.22
Anemia	114 (19.7%)	121 (20.9%)	235 (20.3%)	0.62
Chronic Kidney Disease	130 (22.5%)	125 (21.6%)	255 (22.0%)	0.71
Diabetes	297 (51.3%)	284 (49.0%)	581 (50.1%)	0.43
Medication use				
Antiplatelet medication use	149 (25.7%)	121 (20.9%)	270 (23.3%)	0.05
β-Blocker medication use	316 (54.6%)	253 (43.6%)	569 (49.1%)	0.0002
Diuretic medication use	286 (49.4%)	250 (43.1%)	536 (46.2%)	0.032
Statin medication use	416 (71.8%)	343 (59.1%)	759 (65.5%)	<.0001

Characteristics	Vaccinated n=579 (Column %)	Unvaccinated n=580 (Column %)	Total (% of 1159)	*P* value
Influenza season				
2010–2011	71 (12.3%)	82 (14.1%)	153 (13.2%)	0.41
2011–2012	40 (6.9%)	37 (6.4%)	77 (6.6%)	
2012–2013	111 (19.2%)	118 (20.3%)	229 (19.8%)	
2013–2014	110 (19.0%)	123 (21.1%)	233 (20.1%)	
2014–2015	169 (29.2%)	138 (23.8%)	307 (26.5%)	
2015–2016	78 (13.5%)	82 (14.1%)	160 (13.8%)	
Influenza testing relative to peak month				
During Peak	148 (25.6%)	140 (24.1%)	288 (24.8%)	0.58

Table 4.3. Influenza vaccine effectiveness against laboratory-confirmed influenza among CVD-related hospitalization 2010-2016

Analysis	Odds Ratios	95% Confidence Interval		Vaccine Effectiveness	95% Confidence Interval		p-Value
		Lower	Upper		Lower	Upper	
Crude model: vaccinated	0.677	0.497	0.922	32%	8%	50%	0.01
Adjusted model: vaccinated	0.568	0.404	0.797	43%	20%	60%	0.001

Model adjusted for sex, age group, neighbourhood income quintile, rurality, number of outpatient visits, beta-blocker medication use, statin medication use, use of home care services, and influenza testing relative to the peak month of the season, and year of influenza season.

Table 4.4. Adjusted model output of influenza vaccine effectiveness against laboratory- confirmed influenza among CVD-related hospitalization 2010-2016 (n=1159) by interaction terms

Interaction Terms		Model Output						
Analysis: Vaccinated 1 vs 0		OR	95% Confidence Interval		Vaccine Effectiveness	95% Confidence Interval		p-Value
			Lower	Upper		Lower	Upper	
Full adjusted model		0.568	0.404	0.797	43%	20%	60%	0.001
Vaccinated* Sex	Full model with interaction terms							0.33
	Males[1]	0.651	0.420	1.010	35%	-1%	58%	0.06
	Females[1]	0.472	0.284	0.785	53%	22%	72%	0.004
Vaccinated* Age group	Full model with interaction terms							0.42
	Age =<80 y[1]	0.649	0.407	1.036	35%	-4%	59%	0.07
	Age >80 y[1]	0.497	0.312	0.792	50%	21%	69%	0.003

[1] Subgroup-specific estimates were obtained from interaction models using the full sample rather than stratified analyses.

4.8 Supplementary Notes: Assessment of effect modification

Effect measure modification was also analyzed through stratification, with the results presented in the supplementary notes of this chapter. The assessment of effect measure modification by stratification was carried out by creating two sets of strata; a set by sex and a set by age group.

4.8.1 Assessment of effect modification by stratification

Methods

First, for each stratum, defined by sex and by age group, the descriptive statistics by exposure to vaccination were compared by chi-square tests. The data were stratified by each potential effect modifier separately and stratum-specific logistic regression models were conducted using the same variables of the main model minus the stratification variable. Stratified analysis yielded separate measures of effect (ORs) for vaccination among cases versus controls in each stratum (stratum-specific). I then derived stratum specific VEs and performed visual comparison of point estimates (VEs) and their corresponding 95%CI, across strata.

4.8.2 Results by Stratification

4.8.2.1 Study Samples per stratum

This study included 1,159 patients who were 66 years or older, tested for influenza within three days of hospitalization due to a cardiovascular event. There were 523 (45.1%) individuals who were female and 636 (54.9%) individuals who were male and 597 (51.5%) and 562 (48.5%) who were aged ≤80 and >80, respectively.

4.8.2.2 Descriptive Analyses of stratification

Because the study participants were stratified according to two variables, two descriptive tables by vaccination status (exposure) and by influenza testing results (outcome) were produced based on the characteristics corresponding to each stratum for a total of four tables. *P*-values are illustrated for within each stratum.

Within the sex stratified analysis, the overall proportion testing positive for influenza was higher among males (17.6%) versus females (16.4%) (Table 4.8.1). The proportion testing positive among vaccinated patients was lower among females than among males (12.3% versus 15.9% respectively; Table 4.8.1). Relative to males, females were older (32.1% aged 86+ versus 23.0% in the males group), had a lower proportion living in rural areas (7.3% versus 9.9%), a higher proportion with low socioeconomic status (27.5% versus 23.9%), and a higher proportion receiving home care (44.4% versus 34.9%) (Table 4.8.1). Males compared to females were more likely to test positive across the relatively older age groups (76-85 and 86+) (Table 4.8.2). Among those with diabetes, males were more likely to test positive than females (56.3% vs. 41.9%; Table 4.8.2).

The proportion testing positive among those older than 80 years was higher (18.5%) compared to those 80 years or younger (15.7%) (Table 4.8.3). The most common influenza complication risk factor across both age groups was diabetes (Table 4.8.3). Compared to those older than 80 years, vaccinated

patients 80 years old or younger had a higher proportion testing positive for influenza, despite being vaccinated (42.6% vs. 41.3%; respectively) (Table 4.8.4).

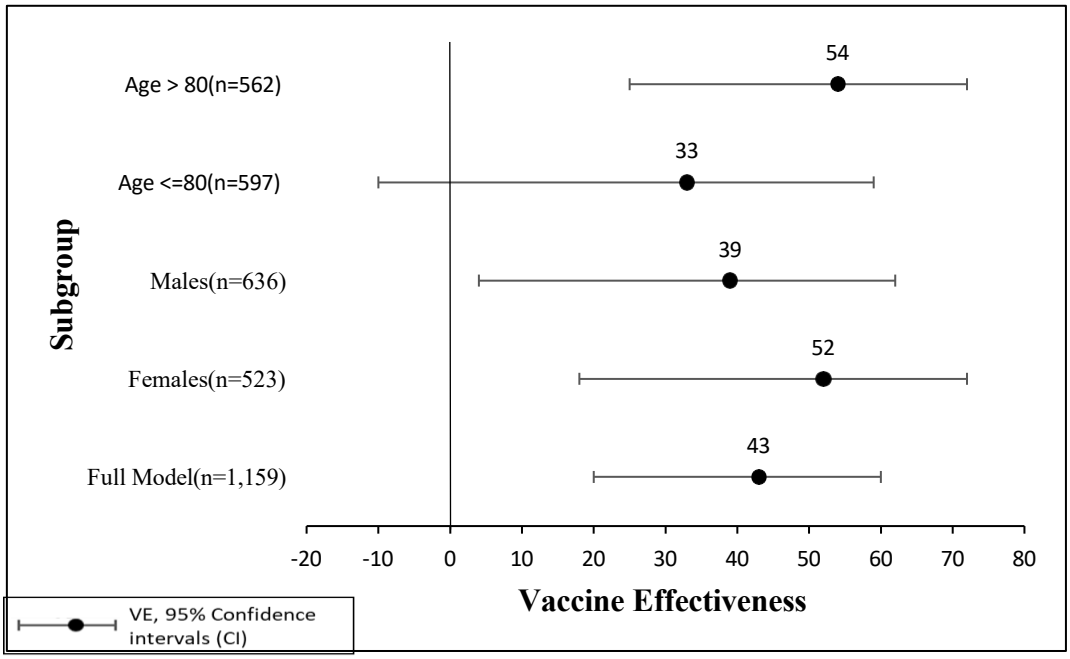
Supplemental tables that compare characteristics of females vs. males, and younger vs. older, with chi-square (χ^2) results are available in Table 4.8.6.

4.8.2.3 Results for model building by stratification

Full model outputs were produced for each subgroup of the two comparing strata, resulting in four different model outputs (Table 4.8.5).

The overall VE of the full adjusted model will be discussed here for comparison. Figure 4.8.1 illustrates the four adjusted model outputs for VE corresponding to each stratum. Table 4.8.5 illustrates in detail the adjusted model output ORs and derived VE including their corresponding *p*-values and 95% confidence intervals. The stratified analysis showed higher VE for females, and those aged ≤ 80 compared to males and those aged > 80 respectively. The larger difference in VE among the corresponding subgroups was between the two age groups: percentage point difference of 21% in influenza VE. The smaller difference was among the sex subgroup of females and males; the percentage point difference was 13%. Strata with overlapping 95%CI with 0% were statistically non-significant. Therefore, although being male or in the 80 or younger strata were showing lower VE than their counterparts, these findings were statistically non-significant.

Figure 4.8.1 Adjusted Model Outputs of VE against laboratory-confirmed influenza among cardiovascular-related hospitalization 2010-2016 by stratification



4.8.3 Discussion

This study aimed to examine if sex or age group play a role of effect measure modification in influenza VE against laboratory-confirmed influenza infection among older patients hospitalized for a cardiovascular event. Linked laboratory and health administrative databases in Ontario were the data sources. The TND with stratified analysis and logistic regression models were used to analyse the data. Results illustrate that influenza VE may differ by sex or age group using stratification. Females (VE, 52%; *p*-value= 0.0067), and those aged above 80 years (VE, 54; *p*-value=0.0018), recorded higher VE in comparison to their counterparts; males (VE, 39%; *p*-value=0.0334) or 80 years or younger (VE, 33%; *p*-value=0.1105). This was mostly shown in the

stratified analysis rather than in testing for interactions, thus suggesting biological differences across strata. It should be noted that the negative estimates of the lower 95% confidence intervals in VE are due to the intervals being wide perhaps because of relatively small cell sizes in some cases and variation in the population.

Nevertheless, the exploration of effect modification, demonstrated in this study, underscores the importance of such studies in generating hypotheses for future research to investigate causal mechanisms for explaining VE variations among subgroups.

4.8.4 Conclusion

This work tested age and sex for effect modification by stratification to investigate and better understand the modifying roles these suggested variables may be playing on VE against laboratory-confirmed influenza infection among older adults hospitalized due to a cardiovascular event. Females or older adults (>80) seem to derive higher VE in comparison to their counterparts. These findings may suggest a level of comparison; however, it is unclear if they provide impactful recommendations to clinicians and policy makers for increasing vaccination in groups at a lower advantage from the influenza vaccine given there exists limitations with the study's findings, rendering the overall findings as statistically non- significant. Perhaps vulnerable groups can be most at risk from the influenza virus as this virus can be causing a significant burden unto those most at risk of experiencing a cardiovascular hospitalization with certain characteristics. However, these

findings require further research to conclusively investigate interactions to further support clinicians in identifying patients who may be experiencing lower effectiveness from the influenza vaccine compared to their counterparts and possibly identify further measures for influenza prevention.

4.8 Supplementary Tables

Table 4.8.1 Females vs. Males: descriptive characteristics of vaccinated and unvaccinated patients with cardiovascular -related hospitalization 2010-2016

Females					Males				
Characteristics	**Vaccinated (n=252) (Column %)**	**Unvaccinated (n=271) (Column %)**	**Total N=523**	***P* Value (Females Stratum)**	**Characteristics**	**Vaccinated (n=327) (Column %)**	**Unvaccinated (n=309) (Column %)**	**Total N=636**	***P* Value (Males Stratum)**
Tested Positive for Influenza	31 (12.3%)	55 (20.3%)	86 (16.4%)	0.0137	**Tested Positive for Influenza**	52 (15.9%)	60 (19.4%)	112 (17.6%)	0.2447
Age group					**Age group**				
66-75 y	75 (29.8%)	87 (32.1%)	162 (31.0%)	0.4446	66-75 y	105 (32.1%)	125 (40.5%)	230 (36.2%)	0.0885
76-85 y	100 (39.7%)	93 (34.3%)	193 (36.9%)		76-85 y	141 (43.1%)	119 (38.5%)	260 (40.9%)	
86+ y	77 (30.6%)	91 (33.6%)	168 (32.1%)		86+ y	81 (24.8%)	65 (21.0%)	146 (23.0%)	
Rural Residence	20 (7.9%)	18 (6.6%)	38 (7.3%)	0.5688	**Rural Residence**	31 (9.5%)	32 (10.4%)	63 (9.9%)	0.7117
Neighbourhood income quintile					**Neighbourhood income quintile**				
1 (least affluent)	68 (27.0%)	76 (28.0%)	144 (27.5%)	0.1659	1 (least affluent)	72 (22.0%)	80 (25.9%)	152 (23.9%)	0.0382
2	54 (21.4%)	57 (21.0%)	111 (21.2%)		2	91 (27.8%)	60 (19.4%)	151 (23.7%)	
3	40 (15.9%)	55 (20.3%)	95 (18.2%)		3	74 (22.6%)	68 (22.0%)	142 (22.3%)	
4	32 (12.7%)	42 (15.5%)	74 (14.1%)		4	36 (11.0%)	53 (17.2%)	89 (14.0%)	
5	58 (23.0%)	41 (15.1%)	99 (18.9%)		5	54 (16.5%)	48 (15.5%)	102 (16.0%)	
Number of outpatient visits in the past year					**Number of outpatient visits in the past year**				

Females					Males				
Characteristics	**Vaccinated (n=252) (Column %)**	**Unvaccinated (n=271) (Column %)**	**Total N=523**	***P* Value (Females Stratum)**	**Characteristics**	**Vaccinated (n=327) (Column %)**	**Unvaccinated (n=309) (Column %)**	**Total N=636**	***P* Value (Males Stratum)**
0-6	52 (20.6%)	120 (44.3%)	172 (32.9%)	<.0001	0-6	65 (19.9%)	134 (43.4%	199 (31.3%)	<.0001
7-14	106 (42.1%)	76 (28.0%)	182 (34.8%)		7-15	142 (43.4%)	91 (29.4%)	233 (36.6%)	
15+	94 (37.3%)	75 (27.7%)	169 (32.3%)		16+	120 (36.7%)	84 (27.2%)	204 (32.1%)	
Number of hospitalizations in the past 3 years					**Number of hospitalizations in the past 3 years**				
Never	115 (45.6%)	114 (42.1%)	229 (43.8%)	0.6774	Never	171 (52.3%)	144 (46.6%)	315 (49.5%)	0.3571
Once	62 (24.6%)	74 (27.3%)	136 (26.0%)		Once	74 (22.6%	78 (25.2%)	152 (23.9%)	
More than once	75 (29.8%)	83 (30.6%)	158 (30.2%)		More than once	82 (25.1%)	87 (28.2%)	169 (26.6%)	
Received homecare in past year	105 (41.7%)	127 (46.9%)	232 (44.4%)	0.232	**Received homecare in past year**	112 (34.3%)	110 (35.6%)	222 (34.9%)	0.7215
Influenza complication risk factors					**Influenza complication risk factors**				
Cancer	51 (20.2%)	50 (18.5%)	101 (19.3%)	0.6048	Cancer	83 (25.4%)	78 (25.2%)	161 (25.3%)	0.9677
Asthma	78 (31.0%)	70 (25.8%)	148 (28.3%)	0.1938	Asthma	51 (15.6%)	56 (18.1%)	107 (16.8%)	0.3946
Ischemic Heart Disease	99 (39.3%)	102 (37.6%)	201 (38.4%)	0.6988	Ischemic Heart Disease	167 (51.1%)	147 (47.6%)	314 (49.4%)	0.3779
COPD	106 (42.1%)	128 (47.2%)	234 (44.7%)	0.2349	COPD	140 (42.8%)	139 (45.0%)	279 (43.9%)	0.5814
Anemia	45 (17.9%)	59 (21.8%)	104 (19.9%)	0.2625	Anemia	69 (21.1%)	62 (20.1%)	131 (20.6%)	0.7467
Chronic Kidney Disease	49 (19.4%)	47 (17.3%)	96 (18.4%)	0.5351	Chronic Kidney Disease	81 (24.8%)	78 (25.2%)	159 (25.0%)	0.8907

Females					Males				
Characteristics	**Vaccinated (n=252) (Column %)**	**Unvaccinated (n=271) (Column %)**	**Total N=523**	***P* Value (Females Stratum)**	**Characteristics**	**Vaccinated (n=327) (Column %)**	**Unvaccinated (n=309) (Column %)**	**Total N=636**	***P* Value (Males Stratum)**
Diabetes	123 (48.8%)	116 (42.8%)	239 (45.7%)	0.1684	Diabetes	174 (53.2%)	168 (54.4%)	342 (53.8%)	0.7697
Medication Use					**Medication Use**				
Antiplatelet medication use	64 (25.4%)	55 (20.3%)	119 (22.8%)	0.1644	Antiplatelet medication use	85 (26.0%)	66 (21.4%)	151 (23.7%)	0.1698
β-Blocker medication use	134 (53.2%)	109 (40.2%)	243 (46.5%)	0.003	β-Blocker medication use	182 (55.7%)	144 (46.6%)	326 (51.3%)	0.0224
Diuretic medication use	131 (52.0%)	125 (46.1%)	256 (48.9%)	0.1805	Diuretic medication use	155 (47.4%)	125 (40.5%)	280 (44.0%)	0.0777
Statin medication use	164 (65.1%)	146 (53.9%)	310 (59.3%)	0.0092	Statin medication use	252 (77.1%)	197 (63.8%)	449 (70.6%)	0.0002
Influenza testing relative to peak month					**Influenza testing relative to peak month**				
During Peak	63 (25.0%)	66 (24.4%)	129 (24.7%)	0.8641	During Peak	85 (26.0%)	74 (24.0%)	159 (25.0%)	0.5515

Table 4.8.2 Females vs. Males: descriptive characteristics of influenza test-positive and influenza test-negative patients with cardiovascular-related hospitalization 2010-2016

Females					Males				
Characteristics	**Test-Positive Patients (n=86) (Column %)**	**Test-Negative Patients (n=437) (Column %)**	**Total N=523 (%)**	***P* Value (Females Stratum)**	**Characteristics**	**Test-Positive Patients (n=112) (Column %)**	**Test-Negative Patients (n=524) (Column %)**	**Total N=636 (%)**	***P* Value (Males Stratum)**
Vaccinated against influenza	31 (36.0%)	221 (50.6%)	252 (48.2%)	0.0137	**Vaccinated (influenza)**	52 (46.4%)	275 (52.5%)	327 (51.4%)	0.2447
Age group					**Age group**				
66-75 y	30 (34.9%)	132 (30.2%)	162 (31.0%)	0.6922	66-75 y	36 (32.1%)	194 (37.0%)	230 (36.2%)	0.0711
76-85 y	30 (34.9%)	163 (37.3%)	193 (36.9%)		76-85 y	41 (36.6%)	219 (41.8%)	260 (40.9%)	
86+ y	26 (30.2%)	142 (32.5%)	168 (32.1%)		86+ y	35 (31.3%)	111 (21.2%)	146 (23.0%)	
Rural Residence	8 (9.3%)	30 (6.9%)	38 (7.3%)	0.4261	**Rural Residence**	9 (8.0%)	54 (10.3%)	63 (9.9%)	0.4655
Neighbourhood income quintile					**Neighbourhood income quintile**				
1 (least affluent)	25 (29.1%)	119 (27.2%)	144 (27.5%)	0.613	1 (least affluent)	25 (22.3%)	127 (24.2%)	152 (23.9%)	0.848
2	20 (23.3%)	91 (20.8%)	111 (21.2%)		2	24 (21.4%)	127 (24.2%)	151 (23.7%)	
3	16 (18.6%)	79 (18.1%)	95 (18.2%)		3	25 (22.3%)	117 (22.3%)	142 (22.3%)	
4	14 (16.3%)	60 (13.7%)	74 (14.1%)		4	19 (17.0%)	70 (13.4%)	89 (14.0%)	
5	11 (12.8%)	88 (20.1%)	99 (18.9%)		5	19 (17.0%)	83 (15.8%)	102 (16.0%)	
Number of outpatient visits in the past year					**Number of outpatient visits in the past year**				
0-6	28 (32.6%)	144 (33.0%)	172 (32.9%)	0.8343	0-6	33 (29.5%)	166 (31.7%)	199 (31.3%)	0.8048

