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Complete List of Authors:	Scott, Allison; Government of Alberta, Ministry of Health; PolicyWise for Children & Families Buchan, Sarah; Institute for Clinical Evaluative Sciences; Public Health Ontario Kwong, Jeff; Institute for Clinical Evaluative Sciences Drews, Steven; Alberta Provincial Laboratory for Public Health; University of Alberta, Division of Preventive Medicine Simmonds, Kimberley; Alberta Ministry of Health, Epidemiology and Surveillance Svenson, Lawrence; Government of Alberta, Ministry of Health; University of Calgary Cumming School of Medicine, Department of Community Health Sciences
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TITLE

Using population-wide administrative and laboratory data to estimate type- and subtype-specific influenza vaccine effectiveness: a surveillance protocol

Allison N Scott[1,2,3]

Sarah A Buchan[4,5,6]

Jeffrey C Kwong[4,5,6,7,8]

Steven J Drews[9,10]

Kimberley A Simmonds[1,11]

Lawrence W Svenson[1,11, 12, 13]

Affiliations

[1]Ministry of Health, Government of Alberta, Edmonton, AB, Canada

[2]PolicyWise for Children & Families, Edmonton, AB, Canada

[3]Department of Public Health, Concordia University of Edmonton, AB, Canada

[4]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada

[5]Public Health Ontario, Toronto, ON, Canada

[6]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

[7]Department of Family & Community Medicine, University of Toronto, Toronto, ON, Canada

[8]University Health Network, Toronto, ON, Canada

[9]The Alberta Provincial Laboratory for Public Health, Edmonton, AB, Canada

[10]Department of Laboratory Medicine & Pathology, University of Alberta, Edmonton, AB, Canada

[11] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

[12] School of Public Health, University of Alberta, Edmonton, AB, Canada

[13] Division of Preventive Medicine, University of Alberta, Edmonton, AB, Canada

Corresponding Author:

Allison N. Scott, Ph.D.

PolicyWise for Children & Families

1000, 9925-109 Street NW

Edmonton, Alberta, Canada T5K 2J8

Email Addresses

Allison N Scott	AScott@policywise.com
Sarah A Buchan	Sarah.Buchan@oahpp.ca
Jeffrey C Kwong	jeff.kwong@utoronto.ca
Steven J Drews	steven.drews@blood.ca
Kimberley A Simmonds	kimberley.simmonds@gov.ab.ca
Lawrence W Svenson	larry.svenson@gov.ab.ca

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ABSTRACT

Introduction

The appropriateness of using routinely collected laboratory data combined with administrative data for estimating influenza vaccine effectiveness (VE) is still being explored. This paper outlines a protocol to estimate influenza VE using linked laboratory and administrative data which could act as a companion to estimates derived from other methods.

Methods and Analysis

We will use the test-negative design to estimate VE for each influenza type/subtype and season. Province-wide individual-level records of positive and negative influenza tests will be linked, by unique personal health numbers, to administrative databases and vaccination records to determine covariates and influenza vaccination status, respectively. Covariates of interests include age, sex, immunocompromising chronic conditions, and healthcare setting. Cases will be defined based on an individual's first positive influenza test during the season, and potential controls will be defined based on an individual's first negative influenza test during the season. One control for each case will be randomly selected based on the week the specimen was collected. We will estimate vaccine effectiveness using multivariable logistic regression.

Ethics and Dissemination

Ethics approval was obtained from the University of Alberta's Health Research Ethics Board – Health Panel under study ID Pro00075997. Results will be disseminated by public health officials in Alberta.

Key Words

Influenza

Vaccine effectiveness

Case Control

Test-negative

Administrative data

Population-level

Laboratory data

Vaccination database

ARTICLE SUMMARY

Strengths and limitations of this study

- This protocol describes near real time estimation of vaccine effectiveness to assist public health in allocating resources and determining the appropriate policies and public messaging during the influenza season.
- Vaccine effectiveness estimates use a test negative design, taking advantage of linked administrative health records for the entire population.
- While many confounders are included in the vaccine effectiveness estimates, not all known confounders can be measured using administrative health data.

INTRODUCTION

Influenza is a respiratory viral pathogen associated with significant morbidity and mortality globally. Infections range from relatively mild presentations (e.g. cough, sore throat) to severe lower respiratory tract infections (e.g. pneumonia). Severe cases may be associated with hospitalization, intensive care admission, and death; young children, the elderly, and individuals with chronic conditions are at highest risk of severe outcomes [1]. In Canada, rates of influenza infections are approximately 200 cases per 100,000 population, with about 50% of cases occurring in patients aged ≤18 years [2]. The causative agents, influenza A (subtypes H3N2 and H1N1pdm(09)) and influenza B (Yamagata and Victoria lineages), are under strong selective pressure to mutate genetically; significant genetic changes can occur in relatively short periods of time (i.e. <1 year) [3].

Influenza prevention relies, in part, on annual vaccination campaigns that rely on vaccine strains selected approximately 9 months prior to the onset of an influenza season; by the time the vaccines are administered, the predominant circulating strains may have mutated to the point such that the effectiveness of the vaccine has diminished or has become completely ineffective [4, 5].

Influenza VE is commonly estimated using the test-negative design, a variation of the case-control design where cases and controls are selected from a pool of individuals who have been tested for influenza [6-10]. Several research groups use sentinel physician networks to recruit patients: influenza testing is performed on patients who meet a case definition for influenza-like illness, and cases and controls are selected from that pool [6-8]. While this has become an established method, there are some limitations to using sentinel physicians. As the physicians are often volunteers, there can be bias in the geographic distribution, leading to clustering of sampling in certain areas and not others. This can lead to inaccuracies as predominant circulating influenza strains vary geographically [7, 11]. Immunization information is commonly self-reported, potentially leading to recall and social desirability biases [12]; volunteer physicians may be more likely to have strong views on influenza immunization, potentially making it more difficult for the patient to admit to not being immunized. Finally, as these studies are labour-intensive for clinic staff, physician recruitment is often

low, resulting in small sample sizes and wide confidence intervals. Estimates are, therefore, typically available after the peak of the influenza season, decreasing their usefulness for public health messaging and resource and operational planning [6-8, 11].

Using administrative data and routinely collected clinical specimens for estimating VE is currently under debate [13]. However, estimating VE in a large jurisdiction with near-real-time data on all influenza laboratory testing and influenza vaccination in the population has the potential to provide more precise and timely VE estimates than has previously been possible. We present a protocol to estimate influenza VE using individually-linked laboratory and administrative data.

METHODS AND ANALYSIS

Study Setting:

Alberta is a province in Canada with a publicly-funded universal health care system; each of the 4.25 million residents is assigned a unique personal health number (PHN) at birth or upon immigration to the province [14]. The PHN is recorded each time a person accesses the healthcare system, allowing for deterministic linkage across multiple administrative data sets held by the Ministry of Health.