Females					Males				
Characteristics	**Test-Positive Patients (n=86) (Column %)**	**Test-Negative Patients (n=437) (Column %)**	**Total N=523 (%)**	***P* Value (Females Stratum)**	**Characteristics**	**Test-Positive Patients (n=112) (Column %)**	**Test-Negative Patients (n=524) (Column %)**	**Total N=636 (%)**	***P* Value (Males Stratum)**
7-14	28 (32.6%)	154 (35.2%)	182 (34.8%)		7-15	44 (39.3%)	189 (36.1%)	233 (36.6%)	
15+	30 (34.9%)	139 (31.8%)	169 (32.3%)		16+	35 (31.3%	169 (32.3%)	204 (32.1%)	
Number of hospitalizations in the past 3 years					**Number of hospitalizations in the past 3 years**				
Never	37 (43.0%)	192 (43.9%)	229 (43.8%)		Never	55 (49.1%)	260 (49.6%)	315 (49.5%)	
Once	22 (25.6%)	114 (26.1%)	136 (26.0%)	0.9663	Once	29 (25.9%	123 (23.5%)	152 (23.9%)	0.8364
More than once	27 (31.4%)	131 (30.0%)	158 (30.2%)		More than once	28 (25.0%)	141 (26.9%)	169 (26.6%)	
Received homecare in past year	42 (48.8%)	190 (43.5%)	232 (44.4%)	0.3605	**Received homecare in past year**	41 (36.6%)	181(34.5%)	222 (34.9%)	0.6773
Influenza complication risk factors					**Influenza complication risk factors**				
Cancer	18 (20.9%)	83 (19.0%)	101 (19.3%)	0.6774	Cancer	24 (21.4%)	137 (26.1%)	161 (25.3%)	0.2974
Asthma	30 (34.9%)	118 (27.0%)	148 (28.3%)	0.138	Asthma	21 (18.8%)	86 (16.4%)	107 (16.8%)	0.5483
Ischemic Heart Disease	37 (43.0%)	164 (37.5%)	201 (38.4%)	0.3383	Ischemic Heart Disease	55 (49.1%)	259 (49.4%)	314 (49.4%)	0.9509
COPD	40 (46.5%)	194 (44.4%)	234 (44.7%)	0.718	COPD	48 (42.9%)	231 (44.1%)	279 (43.9%)	0.8123
Anemia	15 (17.4%)	89 (20.4%)	104 (19.9%)	0.5346	Anemia	22 (19.6%)	109 (20.8%)	131 (20.6%)	0.7831
Chronic Kidney Disease	20 (23.3%)	76 (17.4%)	96 (18.4%)	0.1991	Chronic Kidney Disease	29 (25.9%)	130 (24.8%)	159 (25.0%)	0.81

Females					Males				
Characteristics	**Test-Positive Patients (n=86) (Column %)**	**Test-Negative Patients (n=437) (Column %)**	**Total N=523 (%)**	***P* Value (Females Stratum)**	**Characteristics**	**Test-Positive Patients (n=112) (Column %)**	**Test-Negative Patients (n=524) (Column %)**	**Total N=636 (%)**	***P* Value (Males Stratum)**
Diabetes	36 (41.9%)	203(46.5%)	239 (45.7%)	0.4345	Diabetes	63 (56.3%)	279 (53.2%)	342 (53.8%)	0.5625
Medication Use					**Medication Use**				
Antiplatelet medication use	24 (27.9%)	95 (21.7%)	119 (22.8%)	0.2124	Antiplatelet medication use	31 (27.7%)	120 (22.9%)	151 (23.7%)	0.2808
β-Blocker medication use	48 (55.8%)	195 (44.6%)	243 (46.5%)	0.0571	β-Blocker medication use	68 (60.7%)	258 (49.2%)	326 (51.3%)	0.0274
Diuretic medication use	50 (58.1%)	206 (47.1%)	256 (48.9%)	0.0621	Diuretic medication use	56 (50.0%)	224 (42.7%)	280 (44.0%)	0.1605
Statin medication use	56 (65.1%)	254 (58.1%)	310 (59.3%)	0.2276	Statin medication use	84 (75.0%)	365 (69.7%)	449 (70.6%)	0.2599
Influenza testing relative to peak month					**Influenza testing relative to peak month**				
During Peak	34 (39.5%)	95 (21.7%)	129 (24.7%)	0.0005	During Peak	48 (42.9%)	111 (21.2%)	159 (25.0%)	<0.0001

Table 4.8.3 Age=<80 vs. Age>80: descriptive characteristics of vaccinated and unvaccinated patients with cardiovascular-related hospitalization 2010-2016

Age=<80					Age>80				
Characteristics	**Vaccinated (n=296) %**	**Unvaccinated (n=301) %**	**Total N=597 %**	***P* Value (Age =<80 Stratum)**	**Characteristics**	**Vaccinated (n=283) %**	**Unvaccinated (n=279) %**	**Total N=562 %**	***p* Value (Age >80 Stratum)**
Tested Positive (Influenza)	40 (13.5%)	54 (17.9%)	94 (15.7%)	0.1376	**Tested Positive for Influenza**	43 (15.2%)	61 (21.9%)	104 (18.5%)	0.0418
Sex (M)	178 (60.1%)	170 (56.5%)	348 (58.3%)	0.3649	**Sex (M)**	149 (52.7%)	139 (49.8%)	288 (51.2%)	0.5023
Rural Residence	29 (9.8%)	36 (12.0%)	65 (10.9%)	0.3963	**Rural Residence**	22 (7.8%)	14 (5.0%)	36 (6.4%)	0.1822
Neighbourhood income quintile					**Neighbourhood income quintile**				
1 (least affluent)	78 (26.4%)	87 (28.9%)	165 (27.6%)	0.487	1 (least affluent)	62 (21.9%)	69 (24.7%)	131 (23.3%)	0.0721
2	73 (24.7%)	60 (19.9%)	133 (22.3%)		2	72 (25.4%)	57 (20.4%)	129 (23.0%)	
3	62 (20.9%)	68 (22.6%)	130 (21.8%)		3	52 (18.4%)	55 (19.7%)	107 (19.0%)	
4	34 (11.5%)	43 (14.3%)	77 (12.9%)		4	34 (12.0%)	52 (18.6%)	86 (15.3%)	
5	49 (16.6%)	43 (14.3%)	92 (15.4%)		5	63 (22.3%)	46 (16.5%)	109 (19.4%)	
Number of outpatient visits in the past year					**Number of outpatient visits in the past year**				
0-6	60 (20.3%)	122 (40.5%)	182 (30.5%)	<.0001	0-6	57 (20.1%)	132 (47.3%)	189 (33.6%)	<.0001
7-15	126 (42.6%)	93 (30.9%)	219 (36.7%)		7-13	106 (37.5%)	72 (25.8%)	178 (31.7%)	
16+	110 (37.2%)	86 (28.6%)	196 (32.8%)		14+	120 (42.4%)	75 (26.9%)	195 (34.7%)	
Number of hospitalizations in the past 3 years					**Number of hospitalizations in the past 3 years**				
Never	152 (51.4%)	139 (46.2%)	291 (48.7%)	0.3203	Never	134 (47.3%)	119 (42.7%)	253 (45.0%)	0.2907
Once	69 (23.3%)	70 (23.3%)	139 (23.3%)		Once	67 (23.7%)	82 (29.4%)	149 (26.5%)	
More than once	75 (25.3%)	92 (30.6%)	167 (28.0%)		More than once	82 (29.0%)	78 (28.0%)	160 (28.5%)	
Received homecare in past year	83 (28.0%)	92 (30.6%)	175 (29.3%)	0.4981	**Received homecare in past year**	134 (47.3%)	145 (52.0%)	279 (49.6%)	0.2733
Influenza complication risk factors					**Influenza complication risk factors**				

Age=<80					Age>80				
Characteristics	**Vaccinated (n=296) %**	**Unvaccinated (n=301) %**	**Total N=597 %**	***P* Value (Age =<80 Stratum)**	**Characteristics**	**Vaccinated (n=283) %**	**Unvaccinated (n=279) %**	**Total N=562 %**	***p* Value (Age >80 Stratum)**
Cancer	62 (20.9%)	65 (21.6%)	127 (21.3%)	0.8464	Cancer	72 (25.4%)	63 (22.6%)	135 (24.0%)	0.4273
Asthma	63 (21.3%)	64 (21.3%)	127 (21.3%)	0.9949	Asthma	66 (23.3%)	62 (22.2%)	128 (22.8%)	0.756
Ischemic Heart Disease	153 (51.7%)	135 (44.9%)	288 (48.2%)	0.0945	Ischemic Heart Disease	113 (39.9%)	114 (40.9%)	227 (40.4%)	0.8221
COPD	133 (44.9%)	147 (48.8%)	280 (46.9%)	0.3391	COPD	113 (39.9%)	120 (43.0%)	233 (41.5%)	0.4585
Anemia	59 (19.9%)	62 (20.6%)	121 (20.3%)	0.8397	Anemia	55 (19.4%)	59 (21.1%)	114 (20.3%)	0.6137
Chronic Kidney Disease	77 (26.0%)	71 (23.6%)	148 (24.8%)	0.4926	Chronic Kidney Disease	53 (18.7%)	54 (19.4%)	107 (19.0%)	0.8499
Diabetes	179 (60.5%)	162 (53.8%)	341 (57.1%)	0.1006	Diabetes	118 (41.7%)	122 (43.7%)	240 (42.7%)	0.6264
Medication Use					**Medication Use**				
Antiplatelet medication use	84 (28.4%)	63 (20.9%)	147 (24.6%)	0.0347	Antiplatelet medication use	65 (23.0%)	58 (20.8%)	123 (21.9%)	0.5321
β-Blocker medication use	165 (55.7%)	134 (44.5%)	299 (50.1%)	0.0061	β-Blocker medication use	151 (53.4%)	119 (42.7%)	270 (48.0%)	0.0111
Diuretic medication use	143 (48.3%)	113 (37.5%)	256 (42.9%)	0.0079	Diuretic medication use	143 (50.5%)	137 (49.1%)	280 (49.8%)	0.7353
Statin medication use	223 (75.3%)	185 (61.5%)	408 (68.3%)	0.0003	Statin medication use	193 (68.2%)	158 (56.6%)	351 (62.5%)	0.0046
Influenza testing relative to peak month					**Influenza testing relative to peak month**				
During Peak	65 (22.0%)	73 (24.3%)	138 (23.1%)	0.5064	During Peak	83 (29.3%)	67 (24.0%)	150 (26.7%)	0.1544

Table 4.8.4 Age=<80 vs. Age>80: descriptive characteristics of influenza test-positive and influenza test-negative patients with cardiovascular-related hospitalization 2010-2016

Age=<80					Age>80				
Characteristics	**Test-Positive Patients, n=94 (Column %)**	**Test-Negative Patients n=503 (Column %)**	**Total N=597 %**	***P* Value (Age =<80 Stratum)**	**Characteristics**	**Test-Positive Patients, (n=104) (Column %)**	**Test-Negative Patients, (n=458) (Column %)**	**Total N=562 %**	***P* Value (Age >80 Stratum)**
Vaccinated	40 (42.6%)	256 (50.9%)	296 (49.6%)	0.1376	**Vaccinated**	43 (41.3%)	240 (52.4%)	283 (50.4%)	0.0418
Sex (M)	53 (56.4%)	295 (58.6%)	348 (58.3%)	0.6827	**Sex (M)**	59 (56.7%)	229 (50.0%)	288 (51.2%)	0.2151
Rural Residence	10 (10.6%)	55 (10.9%)	65 (10.9%)	0.9326	**Rural Residence**	7 (6.7%)	29 (6.3%)	36 (6.4%)	0.8808
Neighbourhood income quintile					**Neighbourhood income quintile**				
1 (least affluent)	23 (24.5%)	142 (28.2%)	165 (27.6%)	0.4895	1 (least affluent)	27 (26.0%)	104 (22.7%)	131 (23.3%)	0.5538
2	18 (19.1%)	115 (22.9%)	133 (22.3%)		2	26 (25.0%)	103 (22.5%)	129 (23.0%)	
3	20 (21.3%)	110 (21.9%)	130 (21.8%)		3	21 (20.2%)	86 (18.8%)	107 (19.0%)	
4	17 (18.1%)	60 (11.9%)	77 (12.9%)		4	16 (15.4%)	70 (15.3%)	86 (15.3%)	
5	16 (17.0%)	76 (15.1%)	92 (15.4%)		5	14 (13.5%)	95 (20.7%)	109 (19.4%)	
Number of outpatient visits in the past year					**Number of outpatient visits in the past year**				
0-6	28 (29.8%)	154 (30.6%)	182 (30.5%)	0.5786	0-6	33 (31.7%)	156 (34.1%)	189 (33.6%)	0.3547
7-15	31 (33.0%)	188 (37.4%)	219 (36.7%)		7-13	39 (37.5%)	139 (30.3%)	178 (31.7%)	
16+	35 (37.2%)	161 (32.0%)	196 (32.8%)		14+	32 (30.8%)	163 (35.6%)	195 (34.7%)	
Number of hospitalizations in the past 3 years					**Number of hospitalizations in the past 3 years**				
Never	47 (50.0%)	244 (48.5%)	291 (48.7%)	0.5528	Never	45 (43.3%)	208 (45.4%)	253 (45.0%)	0.3796
Once	18 (19.1%)	121 (24.1%)	139 (23.3%)		Once	33 (31.7%)	116 (25.3%)	149 (26.5%)	
More than once	29 (30.9%)	138 (27.4%)	167 (28.0%)		More than once	26 (25.0%)	134 (29.3%)	160 (28.5%)	
Received homecare in past year	28 (29.8%)	147 (29.2%)	175 (29.3%)	0.9124	**Received homecare in past year**	55 (52.9%)	224 (48.9%)	279 (49.6%)	0.4641
Influenza complication risk factors					**Influenza complication risk factors**				
Cancer	22 (23.4%)	105 (20.9%)	127 (21.3%)	0.5823	Cancer	20 (19.2%)	115 (25.1%)	135 (24.0%)	0.2052
Asthma	25 (26.6%)	102 (20.3%)	127 (21.3%)	0.1695	Asthma	26 (25.0%)	102 (22.3%)	128 (22.8%)	0.5491
Ischemic Heart Disease	56 (59.6%)	232 (46.1%)	288 (48.2%)	0.0166	Ischemic Heart Disease	36 (34.6%)	191 (41.7%)	227 (40.4%)	0.1836
COPD	45 (47.9%)	235 (46.7%)	280 (46.9%)	0.8371	COPD	43 (41.3%)	190 (41.5%)	233 (41.5%)	0.9793
Anemia	25 (26.6%)	96 (19.1%)	121 (20.3%)	0.0964	Anemia	12 (11.5%)	102 (22.3%)	114 (20.3%)	0.014
Chronic Kidney Disease	32 (34.0%)	116 (23.1%)	148 (24.8%)	0.0236	Chronic Kidney Disease	17 (16.3%)	90 (19.7%)	107 (19.0%)	0.4384

Age=<80					Age>80				
Characteristics	**Test-Positive Patients, n=94 (Column %)**	**Test-Negative Patients n=503 (Column %)**	**Total N=597 %**	***P* Value (Age =<80 Stratum)**	**Characteristics**	**Test-Positive Patients, (n=104) (Column %)**	**Test-Negative Patients, (n=458) (Column %)**	**Total N=562 %**	***P* Value (Age >80 Stratum)**
Diabetes	60 (63.8%)	281 (55.9%)	341 (57.1%)	0.1521	Diabetes	39 (37.5%)	201 (43.9%)	240 (42.7%)	0.2346
Medication Use					**Medication Use**				
Antiplatelet medication use	28 (29.8%)	119 (23.7%)	147 (24.6%)	0.2055	Antiplatelet medication use	27 (26.0%)	96 (21.0%)	123 (21.9%)	0.2655
β-Blocker medication use	58 (61.7%)	241 (47.9%)	299 (50.1%)	0.0141	β-Blocker medication use	58 (55.8%)	212 (46.3%)	270 (48.0%)	0.0806
Diuretic medication use	48 (51.1%)	208 (41.4%)	256 (42.9%)	0.0807	Diuretic medication use	58 (55.8%)	222 (48.5%)	280 (49.8%)	0.1791
Statin medication use	66 (70.2%)	342 (68.0%)	408 (68.3%)	0.6709	Statin medication use	74 (71.2%)	277 (60.5%)	351 (62.5%)	0.0424
Influenza testing relative to peak month					**Influenza testing relative to peak month**				
During Peak	42 (44.7%)	96 (19.1%)	138 (23.1%)	<0.0001	During Peak	40 (38.5%)	110 (24.0%)	150 (26.7%)	0.0026

Table 4.8.5 Adjusted Model Outputs of VE against laboratory confirmed influenza among related hospitalization 2010-2016 (n=1159) by Stratification

Stratum	N	Model Output						
Analysis: Vaccinated		**ORs**	**95% Wald Confidence Limits**		**Vaccine Effectiveness %**	**95% (Confidence Interval)**		**p-Value**
			Lower	**Upper**		**Lower**	**Upper**	
Full Adjusted Model	1,159	0.568	0.404	0.797	43%	20%	60%	0.0011
Females	523	0.483	0.285	0.818	52%	18%	72%	0.0067
Males	636	0.609	0.385	0.962	39%	4%	62%	0.0334
Age <=80	597	0.671	0.411	1.095	33%	-10%	59%	0.1105
Age > 80	562	0.462	0.284	0.751	54%	25%	72%	0.0018

Table 4.8.6.1 Supplemental Tables by sex

Characteristics	Females n=523 (column % of females)	Males n=636 (column % of males)	Total (row) (% of total study Sample=1,159)	P Value
Vaccinated	252 (48.2%)	327 (51.4%)	576 (50%)	0.2736
Influenza Positive	86 (16.4%)	112 (17.6%)	198 (17.1%)	0.5995
Age group				
66-75 y	162 (31.0%)	230 (36.2%)	392 (33.8%)	0.0021
76-85 y	193 (36.9%)	260 (40.9%)	453 (39.1%)	
86+ y	168 (32.1%)	146 (23.0%)	314 (27.1%)	
Rural Residence	38 (7.3%)	63 (9.9%)	101 (8.7%)	0.1128
Neighbourhood income quintile				
1 (least affluent)	144 (27.5%)	152 (23.9%)	296 (25.5%)	0.1911
2	111 (21.2%)	151 (23.7%)	262 (22.6%)	
3	95 (18.2%)	142 (22.3%)	237 (20.5%)	
4	74 (14.2%)	89 (14.0%)	163 (14.1%)	
5	99 (18.9%)	102 (16.0%)	201 (17.3%)	
Number of outpatient visits in the past year				
0-6	172 (32.9%)	199 (31.3%)	371 (32.0%)	0.6726
7-14	182 (34.8%)	216 (34.0%)	398 (34.3%)	
15+	169 (32.3%)	221 (34.8%)	390 (33.7%)	
Number of hospitalizations in the past 3 years				
Never	229 (43.8%)	315 (49.5%)	544 (46.5%)	0.1441
Once	136 (26.0%)	152 (23.9%)	288 (24.9%)	
More than once	158 (30.2%)	169 (26.6%)	327 (28.2%)	
Received homecare in past year	232 (44.4%)	222 (34.9%)	454 (39.2%)	0.001
Influenza complication risk factors				
Cancer	101 (19.3%)	161 (25.3%)	262 (22.6%)	0.015
Asthma	148 (28.3%)	107 (16.8%)	255 (22.0%)	<0.0001
Ischemic Heart Disease	201 (38.4%)	314 (49.4%)	515 (44.4%)	0.0002
COPD	234 (44.7%)	279 (43.9%)	513 (44.3%)	0.7656
Anemia	104 (19.9%)	131 (20.6%)	235 (20.3%)	0.7641
Chronic Kidney Disease	96 (18.4%)	159 (25.0%)	255 (22.0%)	0.0066
Diabetes	239 (45.7%)	342 (53.8%)	581 (50.1%)	0.0062
Medication Use				