In 2009, influenza vaccination became universally available to all Albertans aged ≥6 months, regardless of comorbidities or other risk conditions [15]. Influenza vaccines are available at no cost to the patient at public health clinics, pharmacies, physician offices, long-term care facilities, university health centers, and workplaces. Annual vaccine campaigns begin in October, with approximately 60% of all influenza vaccinations given by the end of the second week of the campaign. While the peak of influenza activity has varied widely since 2010, the median influenza peak in Alberta is in mid-January, approximately three months after vaccination campaigns begin.

Laboratory methods for influenza A and B detection and influenza A subtyping

All influenza testing in Alberta is performed at a single diagnostic lab, the Provincial Laboratory for Public Health (ProvLab) and stored in a single laboratory information system, along with test and patient identifiers. Prior to May 2017 a real-time influenza A/B reverse-transcriptase PCR (RT-PCR) was used to diagnose influenza using a protocol previously described [16, 17]. After May 2017, ProvLab has been using a Luminex Respiratory Pathogen Panel for the identification of influenza A (including subtype), influenza B, and other respiratory viruses (e.g. coronavirus and parainfluenza) [14].

Study Design:

We will use the test-negative design to estimate VE. We will estimate VE for the upcoming influenza season (2018/19) and past influenza seasons (2011/12 to 2016/17). The results of all respiratory virus tests conducted at ProvLab will be sent to the Ministry of Health for deterministic linkage to health administrative databases, in order to determine eligibility for inclusion in the analysis, influenza vaccination status, and the following covariates: age, sex, socio-economic status, geographic zone of residence, history of immunocompromising comorbidities, and healthcare setting (inpatient or outpatient setting) at the time of specimen submission. The presence of a diagnostic code for an acute respiratory illness (ARI) at the time of specimen collection will be used in a sensitivity analysis.

Isolates will be considered eligible for inclusion in the analysis if they met all of the following criteria: a valid PHN is recorded, the isolate is not from a resident of a long-term care facility, if the seasonal threshold has been reached, and the isolate was collected at least four weeks after the initiation of the public influenza vaccination program [18-20].

It is important to ensure that the population has the chance to be exposed to influenza and there is sufficient time for immunity to be developed. Residence in a long-term care facility will be determined via the Alberta Continuing Care Information System (ACCIS), which contains information on admissions and discharges from long-term care facilities [21]. PHN validity will be assessed using the Alberta Health Care Insurance

Plan (AHCIP) Adjusted Population Registry, which contains records of all individuals registered for healthcare insurance [21, 22].

Individuals can have multiple laboratory tests over the course of their illness; therefore only the first positive influenza test during the influenza season will be used, and potential control samples will be selected from among those who only tested negative for influenza during that influenza season, using the first negative test. Cases and controls tested <14 days after vaccination will be excluded from the analysis.

Influenza vaccination status will be determined from the Influenza Vaccination Registry. The registry combines data from four databases that record influenza vaccination events (see below).

The following administrative data sets will be used in this study:

- Alberta Health Immunization and Adverse Reaction to Immunization system (Imm/ARI) contains records of all publicly funded vaccines administered through public health, including influenza vaccines administered at mass influenza vaccination clinics, public health clinics, and vaccinations administered by public health nurses in long-term care facilities. Data submission is mandatory and guidelines exist to support complete and accurate vaccination records with descriptions of each, including notes [23, 24].
- The Supplemental Enhance Service Event (SESE) database captures physician claims for billing purposes; International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes, procedure codes, and codes indicating location of service delivery are mandatory data elements for each patient encounter [22, 25, 26].
- Alberta Blue Cross (ABC) administers the pharmacist component of the universal vaccination program. Pharmacists administering influenza vaccines through this program bill ABC for each vaccine provided; they are required to submit patient information such as PHN, name, and address.
- The Pharmaceutical Information Network (PIN) database records privately dispensed pharmacological products, including the rare instances when an influenza vaccine is purchased rather

than administered through the public program (e.g. purchased by travelers prior to the launch of the public campaign). PIN captures dispensed events from >95% of pharmacists[21].

- Provincial Vaccine Registry combines influenza vaccinations given in the province and recorded in four source databases (PIN, ABC, SESE and Imm/ARI).
- Alberta Health Care Insurance Plan Adjusted Population Registry (AHCIP) Adjusted Population Registry contains demographic variables, age, sex, socio-economic status, and geographic zone of residence.
- Morbidity and Ambulatory Care Abstracting Reporting (MACAR) system contains diagnosis codes, procedure codes, the date of admission, and date of discharge for every visit to hospitals, emergency rooms, and outpatient clinics.

Individuals will be considered inpatients if they have at least one physician claim for inpatient services on the same day as specimen collection or if specimen collection occurred during an inpatient stay; all others will be considered outpatients. Individuals with an immunocompromising condition will be defined as those who have a diagnosis of HIV, who received an organ transplant, or received oral corticosteroids (for ≥30 days), antineoplastic agents, or another immunocompromising drug from a community pharmacist in the past 6 months. (Appendix 1 and 2) [27]. HIV diagnosis and acute respiratory illness will be determined through physician claims and MACAR. Organ transplantation will be determined using MACAR, and immunocompromising drug dispensations will be identified through PIN.

Statistical Analysis

We will use multivariable logistic regression to estimate influenza vaccine effectiveness as (1 – adjusted OR) x 100%. We will estimate VE separately by influenza season and influenza subtype (i.e., A(H3N2), A(H1N1)pdm09, and influenza B) [28]. All covariates will be considered for the adjusted model. SAS version 9.4 will be used for all statistical analysis (SAS Institute Inc, Cary, NC). VE estimates will be compared to published estimates of VE (12-14).

As shedding of influenza virus continues for approximately 4-5 days after symptom onset, bias can result if specimens that are collected too long after symptom onset are used [29]. Most studies use a threshold of 7 days [30]. To test the robustness of the findings, a sensitivity analysis will be performed; controls will be restricted to those specimens positive for a different respiratory virus (i.e. coronavirus, human respiratory syncytial virus) (As suggested by Sullivan et al 2016).

A potential limitation to this study is that the samples utilized here are clinical isolates taken through the course of normal patient care, and are not from a standard case definition as is utilized in some other studies [12]. To test the robustness of the findings, the analysis will be repeated using only cases and controls that were given a diagnosis code for acute respiratory infection on the same day as specimen collection, as per the SESE database or MACAR. Appendix 3 lists the ICD-9 and ICD-10 codes used to define an acute respiratory infection.

DISCUSSION

This protocol describes the estimation of seasonal influenza VE using specimens collected for routine influenza diagnostics as well as administrative data and vaccination records.

A key strength of this approach is the large sample size. This approach allows calculation of near real-time, precise influenza VE estimates weeks prior to the influenza season peak, creating an early warning system for public health if, as in the 2014-2015 season, the vaccine is found to have exceedingly low effectiveness. Early notification of VE can assist public health in determining policies, messaging, and allocation of resources (antiviral agents, staffing emergency departments) to counter a potentially more severe influenza season [31, 32]. The large sample size also allows for stratified analyses of VE based on product, age group, or region.