Characteristics	Females n=523 (column % of females)	Males n=636 (column % of males)	Total (row) (% of total study Sample=1,159)	P Value
Antiplatelet medication use	119 (22.8%)	151 (23.7%)	270 (23.3%)	0.6919
β-Blocker medication use	243 (46.5%)	326 (51.3%)	569 (49.1%)	0.1042
Diuretic medication use	256 (49.0%)	280 (44.0%)	536 (46.3%)	0.0944
Statin medication use	310 (59.3%)	449 (70.6%)	759 (65.5%)	<0.0001
Influenza testing relative to peak month				
During Peak	129 (24.7%)	159 (25.0%)	871 (75.2%)	0.8956

Table 4.8.6.2 Supplemental Tables by age

Characteristics	≤80 years n=597 (column % from total of ≤80)	>80 years n=562 (column % from total >80 years)	Total (row) (% of total study Sample=1,159)	P Value
Vaccinated	296 (49.6%)	283 (50.4%)	579 (50.0%)	0.7921
Influenza Positive	94 (15.8%)	104 (18.5%)	198 (17.1%)	0.2121
Sex (Male)	348 (58.3%)	288 (51.3%)	636 (54.9%)	0.016
Rural Residence	65 (10.9%)	36 (6.4%)	101 (8.7%)	0.0069
Neighbourhood income quintile				
1 (least affluent)	165 (27.6%)	131 (23.3%)	296 (25.5%)	0.1316
2	133 (22.3%)	129 (23.0%)	262 (22.6%)	
3	130 (21.8%)	107 (19.0%)	237 (20.5%)	
4	77 (12.9%)	86 (15.3%)	163 (14.1%)	
5	92 (15.4%)	109 (19.4%)	201 (17.3%)	
Number of outpatient visits in the past year				
0-6	182 (30.5%)	189 (33.6%)	371 (32.0%)	0.2028
14-Jul	200 (33.5%)	198 (35.2%)	398 (34.3%)	
15+	215 (36.0%)	175 (31.1%)	390 (33.7%)	
Number of hospitalizations in the past 3 years				
Never	291 (48.7%)	253 (45.0%)	544 (46.9%)	0.3506
Once	139 (23.3%)	149 (26.5%)	288 (24.9%)	
More than once	167 (28.0%)	160 (28.5%)	327 (28.2%)	
Received homecare in past year	175 (29.3%)	279 (49.6%)	454 (39.2%)	<0.0001
Influenza complication risk factors				
Cancer	127 (21.3%)	135 (24.0%)	262 (22.6%)	0.2636
Asthma	127 (21.3%)	128 (22.8%)	255 (22.0%)	0.5371
Ischemic Heart Disease	288 (48.2%)	227 (40.4%)	515 (44.4%)	0.0072
COPD	280 (46.9%)	233 (41.5%)	513 (44.3%)	0.0623
Anemia	121 (20.3%)	114 (20.3%)	235 (20.3%)	0.9944
Chronic Kidney Disease	148 (24.8%)	107 (19.0%)	255 (22.0%)	0.0182
Diabetes	341 (57.1%)	240 (42.7%)	581 (50.1%)	<0.001
Medication Use				

Characteristics	≤80 years n=597 (column % from total of ≤80)	>80 years n=562 (column % from total >80 years)	Total (row) (% of total study Sample=1,159)	P Value
Antiplatelet medication use	147 (24.6%)	123 (21.9%)	270 (23.3%)	0.2706
β-Blocker medication use	299 (50.1%)	270 (48.0%)	569 (49.1%)	0.4873
Diuretic medication use	256 (42.9%)	280 (49.8%)	536 (46.3%)	0.0179
Statin medication use	408 (68.3%)	351 (62.5%)	759 (65.5%)	0.0352
Influenza testing relative to peak month				
During Peak	138 (23.1%)	150 (26.7%)	288 (24.9%)	0.1593

Chapter 5: Influenza vaccine effectiveness against cardiovascular hospitalization among older patients in Ontario: A Test-Negative Design

5.1 Overview

Background: There is a strong association between influenza infection and cardiovascular hospitalization. As influenza vaccination is one of the best available preventive measures for influenza, observational studies have attempted to measure its effectiveness against cardiovascular hospitalization. However, residual confounding has been a major limitation in these studies resulting in inconclusive results. The test-negative design (TND), although a well- established method for estimating influenza vaccine effectiveness (VE) and minimizing residual confounding, has never been used for estimating VE against cardiovascular hospitalization. The objective of this study was to assess influenza VE against cardiovascular hospitalizations among older patients in Ontario using the test-negative design.

Methods: Using various linked administrative datasets, this study used the TND to estimate influenza VE against cardiovascular hospitalization among older adults (66 years and above) in Ontario during the 2010-11 to 2015-16 influenza seasons. The study sample was restricted to patients who were tested for influenza and hospitalized within three days of testing for influenza. Logistic regression models were fitted to estimate the odds ratios (ORs) of vaccination among cases who tested positive for influenza and were hospitalized due to a cardiovascular outcome (acute myocardial infarction, unstable angina or stroke) versus controls who tested negative for influenza and were hospitalized due to a different reason. The model was adjusted for age, sex, number of hospitalizations in the past three years, five comorbidities

(asthma, chronic obstructive pulmonary disease, diabetes, ischemic heart disease, and β-blocker use), diuretic and statin medication use, home care services usage, area of residence median income quintile and rurality, influenza season, and testing time relative to the peak month of the season.VE was derived as (1 − OR) ×100%.

Results: This study included 33,710 patients tested for influenza and hospitalized within three days of testing. Over half of the study sample were vaccinated (55%). Among cases, 42.1% were vaccinated, whereas among controls, 55% were vaccinated. Logistic regression yielded an adjusted OR of 0.57 (95% CI: 0.42–0.75), translating to a VE of 43% (95% CI: 25–58%).

Conclusion: The influenza vaccine showed 43% effectiveness against cardiovascular hospitalization. This unique study informs policy makers and clinicians about the effectiveness of influenza vaccination against cardiovascular hospitalization during the influenza season, revealing the vaccine's ability in reducing one of the most common influenza-related outcomes causing significant hospitalization and mortality globally.

5.2 Introduction

Worldwide, influenza affects about 3-5 million people resulting in around 290,000 - 650,000 respiratory-illness-related deaths annually.[5] Vaccination is one of the most effective interventions to prevent influenza and its complications.[68] Patients infected with influenza can develop complications beyond the pulmonary system, such as the cardiovascular system.[32,34] There is increasing evidence for the association between influenza infection and cardiovascular- related hospitalization and mortality.[48,49,260] Findings suggest that those with recent influenza, influenza-like illness, or respiratory infection are twice as likely to suffer an Acute Myocardial Infarction (AMI).[49] In a self- controlled case series analysis, it was found that the risk for an acute myocardial infarction (AMI) admissions is highest in the first 3-7 days after being tested for influenza,[50] compared to their self-controls of one year before and one year after the risk interval (Incidence Ratio 6.05 [95% CI, 3.86 to 9.50]).[51] The risk then tends to decline after day seven.[51–53]

Related to specific populations, a seminal study conducted a systematic review and meta- analysis of randomized controlled trials (RCTs) to examine the association between influenza vaccination and CVD outcomes in high-risk patients.[171] One of the subgroup analyses in the systematic review looked at patient cohorts who experienced a CVD event, whether being a recent event (in the past year of receiving the vaccine), or not a recent event (the past CVD event was more than one year from when the vaccine was received).[171] The outcome measured was risk-ratio (RR) of treatment effect (vaccine)

against a CVD event. The overall association showed a significant lower risk of CVD events (RR, 0.64 [95%CI, 0.48-0.86], $P = .003$).[171]

In examining the causal relationship between the influenza vaccine and CVD outcomes, RCTs are quite valuable in showing the effect of vaccines through experimental design. RCTs are typically conducted under controlled conditions with carefully selected populations, which may not fully reflect the diverse characteristics, comorbidities, and behaviours of patients in routine clinical settings. Therefore, observational studies, such as case-control studies, are essential to complement RCT findings by assessing VE in broader, more heterogeneous "real-world" populations. For instance, a meta-analysis of observational studies, specifically case-control studies, estimated influenza VE against AMI and reported effectiveness to be 29% [95% CI 9-44%].[49]

Although a large body of literature has investigated the associations between vaccination and cardiovascular outcomes,[151–153,171,261–264] there is a paucity of research measuring influenza vaccine effectiveness (VE) against cardiovascular hospitalization.[51] In addition, previous studies attempting to measure VE against cardiovascular hospitalization were prone to several biases affecting their estimates including not accounting for the influenza season (i.e. within season or outside the influenza season) and disregarding the effectiveness against laboratory-confirmed influenza infection altogether.[48,49,261,265]

The Test-Negative Design (TND) is the preferred method to measure VE,[137]

since it mitigates both misclassification and selection bias in case-control design.[138] In theory, the TND is very similar to a nested-case control study. As such, both cases (individuals who had the outcome) and controls (individuals who did not have the outcome) are derived from a cohort of individuals who sought care because of their acute respiratory illness and were tested for influenza.

Accordingly, TND minimizes to a great extent misclassification bias and health care-seeking behaviour bias by limiting the study population to those who sought care due to illness and were eligible for testing, were tested, and had influenza confirmed through laboratory testing.[139]

There is a need for robust studies of influenza VE against cardiovascular hospitalization, one of the confirmed serious complications of the influenza infection. The aim of this study was to measure influenza VE against cardiovascular hospitalization among older patients in Ontario using the TND.

5.3 Methods

5.3.1 Study Design

This was a retrospective and population-based TND study.[138] The study included six influenza seasons (2010-11 to 2015-16). The influenza season is generally identified during all weeks when 5% or more of specimens test positive for influenza.[191] Ethics approval for this study was obtained from the Office of Research Ethics at the University of Waterloo (CREB: IRB00007409).

5.3.2 Data sources

Multiple health administrative databases were linked using unique encoded identifiers and analyzed at ICES (linkage rate= 97.8%).[173] ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement.[172] Further details on the data sources used are available in Chapter 2.

Hospitalization data

Determination of hospitalization was identified using the Discharge Abstract Database (DAD) of the Canadian Institute for Health Information (CIHI), hereafter referred to as CIHR-DAD.[181]

Laboratory Data

The Flu and Other Respiratory Viruses Research (FOREVER) Cohort dataset includes data about all patients with respiratory virus testing results from the 11 Public Health Ontario laboratories and eight academic hospital-based laboratories. Details of the kits used for the testing are available in Appendix C and also at Public Health Ontario.[64]

Influenza Vaccination

Ontario Health Insurance Plan (OHIP) is a publicly funded health plan provided to Ontario residents. Through OHIP, Ontario residents have free access to influenza vaccines and medically necessary physician, diagnostic, and hospital services. Through the Ontario Drug Benefit (ODB) program,

most prescription medications are covered publicly for Ontarians aged 65 years and older, residents of long-term care homes, and individuals receiving social assistance. Coverage may include formulary drugs, with small co-payments or deductibles depending on income.[182,183] ODB database captures billing of prescription medication costs and, as of October 2012, influenza vaccine administration to Ontario residents (irrespective of age).

Other data sources

I obtained demographic information (sex, age, neighbourhood income quintile, and rurality) from the Registered Persons Database and the Postal Code Conversion File, Ontario. Comorbidities were identified using the National Ambulatory Care Reporting System (NACRS), OHIP, and CIHI-DAD.

5.3.3 Study Sample

The following exclusion and inclusion criteria were applied to define the study sample.

Inclusion Criteria

1. Patients with at least one influenza testing episode, in any influenza season of the study period (2010-11 to 2015-16), during any health care setting encounter including physician or hospital visits. The test date was considered the index date. To uphold statistical assumptions for logistic regression model analysis, and to prevent inter and intra dependence of observations, no observation was included more than once in the study sample; thus, only the first was retained.
2. Hospitalization admission episode occurring within three days before or after specimen collection. The time window was restricted to three days

within hospitalization to closely link/ associate the hospitalization event with the influenza infection and rule out nosocomial infection (hospital-acquired influenza).[254] Further, based on previous studies, the highest risk of experiencing an AMI was within the specified time window of three days of testing positive for influenza.[51,266] An episode of care was assigned when a patient was tested for influenza and hospitalized within the three-day window before or after testing for influenza.

3. Survived for at least four days from index date. That was to confirm that VE was being measured against hospitalization and not against a composite outcome such as hospitalization and mortality.

Exclusion Criteria

1. Those in the laboratory datasets whose records could not be linked to ICES administrative databases. Unlinked data was expected to be low (<5%).[173]
2. Age <66 or > 105 on index event. The age cut-off inclusion for this study was 66 years. This was to ensure at least one year of medication use data was available for all included study participants. The maximum age allowed was 105, as all algorithms validated at ICES use 105 as the maximum age cut-off for better accuracy.[267]
3. Non-Ontario residents or not eligible for OHIP.
4. Individuals who were residents of long-term care (LTC) on index date. LTC residents were excluded because of challenges in ascertaining their

vaccination status using OHIP and ODB. LTC residency was identified using OHIP, ODB, DAD, or the Continuing Care Reporting System (CCRS). The CCRS is a reporting system of continued care services offered at hospitals or LTC facilities. Identified LTC residents were excluded from the current influenza season and beyond.[268]

5. Influenza vaccine administered less than 14 days of being tested for influenza. Because it takes 14 days for the human body to reach the full immune response after receiving the vaccine,[247,269] only patients vaccinated more than 14 days of being tested for influenza were retained to confirm complete vaccination-related protection.

6. Discharge from a hospitalization for a cardiovascular outcome 30 days prior to the index date, to exclude the association of a previous cardiovascular outcome with the current event of interest.[270]

5.3.4 Measures

Cardiovascular Hospitalization

Cardiovascular-related hospitalizations of interest in this study included those that met the following ICD-10-CA diagnosis codes under diagnosis type =M (most responsible diagnosis or required the most resources) for:

- Myocardial Infarction: I21, I22.
- Unstable angina: I20.0, I25.
- Cerebral infarction specifically for detecting ischemic stroke (except cerebral infarction due to cerebral venous thrombosis, non-pyogenic): I63 (except I63.6)

- Central retinal artery occlusion: H341.

Exposure: independent variable

The exposure of interest was seasonal influenza vaccination status (vaccinated vs. unvaccinated). The vaccination status was determined using administrative databases (OHIP and ODB). For the purpose of this study, the term "influenza vaccine" (or "the influenza vaccine") is used broadly to refer to all types of influenza vaccines available during the study period, rather than a specific formulation. Fee/billing codes are provided in Appendix H.[247,269]

Outcome: dependent variable

The dependent variable was the cardiovascular outcome with the laboratory-confirmed influenza infection test results. Cases were those testing positive for influenza and hospitalized for a cardiovascular outcome, while those who tested negative for influenza and hospitalized for a different reason were considered as controls. Testing results were collected using any of the following influenza testing procedures including multiplex-PCR, PCR, culture, direct fluorescent antibody staining, or enzyme immunoassay rapid antigen test.

Covariates and descriptive characteristics

Based on previous literature,[126,139] the following baseline characteristics were examined as potential confounders: demographics, healthcare utilization, comorbidities, medication use, and frailty. Demographics at time of index included age (categorized into three groups of 66-75, 76- 85 and ≥86 years),

biological sex, rural residence (communities with <10000 residents; yes/no), neighbourhood's median household income quintile (at census dissemination area-level).

Neighbourhood income quintile was a covariate used to control for socioeconomic status. Healthcare utilization variables relative to index date included number of outpatient visits in the past year, number of hospitalizations in the past three years, and receipt of home care services in the past year. The lookback window for comorbidities depended on the comorbidity and the data source. NACRS, as an example was a data source available since the 2001. Comorbidities included were cancer, asthma, ischemic heart disease, COPD, anemia, chronic kidney disease, and diabetes. Further details on the measurement of comorbidities are provided in Appendix E. Medication use in the past year was explored for use of all medication mentioned in Appendix B. The medications included in this study were antiplatelet agents, β-blockers, diuretics, and statins. Frailty was assessed using the binary measure criteria established at ICES, where the lookback for frailty was within a year before index date, based on rules identified by ICES (See Appendix F).[217,218]

Due to antigenic drifts and the change of the dominant circulating viruses across seasons, a time- related variable was of the essence.[71] The time-related variables that were used in the models were season (to control for year-to-year variations) and peak (to control for virus circulation within an influenza season). Samples relative to the peak month of each season were flagged and

a binary variable relative to the peak (during and outside the peak month) was used. The ***peak month*** of influenza activity is defined by the CDC as "the month with the highest percentage of respiratory specimens testing positive for influenza virus infection during that influenza season".[192]

5.3.5 Data analysis

Descriptive statistics summarized the baseline characteristics according to exposure and outcome. In order to measure VE against cardiovascular hospitalization, the analysis was stratified by influenza laboratory results and cardiovascular outcomes, and their corresponding vaccination status. Tested patients were placed in one of the eight cells in the table below.

Table 5.3.1: Stratification of tested patients who sought care for acute respiratory illness during influenza season, depending on influenza test results and cardiovascular outcomes

	Tested positive for influenza (+)		**Tested negative for influenza (-)**	
	Column 1	**Column 2**	**Column 3**	**Column 4**
	Had a cardiovascular outcome (+/+)	Did NOT have a cardiovascular outcome (+/-)	Had a cardiovascular outcome (-/+)	Did NOT have a cardiovascular outcome (-/-)
Vaccinated	*e*	*f*	*i*	j
Not Vaccinated	*g*	*h*	*k*	l

This study focused on the analysis for calculating VE using columns 1 and 4, shaded in grey, thus calculating the odds of exposure (vaccinated vs. unvaccinated) between cases versus controls. Cases were hospitalized patients that tested positive for influenza and had a cardiovascular outcome,

whereas controls were those who tested negative for influenza and hospitalized for a non-cardiovascular outcome. Additional exploratory analyses for measuring VE using the TND were conducted in this study and are included further in this chapter under "Exploratory Analyses".

Equation 5.1: $\text{VE}_{\text{influenza+CVD}} = 1 - \frac{\frac{e}{g}}{\frac{l}{l}} = \mathbf{1 - \frac{el}{gj} \times 100}$

Multicollinearity among categorical covariates were tested in the model using Spearman's Rank correlation to test non-linear associations among binary and multi-level ordinal variables.[271] The cut-off for correlation was explored and set at 0.7.[271] A multivariable logistic regression was fitted to estimate the odds ratio and the corresponding VE was calculated according to Equation 5.1. Age, sex, and influenza season were placed in the model regardless of statistical significance. Before model building, a chi-square ($\chi 2$) test for each categorical variable by exposure (vaccination status) and another by outcome (influenza testing results and CVD hospitalization) was carried out to check for confounding and statistical significance.[139,272] The *p*-value for statistical significance was <0.05. The model was built using the forward selection method. Variables that were significant in the bivariate analyses were retained in the final model if they were significant in the likelihood ratio test (using Wald's t-test); and/ or increased the fit of the model as assessed by the Akaike Information Criterion (AIC).