Whereas sentinel physician networks rely primarily on self-reported measures of influenza vaccination [33], a significant strength of this study is the use of the near-real-time influenza vaccination registry that contains individual-level, linkable data for most influenza vaccinations administered in the province. Use of this registry reduces the likelihood of recall error and information biases such as social desirability bias and

reduces non-differential misclassification, which would bias the odds ratio towards the null, thus underestimating VE [12].

Finally, we are certain to capture the results of all respiratory virus testing in the province, as all respiratory virus testing is centralized at ProvLab and there is limited use of point-of-care testing.

There are some limitations to this methodology compared to the traditional method of VE estimation using sentinel physician networks, because a standardized clinical case definition cannot be applied to determine study eligibility. A sensitivity analysis restricting to healthcare encounters with a diagnosis code for acute respiratory infection will be used as a proxy for a standard case definition.

While the inclusion of confounders is important for VE estimate adjustment, not all known confounders can be measured using administrative data. Frailty has been demonstrated to be a potential confounder of VE [34-36]. Frailty cannot be included in the multivariable model because no validated indices of frailty generated from standard administrative data exist at this time. However, this may not affect the results significantly as a previous study indicated that inclusion of frailty in the multivariate model increased VE estimates only slightly [37].

Laboratory requisitions in Alberta do not contain onset date. Ideally this would be used to ensure that the negative laboratory test results were representative of an acute infectious period and that test-negative specimens were not collected after viral shedding had ceased. Sullivan et al 2016 have indicated this bias may be accounted for by selecting influenza test-negative controls that were positive for another respiratory virus. Requiring controls to be positive for another virus excludes individuals who are tested long after their acute infectious period. However, a recent systematic review found no differences when using different groups of controls [30].

Comparison of the VE results using administrative data to previously published studies, specifically sentinel surveillance for the same seasons (2011/12 – 2018/19) will help to identify further areas of refinement.

This approach could successfully allow for the generation of early influenza VE estimates which could facilitate tailoring of public health messaging and assist in public health operations planning for the peak of the influenza season.

ETHICS

Ethics approval was obtained from the University of Alberta's Health Research Ethics Board – Health Panel under study ID Pro00075997.

LIST OF ABBREVIATIONS

ABC – Alberta Blue Cross

ACCIS – Alberta Continuing Care Information System

AHCIP – Alberta Health Care Insurance Plan Adjusted Population Registry

CCI – Canadian Classification of Health Interventions

CCP – Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures

CIHI – Canadian Institute for Health Information

DAD – Alberta Hospital Discharge Abstract Database

ICD-9 – International Classification of Diseases, Ninth Revision

ICD-10 – International Classification of Diseases, Tenth Revision

Imm/ARI – Alberta Health Immunization and Adverse Reaction to Immunization system

MACAR – Morbidity and Ambulatory Care Abstracting Reporting

PHN – Personal Health Number

PIN – Pharmaceutical Information Network

ProvLab – Alberta Provincial Laboratory for Public Health

RT-PCR – Reverse Transcriptase Polymerase Chain Reaction

SESE – Supplemental Enhance Service Event

VE – Vaccine Effectiveness

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was obtained from the University of Alberta's Health Research Ethics Board – Health Panel under study ID Pro00075997.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

Not applicable

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

Not applicable

AUTHOR STATEMENT

ANS and SJD conceived of and designed the protocol and drafted and revised the manuscript. KS and LS planned the original approach, providing guidance on available administrative database resources. SAB and JCK made substantial contributions to the design and critically revised the manuscript.

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Appendix 1. List of CCP, CCI, and CMG codes utilized to define individuals who have had an organ transplant

CCP Code	Description
495	Heart Transplantation
455	Lung Transplant
456	Combined Heart-Lung Transplantation
624	Liver Transplant
675	Transplant of Kidney
648	Transplant of Pancreas

CCI Code	Description
1HY85	Transplant, Heart With Lung(S)
1HZ85	Transplant, Heart Nec
1GT85	Transplant, Lung Nec
1GR85	Transplant, Lobe of Lung
1OA85	Transplant, Liver
1PC85	Transplant, Kidney
1OJ85	Transplant, Pancreas
1OK85	Transplant, Pancreas With Duodenum
1NK85	Transplant, Small Intestine
1NP85	Transplant, Small And Large Intestine

CMG 1992 To 2005	
175	Heart or Lung Transplant
253	Major Intestinal And Rectal Procedures
310	Liver Transplant
311	Major Pancreatic Procedures
500	Kidney Transplant

CMG 2007 To 2016	
110	Lung Transplant
160	Heart Transplant
220	Major Upper Gastrointestinal Reconstruction/Excision
270	Liver/Pancreas/Duodenum Transplant
450	Kidney Transplant

Appendix 2. List of drug names and DINs utilized to define immunocompromising conditions

DIN	Drug Name	Route of Administration	Strength
00616192	ETOPOSIDE	CAP	50MG
00523410	ETOPOSIDE	IV SOL	20MG/ML
02080036	ETOPOSIDE	IV SOL	20MG/ML
02241182	ETOPOSIDE	IV SOL	20MG/ML
02231622	IRINOTECAN HCL	IV SOL	20MG/ML
02258218	IRINOTECAN HCL	IV SOL	20MG/ML
00015431	VINBLASTINE SULFATE	IV PWS	1MG/ML
00611182	VINCRISTINE SULFATE	IV SOL	1MG/ML
02143305	VINCRISTINE SULFATE	IV SOL	1MG/ML
00004618	BUSULFAN	TAB	2MG
00297763	CARMUSTINE	IV PWS	100MG
09851399	CARMUSTINE	TOP SOL	NOT AVLE
00004626	CHLORAMBUCIL	TAB	2MG
00344915	CYCLOPHOSPHAMIDE	INJ PWS	2GM
00013544	CYCLOPHOSPHAMIDE	IV PWS	200MG
00013552	CYCLOPHOSPHAMIDE	IV PWS	200MG
02241797	CYCLOPHOSPHAMIDE	IV PWS	200MG
02241799	CYCLOPHOSPHAMIDE	IV PWS	1000MG
00013749	CYCLOPHOSPHAMIDE	TAB	50MG
00262676	CYCLOPHOSPHAMIDE	TAB	25MG
00344877	CYCLOPHOSPHAMIDE	TAB	25MG
00344885	CYCLOPHOSPHAMIDE	TAB	50MG
02241795	CYCLOPHOSPHAMIDE	TAB	25MG
02241796	CYCLOPHOSPHAMIDE	TAB	50MG
02063794	ESTRAMUSTINE DISODIUM PHOSPHATE	CAP	140MG
00780278	ESTRAMUSTINE PHOSPHATE	CAP	140MG
00360414	LOMUSTINE	CAP	100MG
00360422	LOMUSTINE	CAP	40MG
00360430	LOMUSTINE	CAP	10MG
00016063	MECHLORETHAMINE	IV PWS	10MG
00004715	MELPHALAN	TAB	2MG
02312794	TEMOZOLOMIDE	CAP	140MG
02312816	TEMOZOLOMIDE	CAP	180MG
02395274	TEMOZOLOMIDE	CAP	20MG
02395282	TEMOZOLOMIDE	CAP	100MG
02395290	TEMOZOLOMIDE	CAP	140MG
02395312	TEMOZOLOMIDE	CAP	250MG
02443473	TEMOZOLOMIDE	CAP	5MG
02443481	TEMOZOLOMIDE	CAP	20MG