Sensitivity analysis

The main analysis accepts the cardiovascular hospitalization to occur within

three days of influenza sample collection. In the first sensitivity analysis, I re-defined the hospitalization time- window to occur within; zero, one, and two days from index date, to compare it with the original analysis of three days. Also, to eliminate the possibility for nosocomial infections, a sensitivity analysis was carried out by removing patients tested for influenza ***after*** two days of their hospital admission (i.e., tested more than 48 hours upon admission).[254] A final sensitivity analysis was conducted for those tested during periods outside of influenza activity to confirm the robustness of the TND.

5.3.6 Exploratory Analysis in Calculating Vaccine Effectiveness

I conducted six exploratory analyses to estimate influenza vaccine effectiveness (VE) using Table 5.3.1, applying the same exclusion and inclusion criteria as the original analysis. Each exploratory analysis corresponds to a specific column in the table and outlines the equation used for VE estimation.

1- Comparing column 1 (cases) vs. column 3 (controls)

This analysis compared the odds of vaccination between testing positive for influenza (cases) and those testing negative (controls) among everyone hospitalized for a CVD event. The results of this analysis can be interpreted as the VE of influenza vaccine against laboratory-confirmed influenza among patients hospitalized for cardiovascular hospitalization within 3 days of testing. The equation below illustrates the measurement used.

$$VE_{Influenza}\ \% = 1\text{-}\frac{\frac{e}{g}}{\frac{i}{k}} = 1 - \frac{ek}{gi} \times 100$$

This particular analytical approach directly informed the development of Study #2 (Chapter 4), the methodologies and findings of which are detailed in Chapter 4.

2- Comparing column 1 (cases) and column 2 (controls)

The second exploratory analysis measures the odds of vaccination in influenza positive patients hospitalized for a CVD outcome in comparison to influenza positive patients hospitalized without a CVD outcome. The influenza VE here is against CVD hospitalization among influenza positive patients.

$$VE_{CVD}\ \%= 1\text{-}\frac{\frac{e}{g}}{\frac{f}{h}} = 1 - \frac{eh}{gf} \times 100$$

3- Comparing column 2 (cases) vs. column 4 (controls)In this third exploratory analysis, the odds of vaccination was calculated in patients who had tested positive for influenza and hospitalized for a non-CVD outcome in comparison to patients who had neither outcome (i.e., tested negative for influenza and were hospitalized for a non- CVD event). Influenza VE was measured against laboratory-confirmed influenza among patients hospitalized for a non-CVD event. In this exploratory analysis, hospitalization was for a different reason other than a CVD outcome (the equation is illustrated below).

$$VE_{influenza}\ \% = 1\text{-}\frac{\frac{f}{h}}{\frac{j}{l}} = 1 - \frac{fl}{hj} \times 100$$

4- Comparing column 3 (cases) and 4 (controls)

The fourth exploratory analysis measured the odds of vaccination in influenza negative patients who had a CVD outcome vs. influenza negative patients without a CVD outcome. Influenza VE was against CVD hospitalization among influenza negative patients.

$$VE_{CVD}\ \%= 1-\frac{\frac{i}{k}}{\frac{j}{l}} = 1-\frac{il}{kj} \times 100$$

5- Comparing columns [1+2] (cases) and [3+4] (controls)

The odds were estimated by comparing all hospitalized patients who tested positive for influenza to those who tested negative, irrespective of cardiovascular hospitalization status. Influenza VE was against laboratory-confirmed influenza infection among hospitalized patients and regardless of event type (CVD or non-CVD).

$$VE_{influenza}\ \%= 1-\frac{\frac{e+f}{g+h}}{\frac{i+j}{k+l}} = 1-\frac{(e+f)(k+l)}{(g+h)(i+j)} \times 100$$

6- Comparing columns [1+3] (cases) and [2+4] (controls)

The sixth exploratory analysis compared the odds of vaccination among all hospitalized patients who had a CVD outcome (cases) in comparison to patients who did not have CVD

outcome (controls) regardless of influenza testing results. The VE here was against CVD hospitalization irrespective of influenza test results.

$$VE_{influenza}\ \%= 1-\frac{\frac{e+f}{g+h}}{\frac{i+j}{k+l}} = 1-\frac{(e+f)(k+l)}{(g+h)(i+j)} \times 100$$

5.4 Results

5.4.1 Study Sample

The initial count of individuals with influenza testing results linked to their hospitalization data was 137,768 (linkage rate= 97.8%).[173] Figure 5.1 outlines the steps used to obtain the final study cohort after applying the exclusion and inclusion criteria. The final study sample consisted of 33,710 study participants who were 66 years or older Ontario residents, tested for influenza within three days of hospitalization and also survived for at least four days from index date (date of testing). In order to measure influenza VE against CVD outcomes, every individual either tested positive for influenza and was hospitalized due to a CVD event (cases) or tested negative for influenza and were hospitalized for non-CVD event.

5.4.2 Descriptive Statistics

Table 5.1 illustrates the characteristics of the study sample according to influenza test results. There were 0.6% of the study sample testing positive for influenza and hospitalized for a cardiovascular outcome (197/33710). There were 18,519 vaccinated patients (54.9%) in the sample. Among vaccinated individuals, 42.1% tested positive for influenza, while 55.0% tested negative ($p = 0.0003$). Around 7% of the study sample were rural residents and around a quarter (25.0%) of the study sample lived in neighbourhoods with the lowest incomes. Individuals who tested positive for influenza and hospitalized due to a cardiovascular outcome, were more likely to have underlying conditions

such as ischemic heart disease, or diabetes, and were more likely using cardiovascular medications, including anti-platelets, β-blockers, diuretics, and statins.

Table 5.2 illustrates the characteristics of the study sample according to their vaccination status. There were 48.1% who were men, 49.1% of which were vaccinated (Table 5.2). Of those vaccinated, 0.4% (83/18519) tested positive for influenza and were hospitalized due to a cardiovascular outcome, compared with 0.8% (114/15191) among unvaccinated individuals (*p*-value=0.0003). Vaccinated individuals were more likely women, were never hospitalized in the past three years, have underlying conditions such as asthma, COPD, ischemic heart disease, or diabetes, and were more likely using cardiovascular medications, including β-blockers, diuretics, and statins. However, unvaccinated individuals were more likely to reside in a lower socioeconomic status area, have a lower number of outpatient visits in the previous year, and lower use of cardiovascular medications.

5.4.3 Measurement of VE

Fifteen covariates were used in the final model. They were sex, age group, neighbourhood income quintile, rurality, number of hospital visits in the past three years, medication use of beta- blockers, diuretics, statins, use of home care services, year of influenza season, influenza testing relative to the peak month of the season, and the following comorbidities; asthma, COPD, Ischaemic Heart Disease, and diabetes. As mentioned previously, age, sex and

season were added to the model regardless of statistical significance as a priori. Some variables, although showing no statistical significance (age, rurality, neighbourhood income quintile), were still used as they improved the model fit. No significant correlation was noted between the covariates used in the model.

Table 5.3 illustrates the model output where the odds ratios (ORs) estimate the odds of vaccination among cases vs. controls. After deriving VE, the crude model showed that the influenza vaccine was 41% [95% CI, 21% to 55%] effective. The overall adjusted VE increased to 43% [95% CI, 25% to 58%] after adjusting for potential confounders.

5.4.4 Sensitivity Analysis

When the hospitalization time window was varied to include admissions within 0, 1, or 2 days of the index date, the VE did not substantially change (Appendix K). The VEs ranged from 40% for those hospitalized on the same day of testing (Day 0) to 47% for those tested within one day of hospitalization (Appendix K). The VE was 45% after excluding the possibility for nosocomial infection (i.e., excluding influenza tests done on days 2 and 3 after hospitalization).

The number of individuals testing positive for influenza outside of the influenza season was extremely low. As a result, logistic regression models could not be conducted for this group, and descriptive characteristics were not reported due to low cell counts as per ICES confidentiality maintaining

rules.[172]

5.4.5 Exploratory Analysis

Table 5.4 summarizes the results of the original and exploratory analyses. In the primary analysis, VE was 43% against CVD hospitalization (95% CI: 25% to 58%). Exploratory analyses yielded varying estimates. The first analysis found VE to be 43% (95% CI: 20% to 60%) among those hospitalized for CVD hospitalization. The second analysis was 28% (95% CI, 3% to 47%) against CVD hospitalization among those testing positive for influenza. On the other hand, the third analysis showed 21% (95% CI, 17% to 26%), against laboratory confirmed influenza among those not hospitalized for CVD event. The fourth analysis found VE against CVD hospitalization among influenza-negative individuals to be 12% (95% CI, -1% to 23%). The fifth analysis estimated VE against laboratory-confirmed influenza-related hospitalizations to be 22%
(95% CI, 17% to 25%). The final sixth analysis measured VE against CVD hospitalization irrespective of influenza status to be 12% (95% CI, 1% to 22%). All analyses demonstrated statistical significance, with the exception of the fourth analysis.

5.5 Discussion

Using multiple health administrative databases, this retrospective, population-based study employed the TND design to measure influenza VE against cardiovascular hospitalization among 33,710 older adults in Ontario during six influenza seasons (2010-11 to 2015-16). More than half of the study

cohort were vaccinated (55%) and only 0.4% of those vaccinated tested positive for influenza. The adjusted influenza VE against cardiovascular hospitalization was 43% [95% CI, 25% to 58%]. Several sensitivity analyses confirmed the robustness of the results.

It is challenging to compare corresponding studies measuring VE given their dissimilar methods used in measurement. To date, no comparative studies have been identified that evaluate influenza VE against cardiovascular hospitalization using the test-negative design approach applied in this study. In this discussion I will carry out two types of research comparisons by: (i) comparing my findings against findings of research studies measuring VE against influenza-related hospitalization; and (ii) comparing with VE studies which focused on subgroup populations with certain chronic diseases. Starting by the earliest, and consistent with what I found in this study, Kwong et al. measured influenza VE against hospitalization among 2,230 elderly adults (>65 years) during the 2010-11 season in Ontario and found the influenza VE to be 42%; (95% CI, 29% to 53%).[273] My study recorded a similar VE for a similar study population of interest; 43% (95% CI, 25% to 58%).

This may suggest that influenza VE is comparable across different types of hospitalization. Comparing VE across countries within similar influenza seasons or even within different outcomes (e.g., VE against influenza infection versus VE against hospitalization) presents several challenges. Even among studies conducted within the same country and year, differences in findings

are frequently observed. For example, in Canada during the 2013 influenza season,[274] interim VE estimates for national-level data and those specific to hospitalization showed inconsistencies.[275] The interim VE estimates against laboratory- confirmed influenza was 71% (95% CI, 54% to 81%)[274], while the VE against hospitalization was 58.5% (95% CI, 43.9% to 69.3%), suggesting a lower protection against influenza-related hospitalization.[275]

A meta-analysis measuring the effects of the influenza vaccine on cardiovascular outcomes in patients with cardiovascular disease, which included four RCTs and 12 observational studies, found that the influenza vaccine was associated with a lower risk of major adverse cardiovascular hospitalization (RR, 0.87; 95% CI, 0.80–0.94 [P<0.001]) compared with control.[276] In alignment with my study, this supports the protective effect of the influenza vaccine against CVD hospitalization.

One of the key methodological challenges in VE studies is the measurement of protection against severe outcomes, such as hospitalization and mortality. Hospitalization is a severe endpoint that is influenced by multiple factors beyond VE, including healthcare-seeking behaviour, comorbidities, and access to medical care. This PhD study represents one of the first efforts to explore VE against a severe outcome in a comprehensive manner using the TND, considering the numerous challenges inherent in such analyses. By accounting for these complexities, this study contributes valuable insights into the effectiveness of influenza vaccination in preventing severe disease, adding

to the growing body of evidence necessary for public health decision-making. Differences in VE findings between this study and other research may have been impacted by the differences in study sample characteristics and limited sample size. Comparing my findings with other studies measuring influenza VE against hospitalization or against the influenza infection itself seem to suggest that my findings cannot be compared with other findings given the unique approach, study design, and measurements. Nevertheless, my study used a robust method. As such, my findings of optimal VE against cardiovascular hospitalization should be of importance to clinicians and policy makers.

The exploratory analysis explored VE estimates against influenza hospitalization and / or cardiovascular hospitalization by changing the definitions of cases and controls. In the original analysis, the influenza vaccine was 43% [95% CI, 25% to 58%] effective against influenza and CVD hospitalization. This was one of the highest VE observed, suggesting high protection against cardiovascular hospitalization that was influenza-infection related. The results highlight variations in VE depending on influenza test results and CVD hospitalization status. The first exploratory analysis to measure VE against influenza among CVD hospitalization was found to be 43% [95% CI, 20% to 60%], which was similar to the original analysis, reinforcing the vaccine's effectiveness against CVD hospitalization in this high-risk group. The second exploratory analysis for measuring VE against CVD hospitalization in patients positive for influenza was 28%, suggesting

vaccination may be helping in reducing CVD hospitalization risk in influenza-positive individuals. The third exploratory analysis for measuring VE against influenza among those *NOT* CVD hospitalized was 21%; much lower than in CVD-hospitalized individuals, possibly due to differences in risk profiles. The fourth exploratory analysis for measuring VE against CVD hospitalization in patients negative for influenza was 12%. This suggests a weak protective effect against CVD hospitalization, implying that there may be factors beyond influenza's influence on CVD hospitalization among those testing negative for influenza. The fifth exploratory analysis measured VE against laboratory-confirmed influenza hospitalizations which was identical to the third exploratory analysis, confirming a consistent VE against influenza-related hospitalization regardless of its type (22%). The final (sixth) exploratory analysis found VE against CVD hospitalization regardless of influenza status to be 12% which matches the fourth analysis, suggesting a limited impact of vaccination on CVD hospitalization overall.

It is disappointing to see in my study that the vaccination proportion among patients experiencing a cardiovascular hospitalization was only about 55%. A previous study estimated the vaccination annual uptake among people with a history of cardiovascular disease to be 58.9%.[250] Vaccination, in spite of being a relatively low-cost and effective intervention, is still underutilized. Lessons from vaccination campaigns during the COVID pandemic era should provide insights about enhancing influenza vaccine uptake among high-risk patients including patients with a history of cardiovascular hospitalization.[256]

Strategies should include building a trustful and constructive relationship with patients with tailored communication and multifaceted implementation efforts of vaccination campaigns. This is expected to contribute significantly to the reduction of cardiovascular diseases burden and save thousands of lives in Canada.[257]

I studied influenza VE against CVD hospitalization among the older population in Ontario (the most populous province in Canada) using a robust design over several influenza seasons.

However, several limitations were recognized in the study. First, the study held a number of assumptions under the TND method which cannot be confirmed. These assumptions include that the influenza virus is most likely circulating to an extent that both cases and controls had similar exposure to the influenza virus.[139] Further, there is no difference in access to healthcare between cases and controls and the vaccine is offered and readily accessible to everyone regardless of their autonomous choice for taking it. Finally, the laboratory tests carried out in every centre were assumed to have similar specificity and sensitivity results. However, it is reasonable to have such assumptions within the universal health care in Ontario. I restricted the study sample by limiting the time of within a three-day window for testing the patient for influenza and hospital admission for a major cardiovascular outcome as the most responsible diagnosis and not because of admission due to a chronic cardiopulmonary disease. This was partly to overcome the bias suggested by Foppa et al. introduced by chronic cardiopulmonary patients

admitted for non- infectious exacerbations which as a result may overestimate the influenza VE if these patients are also vaccinated.[140] In my study, all patients were admitted to the hospital within three days before or after testing for influenza. This design restricts temporality to the best of our ability in such that the infection is very close to the cardiovascular outcome with respect to time. However, any delay in diagnoses, or testing, or reporting, beyond the three days discussed, violate this temporality restriction and may render the event as undetected. In my aim to address this limitation, I carried out a sensitivity analysis by increasing or decreasing the time window between testing and hospital admission, yet the overall adjusted VE did not change substantially and ranged between 40% and 47%. Variability in the physician's discretion in decision making to order laboratory testing for influenza, or even the timing at which the decision is made, cannot be measured or adjusted for in the statistical models. Hence, it was beyond the study's ability to identify whether this might have led to overestimating or underestimating the VE depending on whether the undetected cases were more likely to be vaccinated or unvaccinated. Time of onset

of influenza symptoms or cardiovascular hospitalization has some uncertainty present in the data because the timing for testing for influenza may not be consistent across all individuals included in the study. Lastly, the proportion of people vaccinated was probably an underestimation since I was not able to capture the number of people who received the influenza vaccine outside the physician's office or pharmacy (e.g., a workplace clinic). According to the

survey on vaccine uptake in Canadian adults 2023-2024, 73% of those aged ≥65 years reported taking the influenza vaccine.[111] In addition, among those vaccinated against influenza of all ages, the pharmacy and physician's office was the top two most common places for taking the vaccine (≈ 72%).[111] The study sample comprised of only those aged > 65 years, and it is assumed that a small number of patients were non-differentially misclassified as being unvaccinated. It is also suggested that the VE against CVD hospitalization in this study is an underestimation since the sensitivity of administrative databases in measuring vaccination status is about 70% in this study population, and about 30% classified as unvaccinated may have likely received their vaccine outside physician offices and pharmacies.[248] Therefore, it is perhaps possible to suggest that the influenza VE in my study is an underestimation since having higher proportions of those vaccinated could have increased the VE beyond 43%.

5.6 Conclusion

The study findings help support VE estimates against cardiovascular hospitalization using laboratory-confirmed influenza infection results among high-risk patients using a robust design. The results produce important and specific recommendations for clinicians and policy makers to vehemently recommend the influenza vaccine especially to those most at risk for experiencing a cardiovascular outcome. Measuring VE against cardiovascular hospitalization among older adults in Ontario shines a light on the importance of this treatment effect. The TND method used in this study is the method of

choice in measuring VE. My study also builds foundational knowledge for other similar studies in measuring other influenza-related outcomes using the TND method. Given the difficulty in comparing with past studies or previous influenza VE against influenza infection, I can conclude that this study is unique and highlights the need for further comparative studies that will use the TND method in measuring VE against cardiovascular hospitalization.

5.7 Figure and Tables

Figure 5. 1 Study Sample- Influenza vaccine effectiveness against cardiovascular outcomes

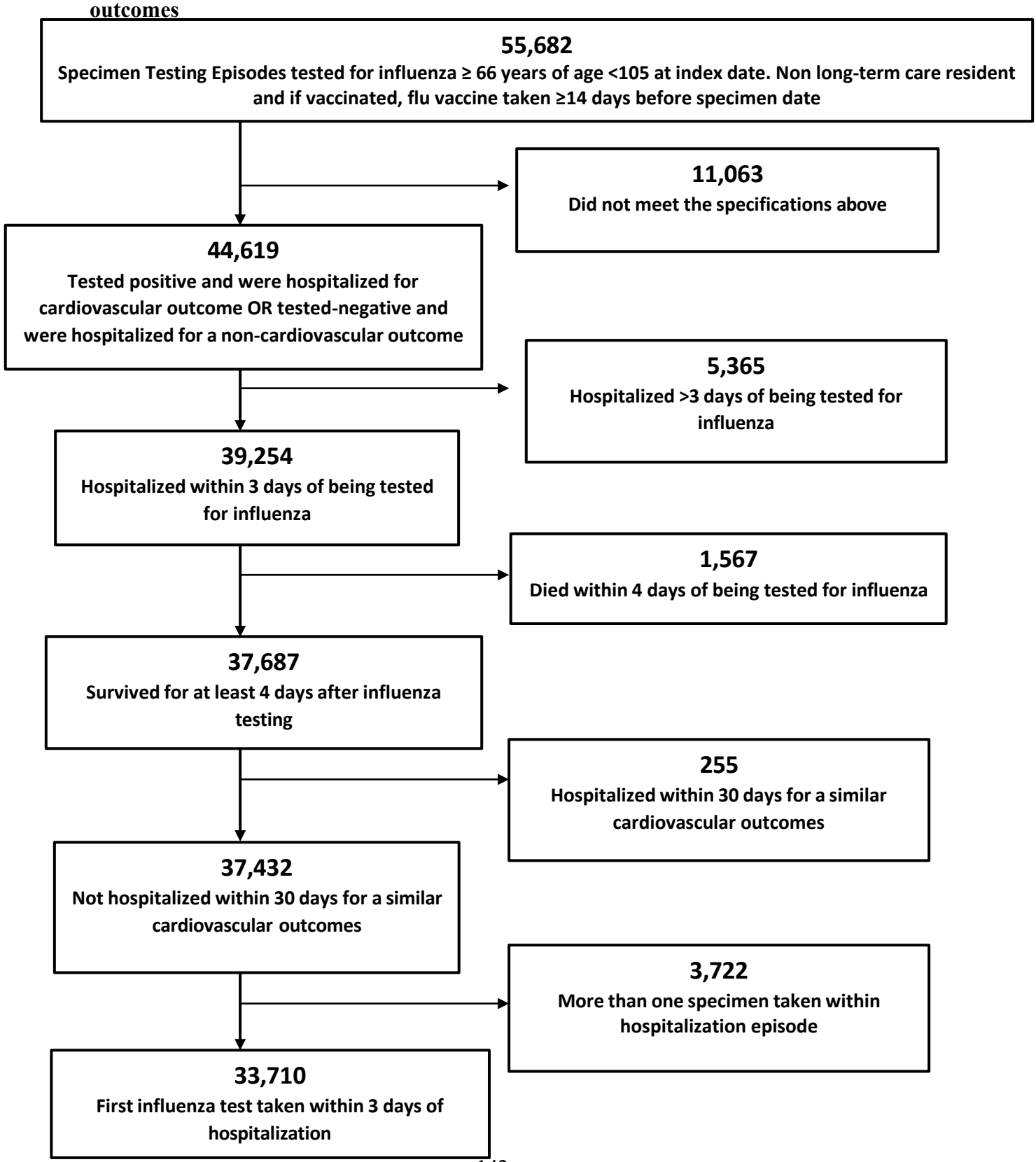


Table 5.1 Descriptive characteristics of influenza test-positive patients with cardiovascular-related hospitalization and influenza test-negative patients without cardiovascular -related hospitalization during seasons 2010-11 to 2015-16

Characteristics	Test-Positive Patients, No. n=197 (Column %)	Test-Negative Patients, No. n=33513 (Column%)	Total (% of 33710)	*P* Value
Vaccinated	83 (42.1%)	18436 (55.0%)	18519 (54.9%)	0.0003
Sex (M)	111 (56.3%)	16089 (48.0%)	16200 (48.1%)	0.0195
Age group				
66-75 y	66 (33.5%)	11484 (34.3%)	11550 (34.3%)	0.3743
76-85 y	71 (36.0%)	13240 (39.5%)	13311 39.5%)	
≥86 y	60 (30.5%)	8789 (26.2%)	8849 (26.3%)	
Rural Residence	17 (8.6%)	2332 (7.0%)	2349 (7.0%)	0.3584
Neighbourhood income quintile				
1 (least affluent)	50 (25.4%)	8370 (25.0%)	8420 (25.0%)	0.8905
2	42 (21.3%)	7600 (22.7%)	7642 (22.7%)	
3	41 (20.8%)	6379 (19.0%)	6420 (19.0%)	
4	33 (16.8%)	5215 (15.6%)	5248 (15.6%)	
5	31 (15.7%)	5949 (17.8%)	5980 (17.7%)	
Number of outpatient visits in the past year				
0-8	79 (40.1%)	11470 (34.2%)	11549 (34.3%)	0.0946
9-16	66 (33.5%)	10934 (32.6%)	11000 (32.6%)	
≥ 17	52 (26.4%)	11109 (33.1%)	11161 (33.1%)	
Number of hospitalizations in the past 3 years				
Never	92 (46.7%)	12990 (38.8%)	13082 (38.8%)	0.0134
Once	53 (26.9%)	8401 (25.1%)	8454 (25.1%)	
More than once	52 (26.4%)	12122 (36.2%)	12174 (36.1%)	
Received home care in past year	81 (41.1%)	16580 (49.5%)	16661 (49.4%)	0.0193
Influenza complication risk factors				
Anemia	36 (18.3%)	8253 (24.6%)	8289 (24.6%)	0.039
Asthma	48 (24.4%)	9475 (28.3%)	9523 (28.2%)	<.0001
Cancer	44 (22.3%)	10055 (30.0%)	10099 (30.0%)	0.0191

Chronic Kidney Disease	49 (24.9%)	7428	(22.2%)	7477 (22.2%)	0.3616
Chronic obstructive pulmonary disease	86 (43.7%)	17889	(53.4%)	17975 (53.3%)	0.0064
Diabetes	100 (50.8%)	14359	(42.8%)	14459 (42.9%)	0.0252
Ischemic Heart Disease	92 (46.7%)	9939	(29.7%)	10031 (29.8%)	<.0001
Characteristics	**Test-Positive Patients, No. n=197 (Column %)**	**Test-Negative Patients, No. n=33513 (Column%)**		**Total (% of 33710)**	***P* Value**
Medication Use					
Antiplatelet medication use	54 (27.4%)	3825 (11.4%)		3879 (11.5%)	<.0001
β-Blocker medication use	115 (58.4%)	13649 (40.7%)		13764 (40.8%)	<.0001
Diuretic medication use	105 (53.3%)	16108 (48.1%)		16213 (48.1%)	0.1426
Statin medication use	140 (71.1%)	19069 (56.9%)		19209 (57.0%)	<.0001
Season					
2010-2011	20 (10.2%)	3752 (11.2%)		3772 (11.2%)	0.0001
2011-2012	9 (4.6%)	2485 (7.4%)		2494 (7.4%)	
2012-2013	45 (22.8%)	6245 (18.6%)		6290 (18.7%)	
2013-2014	22 (11.2%)	7057 (21.1%)		7079 (21.0%)	
2014-2015	72 (36.5%)	8211 (24.5%)		8283 (24.6%)	
2015-2016	29 (14.7%)	5763 (17.2%)		5792 (17.2%)	
Influenza testing relative to peak month					
During Peak	83 (42.1%)	7424 (22.2%)		7507 (22.3%)	<.0001

Table 5.2 Descriptive characteristics of vaccinated and unvaccinated patients during seasons 2010-11 to 2015-16

Characteristics	Vaccinated n=18519 (Column %)	Unvaccinated n=15191 (Column %)	Total (% of 33710)	*P* Value
Tested Positive for Influenza and hospitalized due to cardiovascular outcomes	83 (0.4%)	114 (0.8%)	197 (0.6%)	0.0003
Sex (M)	9093 (49.1%)	7107 (46.8%)	16200 (48.1%)	<.0001
Age group				
66-75 y	5832 (31.5%)	5718 (37.6%)	11550 (34.3%)	<.0001
76-85 y	7678 (41.5%)	5633 (37.1%)	13311 (39.5%)	
≥86 y	5009 (27.0%)	3840 (25.3%)	8849 (26.3%)	
Rural Residence	1192 (6.4%)	1157 (7.6%)	2349 (7.0%)	<.0001
Neighbourhood income quintile				
1 (least affluent)	4483 (24.2%)	3937 (25.9%)	8420 (25.0%)	<.0001
2	4249 (22.9%)	3393 (22.3%)	7642 (22.7%)	
3	3476 (18.8%)	2944 (19.4%)	6420 (19.0%)	
4	2886 (15.6%)	2362 (15.5%)	5248 (15.6%)	
5	3425 (18.5%)	2555 (16.8%)	5980 (17.7%)	
Number of outpatient visits in the past year				
0-8	5087 (27.5%)	6462 (42.5%)	11549 (34.3%)	<.0001
9-16	6469 (34.9%)	4531 (29.8%)	11000 (32.6%)	
≥ 17	6963 (37.6%)	4198 (27.6%)	11161 (33.1%)	
Number of hospitalizations in the past 3 years				
Never	7290 (39.4%)	5792 (38.1%)	13082 (38.8%)	<.0001
Once	4732 (25.6%)	3722 (24.5%)	8454 (25.1%)	
More than once	6497 (35.1%)	5677 (37.4%)	12174 (36.1%)	
Received home care in past year	8772 (47.4%)	7889 (51.9%)	16661 (49.4%)	<.0001

Influenza complication risk factors				
Anemia	4629 (25.0%)	3660 (24.1%)	8289 (24.6%)	0.0555
Asthma	5669 (30.6%)	3854 (25.4%	9523 (28.2%)	<.0001
Cancer	5615 (30.3%)	4484 (29.5%)	10099 (30.0%)	0.1094
Chronic Kidney Disease	4096 (22.1%	3381 (22.3%)	7477 (22.2%)	0.7603
Chronic obstructive pulmonary disease	10247 (55.3%)	7728 (50.9%)	17975 (53.3%)	<.0001
Characteristics	**Vaccinated n=18519 (Column %)**	**Unvaccinated n=15191 (Column %)**	**Total (% of 33710)**	***P* Value**
Diabetes	8096 (43.7%)	6363 (41.9%)	14459 (42.9%)	0.0007
Ischemic Heart Disease	5689 (30.7%)	4342 (28.6%)	10031 (29.8%)	<.0001
Medication Use				
Antiplatelet medication use	2163 (11.7%)	1716 (11.3%)	3879 (11.5%)	0.272
β-Blocker medication use	7818 (42.2%)	5946 (39.1%)	13764 (40.8%)	<.0001
Diuretic medication use	9208 (49.7%)	7005 (46.1%)	16213 (48.1%)	<.0001
Statin medication use	11281 (60.9%)	7928 (52.2%)	19209 (57.0%)	<.0001
Season				
2010-2011	1988 (10.7%)	1784 (11.7%)	3772 (11.2%)	<.0001
2011-2012	1434 (7.7%)	1060 (7.0%)	2494 (7.4%)	
2012-2013	3257 (17.6%)	3033 (20.0%)	6290 (18.7%)	
2013-2014	3950 (21.3%)	3129 (20.6%)	7079 (21.0%)	
2014-2015	4635 (25.0%)	3648 (24.0%)	8283 (24.6%)	
2015-2016	3255 (17.6%)	2537 (16.7%)	5792 (17.2%)	
Influenza testing relative to peak month				
During Peak	3992 (21.6%)	3515 (23.1%)	7507 (22.3%)	0.0005

Table 5.3 Model Output: VE against cardiovascular hospitalization during seasons 2010-11 to 2015-16

Analysis	Odds Ratios	95% Wald Confidence Limits		Vaccine Effectiveness %	95% (Confidence Interval)		p-Value
		Lower	Upper		Lower	Upper	
Crude Model: Vaccinated	0.595	0.448	0.791	41%	21%	55%	0.0003
Adjusted Model: Vaccinated	0.566	0.424	0.754	43%	25%	58%	0.0001

Model adjusted for sex, age group, neighbourhood income quintile, rurality, number of hospital visits in the past three years, beta-blockers medication-use, diuretic medication-use, and statin medication-use, use of home care services, year of influenza season, influenza testing relative to the peak month of the season, and the following comorbidities; asthma, COPD, Ischaemic Heart Disease, and diabetes.

Table 5.4: Exploratory analyses results of VE comparisons

p<0.05 p>0.05

Analysis	Comparison of Columns	Odds Ratio Equations	Crude VE (%), [95% Confidence Interval]	Adjusted VE (%), [95% Confidence Interval]	n	Explanation
Original Analysis	1&4	VEinfluenza%= 1-el/gj ×100	41 [95% CI, 21% to 55%]	43 [95% CI, 25% to 58%]	33710	**VE against influenza and CVD** hospitalization among people who were positive for influenza AND CVD hospitalization in comparison to patients negative for influenza and CVD hospitalization
First exploratory analysis	1&3	VEinfluenza% =1-ek/gi ×100	32 [95% CI, 8% to 50%]	43 [95% CI, 20% to 60%]	1159	**VE against influenza** among those who were CVD hospitalized
Second exploratory analysis	1&2	VE_CVD% = 1-eh/fg ×100	26 [95% CI, 1% to 45%]	28 [95% CI, 3% to 47%]	8463	**VE against CVD hospitalization** among patients who were positive to influenza
Third exploratory analysis	2&4	VEinfluenza% =1-fl/hj ×100	22 [95% CI, 18% to 26%]	21 [95% CI, 17% to 26%]	41002	**VE against influenza** among those who were NOT CVD hospitalized
Fourth exploratory analysis	3&4	VE_CVD% = 1-il/kj ×100	11 [95% CI, -1% to 22%]	12 [95% CI, -1% to 23%]	34297	**VE against CVD hospitalization** among patients who were negative to influenza

Fifth exploratory analysis	[1+2] vs. [3+ 4]	VEinfluenza%= 1- ((e+f)(k+l))/((i+j)(g+h)) ×100	22 [95% CI, 18% to 26%]	22 [95% CI, 17% to 25%]	41929	**VE against influenza** regardless of type of hospitalization (CVD or non- CVD)
Sixth exploratory analysis	[1+3] vs. [2+ 4]	VE_CVD%= 1- ((e+i)(h+l))/((f+j)(g+k)) ×100	12 [95% CI, 1% to 22%]	12 [95% CI, 1% to 22%]	41929	**VE against CVD hospitalization** regardless of influenza infection status (influenza positive or influenza negative)

Chapter 6: Discussion

6.1 Preamble

The purpose of this chapter is to present and discuss the global findings, contributions, and conclusions of the three studies comprising this thesis.

6.2 Research Summary

Influenza remains a significant global public health issue, with the World Health Organization (WHO) estimating that seasonal influenza leads to approximately 3 to 5 million cases of severe illness and 290,000 to 650,000 respiratory deaths annually.[277] In Ontario, the burden of influenza is closely monitored through the Ontario Respiratory Virus Tool, which provides comprehensive epidemiological information on respiratory virus activity, including influenza.[278] The WHO's updated Public Health Research Agenda for Influenza (2024) underscores the need for continued efforts to reduce the burden of seasonal influenza and mitigate the risk and impact of influenza pandemics, emphasizing the importance of enhanced surveillance, improved vaccines, and effective public health strategies.[279] These ongoing challenges highlight the critical need for effective vaccination programs and public health interventions to control the spread and impact of influenza. This thesis sets out to explore the intersection between influenza infection and acute cardiovascular (CVD) events, guided by a growing body of evidence indicating a temporal and potentially causal link between the two. Specifically, I aimed to evaluate whether influenza vaccination is effective not only against laboratory-confirmed influenza infection but also against its serious CVD complications in older adults. To do this, I employed three distinct methodological approaches, each contributing incrementally to the overarching research objective.

Validation of Influenza Vaccination Status in Administrative Data

The first objective addressed a fundamental methodological concern: the accurate ascertainment of influenza vaccination status within routinely collected administrative health data. Using the Ontario Health Insurance Plan (OHIP) and Ontario Drug Benefit (ODB) databases, I conducted a validation study comparing administrative vaccination records to self-reported data from the Canadian Community Health Survey. The findings showed that administrative databases (OHIP and ODB) in Ontario possess improved sensitivity (of about 10% higher) in measuring an individual's influenza vaccination status compared to a previous study which included only OHIP claims.[106] The sensitivity was 60.1% (95% CI, 59.3% to 61.0%), the specificity was 98.5%
(95% CI, 98.3% to 98.7%), the positive predictive value was 96.7% (95% CI, 96.3% to 97.1%) and the negative predictive value was 76.9% (95% CI, 76.4% to 77.5%). The findings revealed that while the administrative data had high specificity (≈99%), their sensitivity was moderate (approximately 60%). This implies that individuals recorded as vaccinated are highly likely to be truly vaccinated (few false positives), but a substantial proportion of vaccinated individuals are not captured in these data sources (i.e., false negatives), likely due to vaccinations administered in non-billing settings such as workplace clinics or public health campaigns. The sensitivity tends to be better among older age groups such as those 65 years or older (72.7% (95% CI, 71.6% to 73.7%).

Influenza Vaccine Effectiveness against Laboratory-Confirmed Influenza Infection Using a Test-Negative Design

Building on the validation work, the second study applied a test-negative design (TND) to estimate the effectiveness of the seasonal influenza vaccine against laboratory-confirmed

influenza infection among older adults hospitalized for CVD conditions. In this design, all participants were tested for influenza during hospitalization due to AMI, unstable angina, or stroke. Those who tested positive formed the case group, while those who tested negative served as controls. The results illustrate that overall, the influenza vaccine was 43% (95% CI, 20%– 60%) effective against laboratory-confirmed influenza infection among older patients hospitalized due to a CVD event, around the time they were tested for influenza. This was found to be similar to the overall effectiveness among the Canadian population (43%) [272,274,280,281] This supports the conclusion that patients vaccinated and facing a CVD event derive similar benefits to the general population.

The TND is particularly useful in minimizing confounding related to healthcare-seeking behaviour, as all included patients had similar clinical presentations and underwent influenza testing. The findings demonstrated that influenza vaccination was effective in this high-risk population. Importantly, vaccine effectiveness (VE) in this CVD cohort was consistent with that observed in broader populations, reinforcing the vaccine's utility even among those with significant comorbidity and hospitalization risk.

A common concern in such analyses is the interpretation of VE in a hospitalized cohort — specifically, whether VE reflects prevention of hospitalization or infection. In this case, since all participants were hospitalized, the analysis estimates VE against influenza infection conditional on hospitalization, rather than against hospitalization itself. The TND framework effectively isolates the protective effect of the vaccine on infection rather than the underlying cause of hospitalization.

Unique Analytical Approach: Influenza Vaccine Effectiveness against Cardiovascular Complications

The third and final study introduced a unique analytical approach to examine whether influenza vaccination reduced the risk of acute CVD events in the context of laboratory-confirmed influenza. Given the temporal association between influenza infection and CVD complications, I aimed to capture the potential downstream protective association effect of vaccination against influenza-triggered CVD hospitalizations.

To do this, I developed a composite outcome of laboratory-confirmed influenza and CVD hospitalization, comparing patients who experienced both to various comparator groups with different influenza and CVD statuses. I found VE against CVD hospitalization to be 43% (95% CI, 25% to 58%]. This study allowed for an exploration of how case and control definitions influence VE estimates. I examined six different comparator scenarios, enabling a nuanced interpretation of the relationship between vaccination, infection status, and CVD outcomes.

The exploratory analyses showed that VE estimates varied depending on the control definition, highlighting the sensitivity of the analysis to methodological choices. For instance, comparing influenza-positive CVD cases to influenza-negative, non-CVD controls provided different VE estimates than comparisons using controls with only one of the two conditions. These results underscore the complexity of measuring VE against secondary complications of infection and the importance of explicitly considering control group selection in such analyses.

6.3 Research Limitations

This thesis presents important findings on influenza VE among older adults with CVD

comorbidities; however, several limitations must be acknowledged. These limitations are not unique to this body of work but reflect broader challenges in observational VE research, particularly when using large-scale administrative and laboratory data sources.