DIN	Drug Name	Route of Administration	Strength
02443511	TEMOZOLOMIDE	CAP	100MG
02443538	TEMOZOLOMIDE	CAP	140MG
02443554	TEMOZOLOMIDE	CAP	250MG
02241093	TEMOZOLOMIDE	CAP	5MG
02241094	TEMOZOLOMIDE	CAP	20MG
02241095	TEMOZOLOMIDE	CAP	100MG
02241096	TEMOZOLOMIDE	CAP	250MG
02441160	TEMOZOLOMIDE	CAPSULE	5MG
00237035	THIOTEPA	INJ PWS	15MG/ML
02421917	CAPECITABINE	FC TAB	150MG
02421925	CAPECITABINE	FC TAB	500MG
02426757	CAPECITABINE	FC TAB	150MG
02426765	CAPECITABINE	FC TAB	500MG
02400022	CAPECITABINE	TAB	150MG
02400030	CAPECITABINE	TAB	500MG
02238453	CAPECITABINE	TAB	150MG
02238454	CAPECITABINE	TAB	500MG
02022117	CLADRIBINE	IV SOL	1MG
00194727	CYTARABINE	INJ PWS	500MG
00386715	CYTARABINE	INJ PWS	100MG
02167867	CYTARABINE	INJ PWS	100MG
00646296	CYTARABINE	IV PWS	1GM
00646318	CYTARABINE	IV PWS	2GM
02246226	FLUDARABINE PHOSPHATE	TAB	10MG
00012882	FLUOROURACIL	IV SOL	
00330582	FLUOROURACIL	TOP CRM	5%
00465283	HYDROXYUREA	CAP	500MG
02242920	HYDROXYUREA	CAP	500MG
02247937	HYDROXYUREA	CAP	500MG
00004723	MERCAPTOPURINE	TAB	50MG
02415275	MERCAPTOPURINE	TABLET	50MG
09857520	METHOTREXATE	INJ SOL	50MG/2ML
02182777	METHOTREXATE	INJ SOL	25MG/ML
02182955	METHOTREXATE	INJ SOL	25MG/ML
00014915	METHOTREXATE	TAB	2.5MG
02170698	METHOTREXATE	TAB	2.5MG
02182750	METHOTREXATE	TAB	10MG
02182963	METHOTREXATE	TAB	2.5MG
02244798	METHOTREXATE	TAB	2.5MG
02398427	METHOTREXATE	VIAL	25MG/ML
00321397	METHOTREXATE DISODIUM	INJ SOL	2.5MG/ML
00321400	METHOTREXATE DISODIUM	INJ SOL	2.5MG/ML

DIN	Drug Name	Route of Administration	Strength
02170663	METHOTREXATE DISODIUM	INJ SOL	50MG/2ML
02170671	METHOTREXATE DISODIUM	INJ SOL	2.5MG/ML
02182947	METHOTREXATE SODIUM	INJ SOL	10MG/ML
00614335	METHOTREXATE SODIUM	IV SOL	10MG/ML
00874132	METHOTREXATE SODIUM	TAB	2.5MG
02171767	METHOTREXATE SODIUM	TAB	2.5MG
00282081	THIOGUANINE	TAB	40MG
02384256	CRIZOTINIB	CAP	200MG
02384264	CRIZOTINIB	CAP	250MG
02409607	DABRAFENIB	CAP	50MG
02409615	DABRAFENIB	CAP	75MG
02320193	DASATINIB	TAB	100MG
02293129	DASATINIB	TAB	20MG
02293137	DASATINIB	TAB	50MG
02293145	DASATINIB	TAB	70MG
02269007	ERLOTINIB HCL	TAB	25MG
02269015	ERLOTINIB HCL	TAB	100MG
02269023	ERLOTINIB HCL	TAB	150MG
02377705	ERLOTINIB HCL	TABLET	100MG
02377713	ERLOTINIB HCL	TABLET	150MG
02434407	IBRUTINIB	CAP	140MG
09857447	IMATINIB MESYLATE	TAB	100MG
02388006	RUXOLITINIB	TAB	5MG
02388014	RUXOLITINIB	TAB	15MG
02388022	RUXOLITINIB	TAB	20MG
02409658	TRAMETINIB RECOMBINANT	TAB	2MG
01926438	ASPARAGINASE	INJ PWS	10MU
02389649	AXITINIB	TAB	5MG
02389630	AXITINIB	TAB FC	1MG
02262452	BORTEZOMIB	IV PWS	3.5MG
00521183	DACARBAZINE	IV PWS	200MG/VIAL
02154854	DACARBAZINE	IV PWS	200MG
02248676	GEFITINIB	TAB	250MG
02244725	IMATINIB MESYLATE	CAP	100MG
02399806	IMATINIB MESYLATE	FC TAB	100MG
02355337	IMATINIB MESYLATE	TAB	100MG
02355345	IMATINIB MESYLATE	TAB	400MG
02397285	IMATINIB MESYLATE	TAB	100MG
02397293	IMATINIB MESYLATE	TAB	400MG
02399814	IMATINIB MESYLATE	TAB	400MG
02431114	IMATINIB MESYLATE	TAB	100MG
02431122	IMATINIB MESYLATE	TAB	400MG

DIN	Drug Name	Route of Administration	Strength
09857448	IMATINIB MESYLATE	TAB	400MG
02253275	IMATINIB MESYLATE	TAB	100MG
02253283	IMATINIB MESYLATE	TAB	400MG
02326442	LAPATINIB DITOSYLATE	TAB	250MG
02315874	NILOTINIB	CAP	200MG
02368250	NILOTINIB	CAP	150MG
02352303	PAZOPANIB HCL	TAB	200MG
00012750	PROCARBAZINE HCL	CAP	50MG
02403390	REGORAFENIB	TAB	40MG
02284227	SORAFENIB TOSYLATE	TAB	200MG
02280795	SUNITINIB MALATE	CAP	12.5MG
02280809	SUNITINIB MALATE	CAP	25MG
02280817	SUNITINIB MALATE	CAP	50MG
02258595	ADALIMUMAB	INJ-SC SOL	40MG
09854785	ADALIMUMAB	INJ-SC SOL	40MG
09857294	ADALIMUMAB	INJ-SC SOL	40MG
09857326	ADALIMUMAB	INJ-SC SOL	40MG
09857327	ADALIMUMAB	INJ-SC SOL	40MG
02130181	ALDESLEUKIN	IV PWS	1.3MG
02331675	CERTOLIZUMAB PEGOL	INJ-SC SOL	200MG/ML
09857394	ETANERCEPT RECOMBINANT	INJ SOL	50MG/ML
02242903	ETANERCEPT RECOMBINANT	INJ-SC PWS	25MG
02274728	ETANERCEPT RECOMBINANT	INJ-SC SOL	50MG/ML
09857322	ETANERCEPT RECOMBINANT	INJ-SC SOL	50MG/ML
02233014	GLATIRAMER	INJ-SC PWS	20MG
02245619	GLATIRAMER	INJ-SC SOL	20MG/ML
02324776	GOLIMUMAB RECOMBINANT	INJ-SC SOL	50MG/0.5ML
02324784	GOLIMUMAB RECOMBINANT	INJ-SC SOL	50MG/0.5ML
02244016	INFLIXIMAB	IV PWS	100MG
09852956	INFLIXIMAB	IV PWS	100MG
02419475	INFLIXIMAB	PWD VIAL	100MG
02239832	INTERFERON	INJ-SC SOL	0.03MG/ML
09852751	INTERFERON	OPH SOL	1MU/ML
02223384	INTERFERON ALFA 2B	INJ PWS	3MMU
02223392	INTERFERON ALFA 2B	INJ PWS	5MMU
02223406	INTERFERON ALFA 2B	INJ PWS	10MMU
02231651	INTERFERON ALFA 2B	INJ PWS	18MMU
00889067	INTERFERON ALFA 2B	INJ SOL	10MMU/2ML
02223414	INTERFERON ALFA 2B	INJ SOL	10MMU/2ML
02238674	INTERFERON ALFA 2B	INJ SOL	3MMU/0.5ML
02238675	INTERFERON ALFA 2B	INJ SOL	5MMU/0.5ML
09853995	INTERFERON ALFA 2B	INJ SOL	10MU/VIAL

DIN	Drug Name	Route of Administration	Strength
09854045	INTERFERON ALFA 2B	INJ SOL	3MMU/0.5ML
09854053	INTERFERON ALFA 2B	INJ SOL	5MMU/0.5ML
00705896	INTERFERON ALFA 2B	INJ-SC SOL	3MMU
00705918	INTERFERON ALFA 2B	INJ-SC SOL	5MMU
00705926	INTERFERON ALFA 2B	INJ-SC SOL	10MMU
02240693	INTERFERON ALFA 2B	INJ-SC SOL	18MMU/1.2ML
02240694	INTERFERON ALFA 2B	INJ-SC SOL	30MMU/1.2ML
02240695	INTERFERON ALFA 2B	INJ-SC SOL	60MMU/1.2ML
01911988	INTERFERON ALFA-2A	INJ PWS	3000MU/ML
01911996	INTERFERON ALFA-2A	INJ PWS	9000MU/ML
01912003	INTERFERON ALFA-2A	INJ PWS	6000MU/ML
00812471	INTERFERON ALFA-2A	INJ PWS	6000MU/ML
00812498	INTERFERON ALFA-2A	INJ SOL	6000MU/ML
00812501	INTERFERON ALFA-2A	INJ SOL	3000MU/ML
02217015	INTERFERON ALFA-2A	INJ SOL	3000MU/ML
02217031	INTERFERON ALFA-2A	INJ SOL	6000MU/ML
02217058	INTERFERON ALFA-2A	INJ SOL	9000MU/ML
02217066	INTERFERON ALFA-2A	INJ SOL	18000MU/ML
02019914	INTERFERON ALFA-2A	INJ SOL	9000MU/ML
01959069	INTERFERON ALPHA-N1	INJ SOL	10MU
01959077	INTERFERON ALPHA-N1	INJ SOL	3MU
00709042	INTERFERON ALPHA-N1	INJ SOL	3MU
00709050	INTERFERON ALPHA-N1	INJ SOL	10MU
02169649	INTERFERON BETA	INJ-SC PWS	0.3MG
02237317	INTERFERON BETA 1A	INJ PWS	11MCG
02237318	INTERFERON BETA 1A	INJ PWS	44MCG
02237770	INTERFERON BETA 1A	INJ-IM PWS	30MCG/1.1ML
02269201	INTERFERON BETA 1A	INJ-IM SOL	30MCG/0.5ML
02318253	INTERFERON BETA 1A	INJ-SC SOL	66MCG/1.5ML
02318261	INTERFERON BETA 1A	INJ-SC SOL	132MCG/1.5ML
02237319	INTERFERON BETA 1A	INJ-SC SOL	22MCG/0.5ML
02237320	INTERFERON BETA 1A	INJ-SC SOL	44MCG/0.5ML
09857395	INTERFERON BETA-1A	PREF AUTOINJ PEN	30MCG/0.5ML
02337819	INTERFERON BETA-1B RECOMBINANT	INJ-SC PWS	0.3MG
00846368	LEVAMISOLE HCL	TAB	50MG
02234217	LEVAMISOLE HCL	TAB	50MG
09857505	PEGINTERFERON ALFA 2A RECOMBINANT	INJ-SC SOL	180MCG/0.5ML
02248077	PEGINTERFERON ALFA 2A RECOMBINANT	INJ-SC SOL	180MCG/0.5ML
02248078	PEGINTERFERON ALFA 2A RECOMBINANT	INJ-SC SOL	180MCG/ML

DIN	Drug Name	Route of Administration	Strength
00258482	BLEOMYCIN SULFATE	INJ PWS	15U
00163899	DAUNORUBICIN HCL	INJ PD	20MG
01926683	DAUNORUBICIN HCL	IV PWS	20MG
00353078	DOXORUBICIN HCL	IV PWS	50MG
00357391	DOXORUBICIN HCL	IV PWS	10MG
00640050	EPIRUBICIN HCL	INJ PWS	10MG
00640069	EPIRUBICIN HCL	IV PWS	50MG
00381799	MITOMYCIN	IV PWS	5MG
00463221	MITOTANE	TAB	500MG
02415992	AFLIBERCEPT	VIAL	40MG/ML
02273993	ALEMTUZUMAB	IV SOL	10MG/ML
02290960	ALEMTUZUMAB	IV SOL	30MG/ML
02270994	BEVACIZUMAB	IV SOL	25MG/ML
09857407	RITUXIMAB	IV SOL	10MG/ML
02241927	RITUXIMAB	IV SOL	10MG/ML

Appendix 4. ICD-9 codes and ICD-10 codes utilized to define acute respiratory illness in physician, ER and hospital encounters.