A central limitation lies in the incomplete and imperfect capture of vaccination status using administrative data. Although the ODB and OHIP billing databases provide comprehensive coverage of publicly funded and physician/pharmacist-administered vaccines, they do not consistently include vaccinations delivered in non-billed settings such as workplace clinics, public health campaigns, or community healthcare centres outside the scope of reimbursement. As demonstrated in the validation study, this under-ascertainment introduces non-differential misclassification, which typically biases VE estimates toward the null. Therefore, subsequent analyses in this thesis should be interpreted with an understanding that VE may be underestimated due to exposure misclassification.

Despite the improvement of the performance of the combined administrative databases in capturing an individual's vaccination status, there appears to be room for further improvements in sensitivity. The sensitivity estimate observed in this study may reflect the fact that administrative databases used in this thesis were restricted to capturing only those taking the vaccine in a physician office or pharmacy. Combining different administrative database sources from primary care providers who do not bill through the physician's billing system (such as: providers in community healthcare centres, hospitals, nurse practitioner-led clinics, nursing homes, as well as workplace clinics), and public health units in Ontario (which provide vaccination directly to the public and through vaccination clinics in public places) could increase the sensitivity measure. However, data sources from these different care settings are often vastly diverse and combining them with billing records may be

challenging.[282,283] In spite of using a specific personal identifier (such as the health number), patient medical records are usually limited (and sometimes lack) specific standards for recording and reporting clinical information, thus conflicting information could be retrieved and linked with administrative databases.[284] As such, physician and pharmacy billing records remain the most reliable source of information about patient-level ascertainment of vaccination status within the provincial health care system in Ontario and across Canada.[285]

Alternatively, having a vaccine registry (or Immunization Information Systems, IIS) would provide robust data.[286] National or provincial registries,[287] such as those initiated to record the administration of all COVID-19 vaccines (the COVaxON system),[288] played a vital role in combating the pandemic.[289] The launch of COVID-19 provincial registries proved that it was a feasible measure to undertake, despite the cost and time for their construction.[290] Provincial registries better prepare countries for future pandemics and may enhance coverage and access to vaccinations.[291] Not only do vaccine registries provide more accurate information on vaccine uptake, but they can also serve in tracking reported vaccine-related side effects or clinical complications (pharmacovigilance).[292] This does not need to be restricted to influenza vaccine but can be expanded to all human vaccines including pediatric vaccines.[293,294] Canada needs a national vaccine registry,[289] and this would enhance our ability to measure VE robustly in large populations.[295] Creating and maintaining this registry requires legislative changes and cooperation between health authorities in all Canadian provinces and territories. However, a foundation exists to ensure future successes in this area.[296] Current vaccination data sources and systems in Canada should be consolidated and amalgamated to create this registry.[293,297] It took a pandemic (the Severe acute respiratory syndrome, SARS) for the Public Health Agency of Canada to create an initiative called the

Canadian Immunization Registry and Coverage Network (CIRC) to meet the public health needs of Canada.[298,299] The Canadian Immunization Registry Network (CIRN) was established in the last decade[300] to facilitate the process of creating a national vaccine registry.[301] The recent COVID-19 pandemic exposed our deficiencies in data sources for vaccine coverage and such deficits should be taken into account. My study should be seen in this lens as a substantiation of the argument of our dire need of a vaccine registry.

Additionally, all studies in this thesis are observational in nature and therefore remain subject to confounding. Although TND mitigates some important sources of bias—such as differences in healthcare-seeking behaviour or illness severity—it cannot fully account for residual confounding related to health status, healthcare access, or unmeasured covariates like functional status or frailty. While covariate adjustment was applied to strengthen internal validity, the possibility of unmeasured or residual confounding remains a key consideration in interpreting the results.

The third study introduced a unique approach to evaluating influenza VE against CVD outcomes by using a composite influenza-positive and CVD hospitalization endpoint. The primary analysis estimated VE at 43% (95% CI: 25–58%) against combined influenza and cardiovascular (CVD) hospitalization, suggesting strong vaccine protection against influenza-associated cardiovascular complications. When outcome definitions were altered in exploratory scenarios, the first analysis (comparing vaccination odds between influenza-positive and influenza-negative among patients hospitalized for CVD events) produced a similar VE of 43% (95% CI: 20–60%), reinforcing the potential role of vaccination in preventing CVD events is achieved by preventing influenza infection. However, when VE was measured against CVD hospitalization among influenza-positive patients only (second

exploratory analysis), the estimate dropped to 28%, indicating a modest protective effect against CVD beyond influenza infection prevention. Similarly, VE against CVD hospitalization among influenza-negative individuals (fourth exploratory analysis) was just 12%, suggesting also minimal non-specific vaccine protection beyond influenza prevention. For patients who were hospitalized for reasons other than CVD (third exploratory analysis), VE against influenza infection was lower at 21%, potentially reflecting differences in baseline risk profiles. The similarity among VE estimates across related exploratory analyses—such as 22% for laboratory-confirmed influenza hospitalization and 12% for CVD hospitalization regardless of influenza status—supports the robustness of findings but also highlights the influence of case and control definitions on VE estimation. While innovative, this approach presents several interpretive challenges. For instance, the temporal sequence between influenza infection and CVD hospitalization may not be well-defined in all cases. In some patients, influenza may have precipitated the CVD event, whereas in others, the two conditions may have occurred concurrently or independently. Furthermore, the use of multiple control definitions across alternative analytic scenarios introduces variability in effect estimates that complicates interpretation. While this was addressed through sensitivity and exploratory analyses, future research is needed to establish the validity and optimal use of such composite outcome frameworks.

In summary, while the studies in this thesis offer novel contributions to the understanding of influenza VE in a vulnerable population, they also highlight critical gaps and opportunities for future inquiry. Addressing these limitations will require interdisciplinary collaboration, methodological innovation, and sustained investment in high-quality data infrastructure and vaccine research. Several future studies are proposed in the next section.

6.4 Research Impact and Future Directions

Taken together, the three studies presented in this thesis provide distinctive insights into how influenza vaccination may be associated with protecting older adults not only from influenza infection itself but also from its serious CVD consequences. Beyond methodological contributions, these findings have real-world relevance that extends into clinical decision-making, public health policy, and research design. The following section explores the broader implications and potential uses of these findings.

The findings of this thesis have several important implications for clinical practice, public health policy, and future research. At the clinical level, this work reinforces the importance of influenza vaccination as a preventive tool not only for reducing influenza infection but also for mitigating serious CVD complications in older adults with pre-existing heart disease. This population, already at elevated risk of adverse outcomes, may derive meaningful secondary prevention benefits from annual influenza immunization. Clinicians—including cardiologists, internists, and primary care providers—can use this evidence to strengthen their recommendation of influenza vaccination as part of comprehensive CVD risk management. By recognizing influenza immunization as an effective intervention against influenza-related cardiovascular outcomes, vaccine counseling may shift from being seasonal or optional to being an integral part of chronic disease management.

The validation study confirmed the hypothesis that combined OHIP and ODB administrative databases improved the validity of performance measures in detecting an individual's vaccination status. This empowers future research using administrative databases (containing both physician and pharmacy billing records) for capturing an individual's influenza vaccination status to examine influenza VE among large populations.

Misclassification of exposure (i.e., vaccination status) is a major threat to the validity of VE because it introduces bias.[113,302,303] The knowledge generated in this research can be applied to mitigate bias, identify individuals' vaccination status with higher validity, and thus provide a robust estimation of VE.[224,303] Such valid estimations are required for researchers to monitor the success of vaccination campaigns in the community. In addition, policy makers can use the valid estimations to evaluate current

health polices and implement any reforms to vaccination efforts.[304] Gaining and maintaining public trust in the influenza vaccine also require valid estimations of VE.[305]

From a public health perspective, this thesis supports the refinement of vaccine promotion strategies to emphasize the broader protective effects of influenza immunization. Public messaging that connects influenza vaccination with CVD risk reduction may resonate more with older adults who do not perceive themselves as vulnerable to respiratory illness but who do recognize the seriousness of heart disease. These findings can also inform vaccination campaign timing, outreach, and prioritization—particularly in healthcare settings such as hospitals, rehabilitation centers, and long-term care homes, where at-risk individuals are concentrated.

Integrating vaccination into hospital discharge planning for CVD patients, for example, could represent a practical application of these findings.

Methodologically, the thesis offers a contribution to the field of VE research by introducing a novel approach to measuring VE against non-respiratory outcomes. The composite outcome approach, while exploratory, opens the door to future research that examines vaccines' systemic effects. It also highlights the critical role of case and control definitions in shaping VE estimates, drawing attention to the complexity of studying outcomes that lie on causal

pathways beyond the primary infection. As vaccine research continues to evolve in response to emerging pathogens and complex diseases, flexible and innovative methodological frameworks will be essential.

The exploratory analyses in Study 3 provide further context to the interpretation of influenza VE across varying clinical definitions. These results underscore the complex interplay between influenza infection and CVD risk, aligning with previous evidence that influenza infection can trigger acute events and that vaccination may mitigate this risk by preventing infection or reducing its severity.[276,306,307] Clinically, this suggests that influenza vaccination may have its greatest benefit among high-risk older adults, particularly those with underlying CVD, reinforcing recommendations for targeted vaccination strategies.

This study took a robust approach in measuring the VE using the TND. Among high-risk populations, no previous study has used this methodology to estimate VE against hospitalization specifically among patients hospitalized due to CVD events.[308,309] This approach paves the way to future research measuring the VE using the TND among high-risk populations who present with symptoms associated with influenza-related complications like an AMI. It also provides a stepping stone in measuring VE against influenza-related complications in spite of becoming infected with influenza.

Aside from reducing risk of major adverse CVD events,[307,310] the influenza vaccine was found to be supportive in preventing respiratory infection alongside the pandemic caused by another respiratory causative infection (SARS-CoV-2). After COVID-19, this benefit was even more apparent.[311,312] Although the study analyzes pre-pandemic data (2010–2016), its findings remain highly relevant in the current context where influenza continues to co-circulate with other respiratory viruses, including SARS-CoV-2. The COVID-19 pandemic

has highlighted the critical role of vaccines in preventing severe outcomes and the potential added value of influenza vaccination in mitigating strain on healthcare systems. Positioning the study within this broader context underscores how historical evidence of influenza VE in high-risk populations informs future vaccination strategies, including those implemented in a post-pandemic era where respiratory virus seasonality and vaccine uptake patterns may have shifted. Future studies in high-risk populations can follow this methodology to estimate VE robustly in these populations. This reinforces the public trust in the effectiveness of the influenza vaccine and encourages uptake.[276] Despite all efforts to enhance vaccination confidence, coverage among high-risk groups is still far from optimal,[111,313,314] and this seems to be stable over time.[250] Providing robust evidence about VE, including across different population subgroups, is the first step in building public confidence in vaccines.[315] My study contributes to the knowledge generation, and it should provide vaccine advocates with the needed tools to educate the public.

Over the past decade in Ontario, influenza vaccine options and where they are delivered have both expanded in ways that matter for older adults and for evaluating vaccine effectiveness. In addition to IIV-SD, enhanced vaccines for adults ≥65 years—IIV-HD and MF59-adjuvanted inactivated (IIV-Adj)—have become widely used; current Canadian guidance preferentially recommends IIV-HD, IIV-Adj, or recombinant vaccine over IIV-SD for this age group based on improved protection with similar safety.[3,316] In parallel, access points have diversified: since 2012, injection-trained pharmacists in Ontario have been authorized to administer publicly funded influenza vaccines under the Universal Influenza Immunization Program (UIIP), and beginning in the 2020–2021 season, high-dose vaccine for seniors was explicitly included in the pharmacy-based UIIP—contributing to substantial

growth in pharmacy-delivered vaccinations.[317–319] Together, these developments—enhanced vaccine types (high-dose and adjuvanted), broader strain coverage with quadrivalent products, and expanded pharmacy administration—have reshaped influenza prevention in Ontario and should be considered when interpreting vaccine effectiveness over time.[3]

The findings demonstrate that these efforts were effective in preventing both influenza infection and CVD. This indicates that the interventions were beneficial for high-risk populations and had a meaningful impact on key CVD outcomes. The results can inform future studies aimed at estimating the cost-effectiveness of these interventions and their potential to reduce overall public health expenditures in Ontario.

The methodological framework and findings from this study provide a foundation for such work by demonstrating the feasibility and value of using robust, population-based data and the test-negative design to generate reliable vaccine effectiveness estimates among high-risk groups. Future research should examine the comparative real-world effectiveness and cost-effectiveness of high-dose, adjuvanted, and recombinant influenza vaccines across diverse populations, particularly among individuals with cardiovascular comorbidities. In addition, studies should assess how pharmacy-based vaccine administration influences uptake, timeliness of immunization, and influenza-related health outcomes. While ongoing surveillance and post-market effectiveness studies are already established in Ontario, it remains essential that these efforts employ rigorous and standardized methods to produce consistent, comparable, and actionable evidence on how evolving vaccine formulations, delivery models, and population-level coverage affect influenza-associated morbidity and mortality.

Emerging data suggest that sex and age may influence both influenza risk and vaccine

effectiveness. For instance, older males often experience higher hospitalization rates, and differences in immune response by sex have been reported.[320] My studies have attempted to address this question by exploring potential sex-based differences in influenza vaccine effectiveness using population-based data and the test-negative design among older adults hospitalized for cardiovascular conditions. I found suggestive trends indicating variation in vaccine effectiveness by sex, although the estimates were limited by sample size and power constraints, preventing a full stratified analysis. To fill these gaps, future studies should conduct large-scale, sex- and age-stratified observational analyses using linked administrative and laboratory datasets, possibly augmented by immunological biomarkers. Incorporating immunological studies would facilitate understanding of mechanistic pathways—such as hormonal or immunosenescence effects—behind VE differences.[321] Initiatives like the Sex and Age Differences in Immunity to Influenza (SADII) SCORE project further underscore the importance of investigating how sex interacts with age and frailty to shape vaccine responses.[322] Ultimately, such evidence will support more tailored vaccination strategies, optimizing protection for vulnerable subgroups, especially older adults with cardiovascular risk. This work adds to the economic and policy rationale for supporting adult influenza vaccination programs. By demonstrating that vaccination may prevent not only infection but also high-cost hospitalizations due to CVD events, the thesis contributes evidence relevant to cost- effectiveness evaluations. These findings support the allocation of healthcare resources toward sustaining and expanding access to influenza vaccines for older adults and those with chronic conditions. In an aging population with increasing multimorbidity, preventive interventions that reduce both infectious and non-infectious disease burden are particularly valuable.

Several future directions are proposed. First, linking additional data sources such as pharmacy claims, electronic medical records, and provincial immunization registries could significantly enhance the completeness and accuracy of vaccine exposure measurement. Broader and more systematic data capture would improve the validity of VE estimates and facilitate more nuanced subgroup analyses, including by vaccine type, dose, or timing.

Second, replication of these analyses in other high-risk populations—such as individuals with diabetes, or immunocompromising conditions, or those who are pregnant— would enhance the generalizability of the findings and help clarify the population-specific impact of influenza vaccination. Cross-jurisdictional comparisons and pooled analyses using harmonized methods may also help strengthen the external validity of findings. Third, future methodological research should aim to refine analytic strategies for evaluating VE against complex, multi-system outcomes such as CVD events. This may include development of more sophisticated outcome definitions using temporally anchored algorithms, or the application of causal inference methods to account for time-dependent confounding and competing risks.

The exploration of hybrid designs combining elements of test-negative, cohort, and case- crossover approaches may offer additional insights into the dynamic relationship between infection and downstream complications.

Finally, mechanistic and translational studies are needed to better understand the biological plausibility of the observed associations. While the epidemiological evidence supports a protective role for influenza vaccination in reducing CVD risk, more work is needed to elucidate the immunological and pathophysiological pathways through which this protection occurs. This includes investigating how influenza vaccination may dampen systemic

inflammation, reduce plaque instability, or prevent the hemodynamic stress associated with acute respiratory illness.

In sum, this thesis demonstrates that influenza vaccination may offer dual protection—against infection and against serious CVD outcomes—in a high-risk population. Its findings can inform clinical guidelines, public health strategies, data infrastructure planning, and future research aimed at optimizing the impact of vaccination programs on population health.

6.5 Conclusions

This thesis adds to the growing recognition that influenza vaccination is a vital intervention for older adults with CVD comorbidities. By validating data sources, applying robust test-negative design methods, and proposing a novel analytical approach to capture CVD complications of influenza, this work contributes both practical and methodological advances to the field of VE research. Its findings underscore the importance of integrating vaccination into broader strategies for chronic disease prevention and health system resilience. As the global health community continues to emphasize the value of vaccines beyond infectious disease control, the insights from this thesis are timely and relevant for advancing person-centered, preventive care for aging populations.

Influenza infection is still a major threat to the health of Canadians with devastating health and economic outcomes, especially among high-risk individuals. The influenza vaccine is one of the best available preventive measures against influenza viruses and the complications they cause.

Validating the data used to measure vaccination status is important as it is the foundation for all influenza VE studies. To overcome unmeasured confounding in such studies, it is important to use well established methods such as the TND in measuring influenza VE. This

thesis showed the validity of administrative databases to ascertain vaccination status. Identifying those most at risk of not receiving the protection needed by the influenza vaccine is important as it informs policy makers and clinicians to perhaps offer different or more focused and patient-tailored measures of protection from the influenza virus among those unequivocally benefiting from the vaccine. Future research should aim to employ these methods and validate findings in larger datasets, allowing for stratified analyses by age, sex, comorbidity burden, and CVD subtype to assess heterogeneity of vaccine effects. Studies incorporating biomarkers could help elucidate biological mechanisms linking vaccination and cardiovascular protection.

These three studies contribute to bridging knowledge gaps and provide awareness and inspiration towards further research. These studies serve as further steps to expand our knowledge and can be used by future research in the field of measuring effectiveness of vaccines against virus- causing complications.