Description	ICD-9 Code	ICD-10 Code
Viral infection, unspecified site	079	B34
Viral agents as the cause of diseases classified to other chapters	--	B97 (but not B973 or B977)
Acute nasopharyngitis (common cold)	460	J00
Acute sinusitis	461	J01
Acute pharyngitis	462	J02
Acute tonsillitis	463	J03
Acute laryngitis, tracheitis, epiglottitis, croup	464	J04, J05
Acute upper respiratory infections of multiple or unspecified sites	465	J06
Influenza due to identified novel influenza A virus	488	J09
Influenza	487	J10, J11
Pneumonia, organism unspecified	486	--
Viral pneumonia	480	J12
Bacterial pneumonia	481, 482	J13, J14, J15
Pneumonia due to other specified organism	483	J16
Pneumonia in infectious diseases classified elsewhere	484	J17
Bronchopneumonia, organism unspecified	485	J18
Acute bronchitis and bronchiolitis	466	J20, J21
Unspecified diseases respiratory system	519	J22, J39.8, J39.9
Bronchitis, not specified as acute or chronic	490	J40
Acute respiratory distress syndrome	518.82	J80
Pulmonary edema	518.4	J81
Pleural effusion	510.9, 511.0, 511.1, 511.89	J86.9, J90, R09.1
Respiratory failure	518.81	J96.0, J96.9
Atelectasis	--	J98.10
Pulmonary collapse	518.0	J98.19
Other respiratory disorders	786.00, 786.09	J98.0, J98.4, J98.8, J98.9
Hemoptysis	786.30	R04.2
Cough	786.2	R05
Shortness of breath (dyspnea)	786.02, 786.05, 786.09	R06.0
Stridor	786.1	R06.1
Wheezing	786.07	R06.2
Tachypnea	786.06	R06.4
Chest pain on breathing	786.52	R07.1
Hypoxemia	799.02	R09.0
Respiratory arrest	799.1	R09.2
Abnormal sputum	786.4	R09.3
Nasal congestion	478.19	R09.81
Abnormal chest sounds	786.7	R09.89

Description	ICD-9 Code	ICD-10 Code
Fever	780.60	R50
Chills (without fever)	780.64	R68.0
Sepsis, shock	669.11, 669.12, 669.14, 785.50, 785.52, 995.91, 995.92	A41.9, R57.9

BMJ Open

Using population-wide administrative and laboratory data to estimate type- and subtype-specific influenza vaccine effectiveness: a surveillance protocol

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TITLE

Using population-wide administrative and laboratory data to estimate type- and subtype-specific influenza vaccine effectiveness: a surveillance protocol

Allison N Scott[1,2,3]

Sarah A Buchan[4,5,6]

Jeffrey C Kwong[4,5,6,7,8]

Steven J Drews[9,10]

Kimberley A Simmonds[1,11]

Lawrence W Svenson[1,11, 12, 13]

Affiliations

[1]Ministry of Health, Government of Alberta, Edmonton, AB, Canada

[2]PolicyWise for Children & Families, Edmonton, AB, Canada

[3]Department of Public Health, Concordia University of Edmonton, AB, Canada

[4]ICES, Toronto, ON, Canada

[5]Public Health Ontario, Toronto, ON, Canada

[6]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

[7]Department of Family & Community Medicine, University of Toronto, Toronto, ON, Canada

[8]University Health Network, Toronto, ON, Canada

[9]The Alberta Provincial Laboratory for Public Health, Edmonton, AB, Canada

[10]Department of Laboratory Medicine & Pathology, University of Alberta, Edmonton, AB, Canada

[11] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

[12] School of Public Health, University of Alberta, Edmonton, AB, Canada

[13] Division of Preventive Medicine, University of Alberta, Edmonton, AB, Canada

Corresponding Author:

Allison N. Scott, Ph.D.

PolicyWise for Children & Families

1000, 9925-109 Street NW

Edmonton, Alberta, Canada T5K 2J8

Email Addresses

Allison N Scott	AScott@policywise.com
Sarah A Buchan	Sarah.Buchan@oahpp.ca
Jeffrey C Kwong	jeff.kwong@utoronto.ca
Steven J Drews	steven.drews@blood.ca
Kimberley A Simmonds	kimberley.simmonds@gov.ab.ca
Lawrence W Svenson	larry.svenson@gov.ab.ca

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ABSTRACT

Introduction

The appropriateness of using routinely collected laboratory data combined with administrative data for estimating influenza vaccine effectiveness (VE) is still being explored. This paper outlines a protocol to estimate influenza VE using linked laboratory and administrative data which could act as a companion to estimates derived from other methods.

Methods and Analysis

We will use the test-negative design to estimate VE for each influenza type/subtype and season. Province-wide individual-level records of positive and negative influenza tests at the Provincial Laboratory for Public Health in Alberta will be linked, by unique personal health numbers, to administrative databases and vaccination records held at the Ministry of Health in Alberta to determine covariates and influenza vaccination status, respectively. Covariates of interests include age, sex, immunocompromising chronic conditions, and healthcare setting. Cases will be defined based on an individual's first positive influenza test during the season, and potential controls will be defined based on an individual's first negative influenza test during the season. One control for each case will be randomly selected based on the week the specimen was collected. We will estimate vaccine effectiveness using multivariable logistic regression.

Ethics and Dissemination

Ethics approval was obtained from the University of Alberta's Health Research Ethics Board – Health Panel under study ID Pro00075997. Results will be disseminated by public health officials in Alberta.

Key Words

Influenza

Vaccine effectiveness

Case Control

Test-negative

Administrative data

Population-level

Laboratory data

Vaccination database

ARTICLE SUMMARY

Strengths and limitations of this study

- A strength of this protocol is that it provides near real time estimation of vaccine effectiveness to assist public health in allocating resources and determining the appropriate policies and public messaging during the influenza season.
- Vaccine effectiveness estimates use a test negative design, taking advantage of linked administrative health records for the entire population.
- While many confounders are included in the vaccine effectiveness estimates, not all known confounders can be measured using administrative health data.

INTRODUCTION

Influenza is a respiratory viral disease associated with significant morbidity and mortality globally. Infections range from relatively mild presentations (e.g. cough, sore throat) to severe lower respiratory tract infections (e.g. pneumonia). Severe cases may be associated with hospitalization, intensive care admission, and death; young children, the elderly, and individuals with chronic conditions are at highest risk of severe outcomes[1]. In Canada, rates of laboratory-confirmed influenza infections are, on average, approximately 200 cases per 100,000 population, with approximately 50% of cases occurring in patients aged ≤18 years [2]. The causative agents, influenza A (subtypes H3N2 and H1N1pdm(09)) and influenza B (Yamagata and Victoria lineages), are under strong selective pressure to mutate genetically; significant genetic changes can occur in relatively short periods of time (i.e. <1 year) [3].

Influenza prevention relies, in part, on annual vaccination campaigns. Selection of viral strains for inclusion in the vaccine occurs approximately 9 months prior to the onset of the influenza season; by the time the vaccines are administered, the predominant circulating strains may have mutated to the point such that the effectiveness of the vaccine has diminished or has become completely ineffective [4,5].

Influenza VE is commonly estimated using the test-negative design, a variation of the case-control design where cases and controls are selected from a pool of individuals who have been tested for influenza [6–10]. Several research groups use sentinel physician networks to recruit patients: influenza testing is performed on patients who meet a case definition for influenza-like illness, and cases and controls are selected from that pool [6–8]. While this has become an established method, there are some limitations to using sentinel physicians. As the physicians are often volunteers, there can be bias in the geographic distribution, leading to clustering of sampling in certain areas and not others. This can lead to inaccuracies as predominant circulating influenza strains vary geographically [7,11]. Immunization information is commonly self-reported, potentially leading to recall and social desirability biases [12]; volunteer physicians may be more likely to have strong views on influenza immunization, potentially making it more difficult for the patient to admit to not being immunized. Finally, as these studies are labour-intensive for clinic staff, physician recruitment is often

low, resulting in small sample sizes and wide confidence intervals. Estimates are, therefore, typically available after the peak of the influenza season, decreasing their usefulness for public health messaging and resource and operational planning [6–8,11].