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Appendices

Appendix A Databases used for extracted measures at ICES (adapted from Schwartz et al.).[106]

#	Database Name	Description	Extracted Measures	Year
1	Canadian Community Health Survey (CCHS)	Self-reported health information	Influenza vaccination status, Having a regular medical doctor	2013-2014
2	Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD)	Patient-level data for acute, chronic, and day surgery institutions in Ontario	Patient diagnoses and procedures during inpatient admission	1988-2016
3	Canadian Institute for Health Information Same Day Surgery (CIHI-SDS)	Patient-level data for day surgery institutions in Ontario	Patient diagnoses and procedures	2000-2016
4	Canadian Organ Replacement Register (CORR)	Activity and outcomes of vital organ transplantation and renal dialysis for donors and recipients treated in Ontario	Patient condition status (yes/no)	2000-2016
5	Chronic Obstructive Pulmonary Disease (COPD)	All Ontario patients with COPD	Patient condition status (yes/no)	2000-2016
6	Home Care services Data (HCD)	Homecare services	Patient use for homecare services (yes/no)	2000-2016
7	National Ambulatory Care Reporting System (CIHI-NACRS)	Patient visits to hospital and community based ambulatory care: day surgery, outpatient clinics and emergency departments	Patient diagnoses and procedures	2000-2016
8	Ontario Cancer Registry (OCR)	Ontario residents newly diagnosed, or died, with cancer (except non-melanoma skin cancers)	Patient condition status (yes/no)	2000-2016
9	Ontario Congestive Heart Failure (CHF)	All Ontario individuals identified as having CHF	Patient condition status (yes/no)	2000-2016
10	Ontario Diabetes Database (ODD)	All incident cases of diabetes in Ontario	Patient condition status (yes/no)	2000-2016
11	Ontario Drug Benefit (ODB)	Claims for prescription drugs received under the ODB program (most are for those ≥ 65 years of age)	Influenza vaccination status, medication-use	2000-2016
12	Ontario Health Insurance Plan (OHIP)	Ontario Health Insurance Plan for most healthcare professionals in the province	Demographics, diagnoses, vaccination status	1991-2016
13	Ontario Human Immunodeficiency Virus (HIV) database	All Ontario HIV positive patients	Patient condition status (yes/no)	2000-2016

#	Database Name	Description	Extracted Measures	Year
14	Ontario Hypertension Database (HYPER)	All Ontario individuals identified as having hypertension.	Patient condition status (yes/no)	1991-2016
15	Ontario Renal Reporting System (ORRS)	Data on patients with chronic kidney disease and renal dialysis	Patient condition status (yes/no)	2010-2016
16	Registered Persons Database (RPDB)	Registered persons under the Ontario Health Insurance Plan (OHIP)	Demographics, mortality information on date of death in Ontario (if applicable).	1991-2016
17	The Flu and Other Respiratory Viruses Research dataset (FOREVER)	Laboratory testing results of respiratory viruses provided by Public Health Ontario and selected hospital-based laboratories as part of clinical practice to confirm presence of influenza infection in patients (2010-11 to 2015-16 influenza seasons).	Influenza laboratory results	2010-2016

Appendix B Conditions and their corresponding medication measures.[186]

Condition	Medication of Interest
Ventricular Tachyarrhythmia	Beta1-Adrenergic Antagonists Antiarrhythmics
Venous Thromboembolism	Factor Xa Inhibitors
	Low Molecular Weight Heparin
	Thrombin Inhibitors
	Thrombolytics
	Unfractionated Heparin
	Vitamin K Antagonists
Syncope	Alpha1-adrenergic Agonists
	Mineralocorticoids
Supraventricular Tachycardia	Antiarrhythmics
Stable Angina	Antiplatelet Agents
	Beta1-adrenergic Antagonists
	Calcium Channel Blockers
	Nitrates
Raynaud Phenomenon	Alpha1-Adrenergic Antagonists
	Calcium Channel Blockers
	Phosphodiesterase Type 5 Inhibitors
Prevention of Ischemic Stroke	Anticoagulants
	Antiplatelet Agents
Post-myocardial Infarction	Angiotensin-converting-enzyme inhibitors inhibitor
	Antiplatelet Agents
	Angiotensin 2 receptor blockers
	Beta1-adrenergic Antagonists
	Mineralocorticoid Receptor Antagonists (MRAs)
	Statins
Intermittent Claudication	Antiplatelet Agents
	Rheologic Modifiers
Hypertension	Angiotensin-converting-enzyme inhibitors
	Alpha1-Adrenergic Antagonists
	Angiotensin 2 receptor blockers
	Beta1-Adrenergic Antagonists
	Calcium channel blockers
	Centrally Acting Antihypertensive Agents
	Direct Renin Inhibitors
	Diuretics

Condition	Medication of Interest
Heart Failure	Angiotensin-converting-enzyme inhibitors
	Angiotensin Receptor-Neprilysin Inhibitor Combinations
	Angiotensin 2 receptor blockers
	Beta1-adrenergic Antagonists
	Calcium channel blockers
	I(f) Current Inhibitor
	Inotropic Agents
	Loop Diuretics
	Mineralocorticoid Receptor Antagonists (MRAs)
	Thiazides and Related Diuretics
	Vasodilators
Dyslipidemias	Cholesterol Absorption Inhibitors
	Fibrates
	Niacin (Nicotinic Acid) Derivatives
	Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors
	Resins
	Statins
Acute Stroke	Antiplatelet Agents
	Calcium channel blockers
	Thrombolytics
Acute Coronary Syndromes	Angiotensin-converting-enzyme inhibitors
	Antiplatelet Agents
	Beta1-blockers
	Calcium channel blockers
	Direct thrombin inhibitors
	Glycoprotein IIb/IIIa
	Low Molecular Weight Heparin
	Mineralocorticoids Receptor Antagonists
	Nitrates
	Specific Xa inhibitors
	Thrombolytics
	Unfractionated Heparin

Appendix C List of respiratory viral diagnostic assays used by the FOREVER Cohort, by laboratory, testing method, and influenza season[173]

Laboratory	Testing method	Commercial kit or source of testing reagents	2009-10	2010-11	2011-12	2012-13	2013-14	2014-15	2015-16
PHO	Culture	Quidel/Diagnostic Hybrids	✓	✓	✓	✓	✓	✓	✓
	PCR	LDT for influenza A/B (CDC protocol)	✓	✓	✓	✓	✓	✓	✓
	MPX	Seeplex® RV12 Detection kit (Seegene)	✓						
		xTAG® Respiratory Viral Panel (Luminex)	✓	✓					
		Seeplex® RV15 ACE Detection kit (Seegene)			✓	✓	✓	✓	✓
NYGH	EIA (Rapid)	Directigen™ EZ Flu A+B (Becton Dickinson)	✓						
	PCR	ProFlu (Prodesse)		✓	✓				
		Xpert Flu (GeneXpert)				✓	✓	✓	✓
		Simplexa Flu & RSV (Focus Diagnostics)					✓	✓	✓
HSC	DFA	Simulfluor (influenza A/B, RSV, parainfluenza 1-3, adenovirus) monoclonal antibodies (Millipore) hMPV monoclonal antibodies (Diagnostic Hybrids)	✓	✓	✓	✓	✓		
	Culture	Monoclonal antibodies as per DFA and R-Mix shell vials (Diagnostic Hybrids)	✓	✓					
	PCR	RealStar® Influenza RT-PCR Kit (altona Diagnostics)	✓						
		Seeplex® FluA ACE Subtyping kit (Seegene)	✓	✓					
	MPX	Seeplex® RV15 ACE Detection kit (Seegene)	✓	✓	✓	✓	✓		
		xTAG® Respiratory Viral Panel FAST v2 (Luminex)						✓	
		NxTAG® Respiratory Pathogen Panel (Luminex)							✓
		Adenovirus R-gene® Assay (Argene)	✓	✓					
	Other (PCR)	RealStar® Adenovirus PCR Kit 1.0 (altona Diagnostics)			✓	✓	✓		
SHSC	DFA	Simulfluor (influenza A/B, RSV, parainfluenza 1-3, adenovirus) monoclonal antibodies (Millipore) hMPV monoclonal antibodies (Diagnostic Hybrids)	✓						
	Culture	Monoclonal antibodies as per DFA and R-Mix shell vials (Diagnostic Hybrids)	✓						
	MPX	QIAGEN Multiplex PCR Kit (Qiagen)	✓	✓					
		xTAG® Respiratory Viral Panel (Luminex)			✓	✓	✓	✓	✓
UHN & MSH	PCR	Influenza Screen and Type RT-PCR Kit (Astra Diagnostics)	✓	✓	✓	✓			
		Simplexa Flu & RSV (Focus Diagnostics)				✓	✓	✓	✓
WOHS	EIA	BinaxNow® Influenza (Alere)	✓	✓					
		BinaxNow® RSV (Alere)	✓	✓	✓				
		TRU FLU® (Meridian Bioscience)			✓				
		Directigen™ EZ Flu A+B (Becton Dickinson)			✓				
	PCR	ProFlu (Prodesse)				✓			
		Simplexa Flu & RSV (Focus Diagnostics)					✓	✓	✓

CHEO	EIA (Rapid)	xPect Influenza A and Influenza B (Remel)	✓	✓	✓	✓			
		xPect RSV (Remel)	✓	✓	✓	✓			
	DFA	Light Diagnostics™ Influenza A and B DFA Kit (Millipore)	✓	✓	✓	✓	✓		
		Light Diagnostics™ RSV DFA (Millipore)	✓	✓	✓	✓	✓		
		Light Diagnostics™ hMPV DFA (Millipore)		✓	✓	✓	✓		
	Culture	Commercial (Quidel/Diagnostic Hybrids) and non-commercial cell lines	✓	✓	✓	✓	✓	✓	✓
	PCR	LDT for influenza A/B, RSV	✓	✓	✓				
		LDT for hMPV, rhinovirus/enterovirus, adenovirus and parainfluenza 1-3	✓	✓	✓	✓	✓		
		Simplexa Flu & RSV (Focus Diagnostics)				✓	✓	✓	✓
		ARIES® Flu A/B & RSV Assay (Luminex)							✓
	MPX	Anyplex™ II RV16 Detection kit (Seegene)					✓	✓	✓
		Allplex™ Respiratory Virus Panel (Seegene)							✓
HRLMP	DFA	Simulfluor (influenza A/B, RSV, parainfluenza 1-3, adenovirus) monoclonal antibodies (Millipore) hMPV monoclonal antibodies (Diagnostic Hybrids)	✓	✓					
	Culture	Monoclonal antibodies as per DFA and R-Mix shell vials (Diagnostic Hybrids)	✓	✓					
	PCR	LDT for influenza A	✓	✓					
	MPX	LDT for influenza A/B, RSV, hMPV, parainfluenza 1-3, adenovirus			✓	✓	✓	✓	✓
		LDT for rhinovirus/enterovirus					✓		
LHSC	MPX	Seeplex® RV12 ACE Detection kit (Seegene)	✓						
		Seeplex® RV15 ACE Detection kit (Seegene)		✓	✓	✓	✓		
		Anyplex®II RV16 Detection kit (Seegene)						✓	✓

CHEO=Children's Hospital of Eastern Ontario, DFA=direct fluorescent antibody staining, EIA=enzyme immunoassay rapid antigen test, hMPV=human metapneumovirus, HRLMP=Hamilton Regional Laboratory Medicine Program, HSC=Hospital for Sick Children, LDT=Laboratory-developed test, LHSC=London Health Sciences Centre, MPX=multiplex PCR, MSH=Mount Sinai Hospital, NYGH=North York General Hospital. PCR=monoplex polymerase chain reaction, PHO=Public Health Ontario, RSV=respiratory syncytial virus, SHSC=Sunnybrook Health Sciences Centre, UHN=University Health Network, WOHS=William Osler Health System

Appendix D Influenza Seasons from 2010-11 to 2015-16

Influenza Season[173]			
Year	***Beginning (Month, Day)***	***Peak Month (Day)***	***End (Month, Day)***
2010-11	November 14	December (26th)	April 9
2011-12	January 29	March (11th)	May 19
2012-13	November 4	December (23rd)	May 11
2013-14	December 1	December (29th)	May 24
2014-15	November 23	December (28th)	May 16
2015-16	January 17	March (6th)	May 28

Influenza season starts when the positivity rate of laboratory influenza tests are reported to be 5% and a minimum of 15 positive tests are observed.[191]

The ***peak month*** of influenza activity is defined by the CDC as "the month with the highest percentage of respiratory specimens testing positive for influenza virus infection during that influenza season".[192]

Appendix E Definitions of medical conditions increasing risk of influenza-related complications[173]

Medical Condition	Definition
Asthma	Asthma database was used to identify patients with asthma, based on 2 or more ambulatory care visits and/or 1 or more hospitalizations.[216] **OHIP** OHIP diagnostic code: 493 **CIHI-DAD** ICD-9 diagnostic code: 493 ICD-10 diagnostic codes: J45, J46
Chronic obstructive pulmonary disease (COPD)	COPD database was used to identify patients with COPD, based on 1 or more ambulatory care visits and/or 1 or more hospitalizations. Algorithm to identify COPD patients were only validated in those ages 35 and over.[211] **OHIP** OHIP diagnostic codes: 491, 492, 496 **CIHI-DAD** ICD-9 diagnostic codes: 491, 492, 496 ICD-10 diagnostic codes: J41, J42, J43, J44
Diabetes	ODD was used to identify patients with diabetes, based on 2 OHIP diagnostic codes or 1 OHIP service code or 1 CIHI admission within 2 years.[212] **OHIP** OHIP diagnostic code: 250 OHIP service codes: Q040, K029, K030, K045, K046 **CIHI-DAD, CIHI-SDS** ICD-9 diagnostic code: 250 ICD-10 diagnostic codes: E10, E11, E13, E14
Anemia	Patients with a diagnosis of anemia were identified if they had any of the following codes in OHIP, CIHI-DAD, CIHI-SDS or CIHI-NACRS in the 3 years prior to index date: **OHIP** OHIP diagnostic codes: 280, 281, 282, 283, 284, 285, 773 **CIHI-DAD, CIHI-SDS, CIHI NACRS** ICD-10 diagnostic codes: D50, D51, D52, D53, D55, D56, D572, D573, D574, D58, D59, D60, D61. D63, P55, P560, P570
Cancer	**OCR** was used to identify patients with any cancer diagnosed in Ontario except for non-melanoma skin cancer.[206]
Chronic kidney disease (CKD)	Patients with a diagnosis of CKD in the 5 years before index date, using the following diagnostic codes[210]: **OHIP** OHIP diagnostic codes: 403, 585 **CIHI NACRS, CIHI-DAD**

Medical Condition	Definition
	ICD-10 diagnostic codes: E102, E112, E132, E142, I12, I13, N08, N18, N19
	Patients who were on chronic dialysis[205] in the year before index date, identified as those with at least 2 of any of the following codes in OHIP, CIHI-DAD, or CIHI-SDS separated by at least 90 days, but less than 150 days **OHIP** OHIP service codes: R849, G323, G325, G326, G860, G862, G865 G863, G866, G330, G331, G332, G333, G861, G082, G083, G085, G090, G091, G092, G093, G094, G095, G096, G294, G295, G864, H540, H740 **CIHI-DAD, CIHI-SDS** CCI procedure codes: 5195, 6698 CCP procedure code: 1PZ21 **CORR** Treatment codes: 060, 111, 112, 113, 121, 122, 123, 131, 132, 133, 141, 151, 152, 211, 221, 231, 241, 242, 251, 252, 311, 312, 313, 321, 322, 323, 331, 332, 333, 413, 423, 433, 443, 453 **ORRS** Patients included in ORRS
	Exclusion criteria: Patients with kidney transplants [323]: **OHIP** OHIP service codes: S435, S434 **CIHI-DAD** CCP procedure code: 6759 CCI procedure code: 1PC85 **CORR** Treatment code: 171 plus one or more of Transplanted Organ Codes (1-3): 10, 11, 12, 18, 19 **ORRS** Type of event during patient care: Transplanted (tx) (Note: ORRS data only available for 2010 and onwards.)
Immunocompromised	Those identified using the following databases and definitions: **ODB** 30 days of oral corticosteroids in the past 6 months, antineoplastic use in the past 6 months, or use of another immunocompromising drug in the past 6 months **CORRLINK** CORRLINK is a dataset in ICES which links CORR and CIHI-DAD data. This database only includes patients that have received an organ transplant and does not include dialysis patients. **HIV**

Medical Condition	Definition
	HIV database was used to identify patients with HIV, based on 3 physician claims in 3 years with OHIP diagnostic codes: 042, 043 or 044[214]
Dementia	**Dementia:** 1 hospitalization for dementia and/or 3 ambulatory visits for dementia, each separated by at least 30 days, within 2 years and/or 1 prescription from ODB[202] **OHIP** OHIP diagnostic codes: 290, 331 **CIHI-DAD, CIHI-SDS** ICD-9 diagnostic codes: 0461, 290.0, 290.1, 290.2, 290.3, 290.4, 294, 331.0, 331.1, 331.5 ICD-10 diagnostic codes: F00, F01, F02, F03, G30 **ODB** 1 prescription for a cholinesterase inhibitor
Frailty	**CIHI-DAD, HCD and OHIP** databases were used to identify patients with frailty within a year before index date, based on rules that identified[218]: Long-term care residents (i.e., admitted from or discharged to a nursing home after hospitalization, or location of physician billing claim was long-term care facility). Receipt of palliative care Two or more domains derived from frailty scales (i.e., cognitive impairment, general health status, incontinence, falls, nutrition issues, functional performance) and health services utilization (i.e., ≥2 hospitalizations or emergency department visits, geriatrician or home care visit).
History of congestive heart failure (CHF)	CHF database was used to identify patients with CHF, based on 1 CIHI NACRS, CIHI-DAD, CIHI-SDS, or OHIP claim and a second claim (from either) in 1 year. The CHF database is limited to those 40 years of age or older.[203] **OHIP** OHIP diagnostic code: 428 **CIHI-DAD, CIHI-SDS** ICD-9 diagnostic code: 428 ICD-10 diagnostic codes: I500, I501, I509
History of TIA or Acute Ischemic Stroke	**Transient Ischemic Attack:** CIHI-DAD and CIHI-NACRS were used to identify patients with a history of a transient ischemic attack, based on at least 1 hospitalization or ED visit with a diagnosis coded with one of the following codes: ICD-9 diagnostic codes: 435, 3623 ICD-10 diagnostic codes: G450, G451, G452, G453, G458, G459, H340

Medical Condition	Definition
	Acute Ischemic Stroke [252]**:** CIHI-DAD was used to identify patients with a history of acute ischemic stroke, based on at least 1 hospitalization with a main diagnosis coded with one of the following codes: ICD-9 diagnostic codes: 434, 436 ICD-10 diagnostic codes: I63 (excluding I63.6), I64, H34.1
History of cardiac ischemia	CIHI-DAD and CIHI-NACRS were used to identify patients with a history of cardiac ischemia, based on at least 1 hospitalization or ED visit with a diagnosis or procedure coded with one of the following codes: **Angina:** ICD-9 diagnostic codes: 411, 413, 4298 ICD-10 diagnostic codes: I20, I2382, I24 **Chronic Ischemic Heart Disease:** ICD-9 diagnostic codes: 412, 4140, 4141, 4148, 4149, 4292 ICD-10 diagnostic codes: I25 **Myocardial infarction:** ICD-9 diagnostic codes: 410 ICD-10 diagnostic codes: I21, I22 **Coronary Artery Bypass Grafting**[209]**:** CCI procedure codes: 1IJ76, 1IJ80 CCP procedure codes: 481, 4899 **Percutaneous Coronary Intervention**[209]**:** CCI procedure codes: 1IJ26, 1IJ50, 1IJ55, 1IJ57 CCP procedure codes: 4802, 4899, 4804
History of cardiac arrhythmia	CIHI-DAD and CIHI-NACRS were used to identify patients with a history of cardiac arrhythmia, based on at least 1 hospitalization or ED visit with a diagnosis or procedure coded with one of the following codes: **Atrial Fibrillation/Atrial Flutter:** ICD-9 diagnostic codes: 4273 ICD-10 diagnostic codes: I48 **Ventricular Arrhythmia & Tachycardia:** ICD-9 diagnostic codes: 4271, 4274, 4276, 4278 ICD-10 diagnostic codes: I470, I472, I490, I493 **Permanent Pacemaker** [207,208]**:** CCI procedure codes: 1HZ53GRNM, 1HZ53LANM, 1HZ53GRNK, 1HZ53LANK, 1HZ53GRNL, 1HZ53LANL CCP procedure code: 4971 **Implantable Cardioverter- Defibrillator** [204]**:** CCI procedure codes: 1HZ53GRFS, 1HZ53LAFS, 1HZ53SYFS, 1HZ53HAFS CCP procedure codes: 4974
Hypertension	**Adults (20+):**[215]

Medical Condition	Definition
	- ≥1 Hospitalization *or* ≥2 OHIP in a two-year period. *OR* - 1 OHIP *followed by* OHIP/Hosp within two years. *OR* - 1 Hospitalization (<1991) *followed by* 1 Hospitalization (>1991)

CCI=Canadian Classification of Health Interventions, CCP=Canadian Classification of Procedures, CIHI=Canadian Institute of Health, CORR=Canadian Organ Replacement Register, DAD=Discharge Abstract Database NACRS=National Ambulatory Care Reporting System, OCR=Ontario Cancer Registry, ODB=Ontario Drug Benefit, ODD=Ontario Diabetes Database, OHIP=Ontario Health Insurance Plan, ORRS=Ontario Renal Reporting System, SDS=Same Day Surgery

Appendix F Identification of frailty in this study[218]

Seniors are considered frail (flagged as 'yes' for the binary measure of frailty) if they meet at least TWO or more of the following domains from 3a to 3g:

3a. COGNITIVE IMPAIRMENT

Definition	ICD9/10		Notes
DISCHARGE ABSTRACTS (DAD) AND/OR PHYSICIAN BILLINGS/CLAIMS DXCODES1-3			
Senile dementia, uncomplicated	ICD9 ICD10	'2900'<=DXCODE [i] <='2909' 'F0390'<= DXCODE [i] <='F0390'	
Dementia in Alzheimer's disease	ICD9 ICD10	'3310'<=DXCODE [i]<='3310' 'G300'<=DXCODE [i]<='G300'	
Vascular dementia	ICD9 ICD10	'2904'<=DXCODE [i] <='2904' 'F010'<=DXCODE [i]<='F019'	Captured above
Dementia in other diseases classified elsewhere	ICD9 ICD10	'2941'<=DXCODE [i] <='2941' 'F020'<=DXCODE [i]<='F028' 'F03'<=DXCODE [i]<='F03'	Captured above
Unspecified dementia	ICD9 ICD10	'2942'<=DXCODE [i]<='2942' 'F0390'<=DXCODE [i]<='F0391'	
Cerebral generations usually manifest in childhood	ICD9 ICD10	'3300'<=DXCODE [i]<='3309' 'G94'<=DXCODE [i]<='G94'	
Other cerebral degenerations including Alzheimer's	ICD9 ICD10	'3311'<=DXCODE [i]<='3362' 'G310'<=DXCODE [i]<='G328'	
Senility without mention of psychosis	ICD9 ICD10	'797'<=DXCODE [i]<='797' 'R54'<=DXCODE [i]<='R54'	
Delirium	ICD9 ICD10	'293'<=DXCODE [i]<='293' 'F05'<=DXCODE [i]<='F05'	

3b. GENERAL HEALTH STATUS INDICATORS

Definition	Fields/ICD9/10	Data file	Notes
Record of at least one of the following i to iv …			
i. <u>At least 2</u> hospital admissions in past year	Admission dates	DAD	Transfers are a single admission
OR			
ii. <u>At least 2</u> ED visits in past year	DAD: Entry; E=emergency; addate; Billings: location and/or hospital unit (=ED)	DAD Physician billings	The same methods will be used as for the ED quality indicator
OR			
iii. Malaise and fatigue /debility	ICD9: 7807; 7993 ICD10: R53; G933	DAD Physician billings	
OR			

iv. Cachexia	ICD9: 7994 ICD10: R64	DAD Physician billings	

3c. INCONTINENCE

Definition	ICD9/10		Notes
DISCHARGE ABSTRACTS (DAD) AND/OR PHYSICIAN BILLINGS/CLAIMS DXCODES1-3			
Urinary	ICD9 ICD10	7883 R32	
Fecal	ICD9 ICD10	7876 R15	

3d. FALLS

Definition	ICD9/10		Notes
DISCHARGE ABSTRACTS (DAD) DXCODES1-3			
Various falls	ICD9 ICD10	E88, E9177, E9178, E9293 W01, W05, W06-W19	Only count if associated with hospitalization.

3e. NUTRITION ISSUES

Definition	ICD9/10		Notes
DISCHARGE ABSTRACTS (DAD) AND/OR PHYSICIAN BILLINGS/CLAIMS DXCODES1-3			
Record of at least one of the following i to ii…			
i. Abnormal weight loss; underweight; other concerns	ICD9 ICD10	7830, 78321, 78322, 7833, 7839 R630, R633, R634, R636, R638	
OR			
ii. Failure to thrive (adult)	ICD9 ICD10	7837 R627	

3f. FUNCTIONAL PERFROMANCE

Definition	ICD9/10		Notes
DISCHARGE ABSTRACTS (DAD) AND/OR PHYSICIAN BILLINGS/CLAIMS DXCODES1-3			
Record of at least one of the following i to v…			
i. Abnormality of gait	ICD9 ICD10	7812 R26	
OR			
ii. Difficulty in walking	ICD9 ICD10	7197 R262	
OR			

iii. Muscular wasting and disuse atrophy	ICD9 ICD10	7282 M6250	
OR			
iv. Muscular weakness	ICD9 ICD10	72887 M6281	
OR			
v. Pressure ulcer	ICD9 ICD10	70700 - 70709 L89	

3g. TARGETED HEALTH SERVICE UTILIZATION

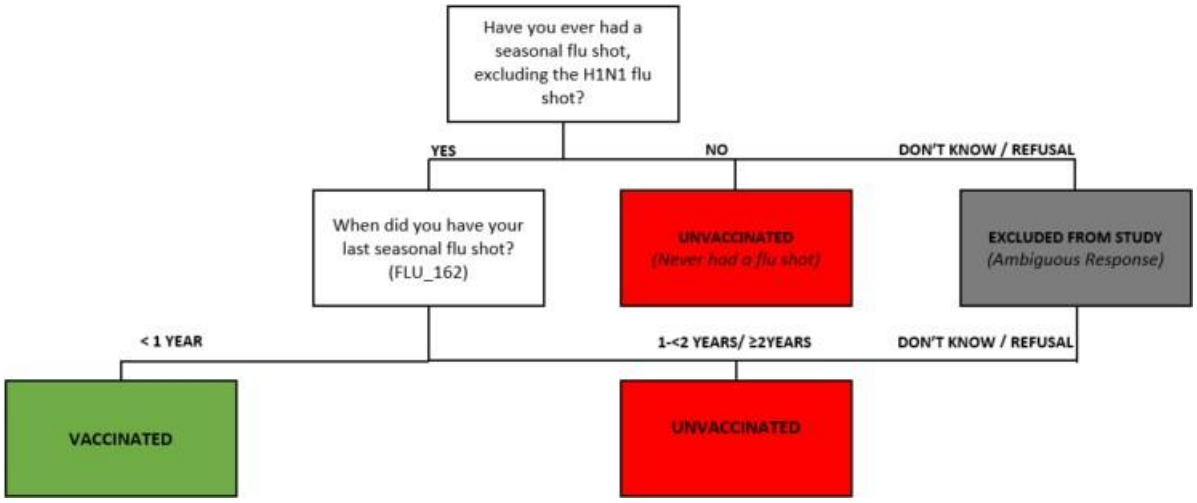
Definition	Fields	Data file	Notes
Record of at least one of the following i to iii …			
i. At least one geriatrician billing claim	Provider type (spec, dspecial, doctype) = Geriatric medicine (GEMD)	Physician billing	
OR			
ii. At least one geriatrician service claim	Main patient service (patserv; mpserv) 72= geriatrics	DAD	
OR			
iii. At least one provider home visit (all types)	Location of service (location, servloc) = Patients home; home hospital care	Physician billings	Provinces may offer a number of categories. We are interested in the 'home' (not a nursing home which is used for decision rule #1)

Appendix G CCHS's core-content questions about receiving the influenza vaccine

***FLU_160*:** Have you ever had a seasonal flu shot, excluding the H1N1 flu shot? 1: Yes 2: No 8: RF (refuse) 9: DK (Don't Know)

***FLU_162*:** When did you have your last seasonal flu shot? 1: Less than 1 year ago
2: 1 year to less than 2 years ago
3: 2 years ago or more
8: RF
9: DK

The algorithm of questions used in the CCHS survey on taking the flu shot.



Appendix H Influenza vaccination administrative billing codes

Available billing codes during years 2010-2016	
Ontario Health Insurance Program (Variable: FEECODE):	G590
	G591
	Q590
	Q690
	Q691
	G592

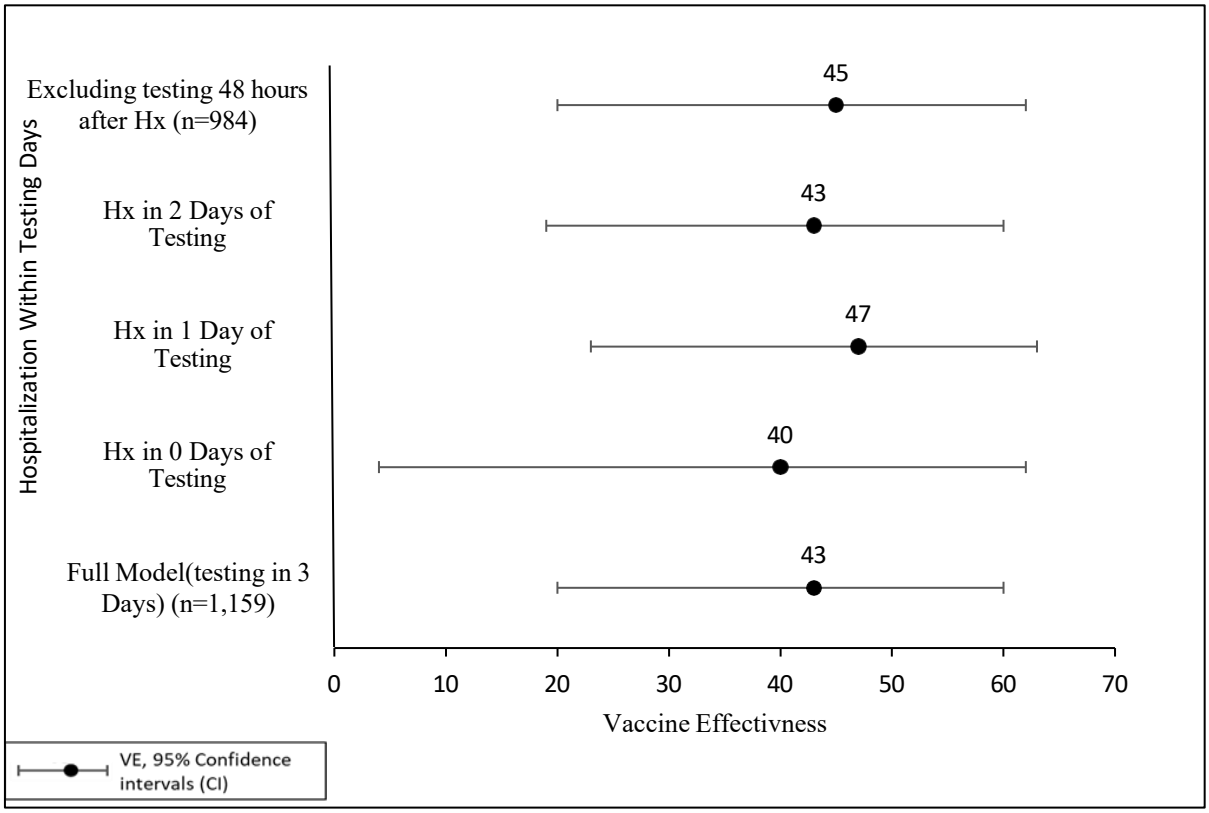
Drug Identification Numbers in Ontario Drug Benefit program publicly funded as of 2012 in Ontario						
DIN	**Influenza Product**	**Eligibility**	**2012-13**	**2013-14**	**2014-15**	**2015-16**
2015986	FLUVIRAL® GlaxoSmithKline Inc.		x	x	x	
2223929	VAXIGRIP® Sanofi Pasteur Limited		x	x	x	
2269562	Influvac® BGP Pharma (Trivalent influenza vaccine (TIV)) 18 years and older					x
2346850	AGRIFLU® Novartis Vaccines and Diagnostics, Inc.		x	x		
2362384	FLUAD® Novartis Vaccines and Diagnostics, Inc. (Trivalent influenza vaccine)	65 years and older	x		x	x
2420686	Fluviral® GlaxoSmithKlineInc. (Trivalent influenza vaccine)	Age 5 and older (* Unless specifically requested the TIVs are primarily targeted to adults 18 years of age and older.)				x
2420783	FluLaval Tetra® GlaxoSmithKline Inc.	Age 5 to 17years (inclusive)				x

	(Quadrivalent influenza vaccine)					
2426544	FLUMIST® Quadrivalent AstraZeneca Canada(Quadrivalent influenza vaccine)	Age 5 to 17 years				x
2428881	Agriflu® Novartis Vaccines and Diagnostics, Inc. (Trivalent influenza vaccine)	Age 5 and older (* Unless specifically requested the TIVs are primarily targeted to adults 18 years of age and older.)				x
2432730	Fluzone Quadrivalent® Sanofi Pasteur Limited(Quadrivalent influenza vaccine)	Age 5 to 17years (inclusive)				x
9857501	FLUZONE® Sanofi Pasteur Limited				x	

Appendix I Sensitivity analysis of performance measures in comparison to main analysis

Type of analysis	True Positive	False Positive	True Negative	False Negative	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Main analysis	8034	274	17758	5324	60.1% (59.3%-61.0%)	98.48% (98.3%-98.7%)	96.7% (96.3%-97.1%)	77.0% (76.4% - 77.5%)
Sensitivity analysis of performance measures after including respondents with only Q130 fee-codes in administrative data as vaccinated (n=31694)	8302	310	17758	5324	60.9% (60.1%-61.8%)	98.28% (98.1%-98.5%)	96.4% (96.0%-96.8%)	76.9% (76.4% - 77.5%)
Performance measures of administrative data (OHIP+ODB) in identifying influenza vaccination status, using CCHS as reference standard (restricted to CCHS interviews from Feb. 1st to Aug. 30th) (n= 16,651)	4208	88	9545	2810	60.0% (58.8%-61.1%)	99.1% (98.9%-99.3%)	98.0% (97.5%-98.4%)	77.3% (76.5% - 78.0%)
Sensitivity analysis of vaccination window restriction in the administrative billing claims to up to 335 days (n= 31390)	7607	211	17821	5751	56.7% (56.1% - 57.8%)	98.8% (98.7% - 99%)	97.3% (96.9% - 97.7%)	75.6% (75.1% - 76.2%)

Appendix J: Sensitivity analysis for time window for hospitalization



***HX: Hospitalization**

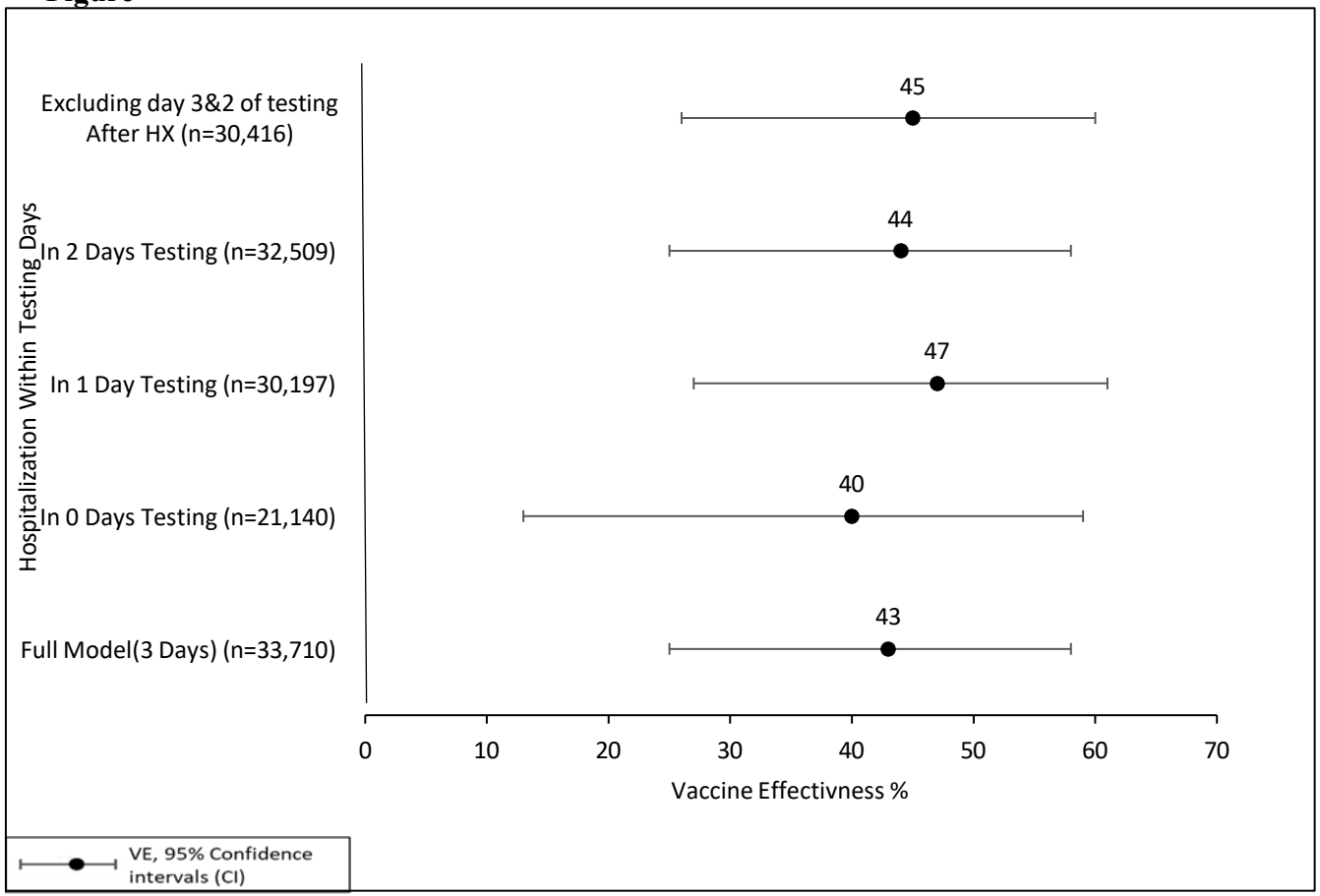
Sensitivity analysis by days between index date and hospitalization

Analysis: Vaccinated (Adjusted Model)	N	Odds Ratios	95% Wald Confidence Limits		Vaccine Effectiveness %	95% (Confidence Interval)		p-Value
			Lower	Upper		Lower	Upper	
HX* within ±3 days of influenza testing	1159	0.568	0.404	0.797	43%	20%	60%	0.001
HX* within 0 days of influenza testing	656	0.605	0.382	0.959	40%	4%	62%	0.03
HX* within ±1 day of influenza testing	972	0.534	0.367	0.775	47%	23%	63%	0.001
HX* within ±2 days of influenza testing	1093	0.572	0.403	0.812	43%	19%	60%	0.002
Day -1 to Day 3	984	0.555	0.384	0.803	45%	20%	62%	0.002

***HX: Hospitalization**

Appendix K Sensitivity analysis for time window for hospitalization

Figure



***HX: Hospitalization**

Model Output of Sensitivity Analysis by Days between index date and Hospitalization

Analysis: Vaccinated	N	Odds Ratios	95% Wald Confidence Limits		Vaccine Effectiveness %	95% (Confidence Interval)		p-Value
			Lower	Upper		Lower	Upper	
Adjusted Model for: Day -1 to day 3	30,416	0.546	0.401	0.744	**45%**	**26%**	**60%**	**0.0001**
Adjusted Model for: HX* within 0 days of influenza testing	21,140	0.596	0.410	0.866	**40%**	**13%**	**59%**	**0.0067**
Adjusted Model for: HX* within ±1 day of influenza testing	30,197	0.532	0.389	0.729	**47%**	**27%**	**61%**	**<0.0001**
Adjusted Model for: HX* within ±2 days of influenza testing	32,509	0.561	0.417	0.755	**44%**	**25%**	**58%**	**0.0001**
Adjusted Model: HX* within ±3 days of influenza testing	33,710	0.566	0.424	0.754	**43%**	**25%**	**58%**	**0.0001**

***HX: Hospitalization**

END