Using administrative data and routinely collected clinical specimens for estimating VE is currently under debate [13]. VE estimates generated using linked health administrative and laboratory data in the province Ontario have been shown to be comparable to previously published estimates [manuscript under review]. There has been one published estimate of Alberta-specific vaccine effectiveness using a sentinel surveillance system[11]; however, because of the small sample size the confidence interval was large, ranging from 8% to 72%. Estimating VE in a large jurisdiction with near-real-time data on all influenza laboratory testing and influenza vaccination in the population has the potential to provide more precise and timely VE estimates than has previously been possible. We present a protocol to estimate influenza VE using individually-linked laboratory and administrative data.

METHODS AND ANALYSIS

Study Setting:

Alberta is a province in Canada with a publicly-funded universal health care system; each of the 4.25 million residents is assigned a unique personal health number (PHN) at birth or upon immigration to the province [14]. The PHN is recorded each time a person accesses the healthcare system, allowing for deterministic linkage across multiple administrative data sets held by the Ministry of Health.

In 2009, influenza vaccination became universally available to all Albertans aged ≥6 months, regardless of comorbidities or other risk conditions [15]. Influenza vaccines are available at no cost to the patient at public health clinics, pharmacies, physician offices, long-term care facilities, university health centers, and workplaces. Annual vaccine campaigns begin in October, with approximately 60% of all influenza vaccinations given by the end of the second week of the campaign. While the peak of influenza activity has

varied widely since 2010, the median influenza peak in Alberta is in mid-January, approximately three months after vaccination campaigns begin.

Laboratory methods for influenza A and B detection and influenza A subtyping

All influenza testing in Alberta is performed at a single diagnostic lab, the Provincial Laboratory for Public Health (ProvLab) and stored in a single laboratory information system, along with test and patient identifiers. Clinical specimens (e.g. nasopharyngeal swabs, nasopharyngeal aspirates, bronchoalveolar lavages) are processed at ProvLab using previously published protocols. Nucleic acid extraction utilizes the easyMAG extractor and reagents (bioMerieux,St.Laurent,Quebec,Canada)[16]. Nucleic acid from clinical specimens are then tested using a series of respiratory detection assays as described below. Prior to May 2017, a real-time influenza A/B reverse-transcriptase PCR (RT-PCR) was used to diagnose influenza using a protocol previously described [17,18]. After May 2017, ProvLab has been using a Luminex Respiratory Pathogen Panel for the identification of influenza A (including subtype), influenza B, and other respiratory viruses (e.g. coronavirus and parainfluenza) [14]. Results of the laboratory testing were imported into specific laboratory information systems depending on the testing time period.

Study Design:

We will use the test-negative design to estimate VE. We will estimate VE for the 2011/12 – 2018/19 influenza seasons. The results of all respiratory virus tests conducted at ProvLab will be sent to the Ministry of Health for deterministic linkage to health administrative databases, in order to determine eligibility for inclusion in the analysis, influenza vaccination status, and the following covariates: age, sex, socio-economic status, geographic zone of residence, history of immunocompromising comorbidities, healthcare setting (inpatient or outpatient setting), and month at the time of specimen submission. The presence of a diagnostic code for an acute respiratory illness (ARI) at the time of specimen collection will be used in a sensitivity analysis.

Isolates will be considered eligible for inclusion in the analysis if they met all of the following criteria: a valid PHN is recorded, the isolate is not from a resident of a long-term care facility, the isolate was collected at least four weeks after the initiation of the public influenza vaccination program, and the isolate was collected during the influenza season, as determined using the method recommended by the WHO r [19–21].

It is important to ensure that the population has the chance to be exposed to influenza and there is sufficient time for immunity to the vaccine to be developed. Residence in a long-term care facility will be determined via the Alberta Continuing Care Information System (ACCIS), which contains information on admissions and discharges from long-term care facilities [22]. PHN validity will be assessed using the Alberta Health Care Insurance Plan (AHCIP) Adjusted Population Registry, which contains records of all individuals registered for healthcare insurance [22,23].

Individuals can have multiple laboratory tests over the course of their illness; therefore only the first positive influenza test during the influenza season will be used, and potential control samples will be selected from among those who only tested negative for influenza during that influenza season, using the first negative test. Cases and controls tested <14 days after vaccination will be excluded from the analysis.

Influenza vaccination status will be determined from the Influenza Vaccination Registry. The registry combines data from four databases that record influenza vaccination events (see below).

The following administrative data sets will be used in this study.

- Alberta Health Immunization and Adverse Reaction to Immunization system (Imm/ARI) contains records of all publicly funded vaccines administered through public health, including influenza vaccines administered at mass influenza vaccination clinics, public health clinics, and vaccinations administered by public health nurses in long-term care facilities. Data submission is mandatory and guidelines exist to support complete and accurate vaccination records with descriptions of each, including notes [24,25].

- The Supplemental Enhanced Service Event (SESE) database captures physician claims for billing purposes; International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes, procedure codes (Canadian Classification of Procedures), codes indicating location of service delivery, and a number of other administrative elements used to support the payment for each patient encounter [23,26,27].
- Alberta Blue Cross (ABC) administers the pharmacist component of the universal vaccination program. Pharmacists administering influenza vaccines through this program submit claims to ABC for each vaccine provided; they are required to submit patient information such as PHN, date of service, name, and address.
- The Pharmaceutical Information Network (PIN) database records dispensed pharmacological products, regardless of payer, including the rare instances when an influenza vaccine is purchased rather than administered through the public program (e.g. purchased by travelers prior to the launch of the public campaign). PIN captures approximately 95% of all dispensed events in the province [22].
- Provincial Vaccine Registry combines influenza vaccinations given in the province and recorded in four source databases (PIN, ABC, SESE and Imm/ARI).
- Alberta Health Care Insurance Plan (AHCIP) Population Registry contains demographic variables, age, sex, socio-economic status, and geographic zone of residence. Neighbourhood-level socio-economic status is derived from census dissemination area income quintiles using postal code.
- Morbidity and Ambulatory Care Abstracting Reporting (MACAR) system contains ICD-10-CA diagnostic codes, procedure codes, the date of admission, and date of discharge for every visit to hospitals, emergency rooms, and outpatient clinics.

The quality of administrative datasets in Alberta has been extensively reviewed [28–30].

Individuals will be considered inpatients if they have at least one physician claim for inpatient services on the same day as specimen collection or if specimen collection occurred during an inpatient stay; all others

will be considered outpatients. Individuals with an immunocompromising condition will be defined as those who have a diagnosis of HIV, who received an organ transplant, or received oral corticosteroids (for ≥30 days), antineoplastic agents, or another immunocompromising drug from a community pharmacist in the past 6 months. (Appendix 1 and 2) [31]. HIV diagnosis and ARI will be determined through physician claims and MACAR. Organ transplantation will be determined using MACAR, and immunocompromising drug dispensations will be identified through PIN.

Statistical Analysis

We will use multivariable logistic regression to estimate influenza vaccine effectiveness as (1 – adjusted OR) x 100%. We will estimate VE separately by influenza season and influenza subtype (i.e., A(H3N2), A(H1N1)pdm09, and influenza B) [32]. When there is a large enough sample size in a particular season to provide adequate power, VE will be estimated for specific age groups such as children under the age of 5 and seniors over the age of 65. The following covariates will be included in the adjusted model, regardless of statistical significance: age, sex, socio-economic status, geographic zone of residence, history of immunocompromising comorbidities, healthcare setting (inpatient or outpatient setting), and month of specimen submission within the influenza season. SAS version 9.4 will be used for all statistical analysis (SAS Institute Inc, Cary, NC). VE estimates will be compared to published estimates of VE [6,7,11,13,33,34] .

As shedding of influenza virus continues for approximately 4-5 days after symptom onset, bias can result if specimens that are collected too long after symptom onset are used [35]. Most studies use a threshold of 7 days [36]. To test the robustness of the findings, a sensitivity analysis will be performed; controls will be restricted to those specimens positive for a different respiratory virus (i.e. coronavirus, human respiratory syncytial virus) (As suggested by Sullivan et al 2016).

A potential limitation to this study is that the samples utilized here are clinical isolates taken through the course of normal patient care, and are not from a standard case definition as is utilized in some other studies [12]. To test the robustness of the findings, the analysis will be repeated using only cases and controls that

were given a diagnosis code for ARI on the same day as specimen collection, as per the SESE database or MACAR. Appendix 3 lists the ICD-9 and ICD-10 codes used to define ARIs.

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not involved in the design of the study, including the development of the research question, outcomes measures, recruitment to or conduct of the study. The results of the study will be disseminated to the public as deemed appropriate by public health officials.

DISCUSSION

This protocol describes the estimation of seasonal influenza VE using specimens collected for routine influenza diagnostics as well as administrative data and vaccination records.

A key strength of this approach is the large sample size. This approach allows calculation of near real-time, precise influenza VE estimates weeks prior to the influenza season peak, creating an early warning system for public health if, as in the 2014-2015 season, the vaccine is found to have exceedingly low effectiveness. Early notification of VE can assist public health in determining policies, messaging, and allocation of resources (antiviral agents, staffing emergency departments) to counter a potentially more severe influenza season [36,37]. The large sample size also allows for stratified analyses of VE based on product, age group, or region.

Whereas sentinel physician networks rely primarily on self-reported measures of influenza vaccination [33], a significant strength of this study is the use of the near-real-time influenza vaccination registry that contains individual-level, linkable data for most influenza vaccinations administered in the province. Use of this registry reduces the likelihood of recall error and information biases such as social desirability bias and reduces non-differential misclassification, which would bias the odds ratio towards the null, thus underestimating VE [12].

Finally, we are certain to capture the results of all respiratory virus testing in the province, as all respiratory virus testing is centralized at ProvLab and there is limited use of point-of-care testing.

There are some limitations to this methodology compared to the traditional method of VE estimation using sentinel physician networks, because a standardized clinical case definition cannot be applied to determine study eligibility. A sensitivity analysis restricting to healthcare encounters with a diagnosis code for ARI will be used as a proxy for a standard case definition.

While the inclusion of confounders is important for VE estimate adjustment, not all known confounders can be measured using administrative data. Frailty has been demonstrated to be a potential confounder of VE [38–40]. Frailty cannot be included in the multivariable model because no validated indices of frailty generated from standard administrative data exist at this time. However, this may not affect the results significantly as a previous study indicated that inclusion of frailty in the multivariate model increased VE estimates only slightly [41].

Laboratory requisitions in Alberta do not contain illness onset date. Ideally this would be used to ensure that the negative laboratory test results were representative of an acute infectious period and that test-negative specimens were not collected after viral shedding had ceased. Sullivan et al 2016 have indicated this bias may be accounted for by selecting influenza test-negative controls that were positive for another respiratory virus. Requiring controls to be positive for another virus excludes individuals who are tested long after their acute infectious period. However, a recent systematic review found no differences when using different groups of controls [42].

Comparison of the VE results using administrative data to previously published studies, specifically sentinel surveillance for the same seasons (2011/12 – 2018/19) will help to identify further areas of refinement. This approach could successfully allow for the generation of early influenza VE estimates which could facilitate tailoring of public health messaging and assist in public health operations planning for the peak of the influenza season.

ETHICS

Ethics approval was obtained from the University of Alberta's Health Research Ethics Board – Health Panel under study ID Pro00075997.

LIST OF ABBREVIATIONS

ABC – Alberta Blue Cross

ACCIS – Alberta Continuing Care Information System

AHCIP – Alberta Health Care Insurance Plan Adjusted Population Registry

CCI – Canadian Classification of Health Interventions

CCP – Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures

ICD-9 – International Classification of Diseases, Ninth Revision

ICD-10 – International Classification of Diseases, Tenth Revision

Imm/ARI – Alberta Health Immunization and Adverse Reaction to Immunization system

MACAR – Morbidity and Ambulatory Care Abstracting Reporting

PHN – Personal Health Number

PIN – Pharmaceutical Information Network

ProvLab – Alberta Provincial Laboratory for Public Health

RT-PCR – Reverse Transcriptase Polymerase Chain Reaction

SESE – Supplemental Enhance Service Event

VE – Vaccine Effectiveness

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was obtained from the University of Alberta's Health Research Ethics Board – Health Panel under study ID Pro00075997.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

Not applicable

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

Not applicable

AUTHOR STATEMENT

ANS and SJD conceived of and designed the protocol and drafted and revised the manuscript. KS and LS planned the original approach, providing guidance on available administrative database resources. SAB and JCK made substantial contributions to the design and critically revised the manuscript.

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Supplementary File - Using population-wide administrative and laboratory data to estimate type- and subtype-specific influenza vaccine effectiveness: a surveillance protocol

Appendix: List of CCP, CCI, and CMG codes utilized to define individuals who have had an organ transplant

CCP Code	Description
495	Heart Transplantation
455	Lung Transplant
456	Combined Heart-Lung Transplantation
624	Liver Transplant
675	Transplant of Kidney
648	Transplant of Pancreas

CCI Code	Description
1HY85	Transplant, Heart With Lung(S)
1HZ85	Transplant, Heart Nec
1GT85	Transplant, Lung Nec
1GR85	Transplant, Lobe of Lung
1OA85	Transplant, Liver
1PC85	Transplant, Kidney
1OJ85	Transplant, Pancreas
1OK85	Transplant, Pancreas With Duodenum
1NK85	Transplant, Small Intestine
1NP85	Transplant, Small And Large Intestine

CMG 1992 To 2005	
175	Heart or Lung Transplant
253	Major Intestinal And Rectal Procedures
310	Liver Transplant
311	Major Pancreatic Procedures
500	Kidney Transplant

CMG 2007 To 2016	
110	Lung Transplant
160	Heart Transplant
220	Major Upper Gastrointestinal Reconstruction/Excision
270	Liver/Pancreas/Duodenum Transplant
450	Kidney Transplant

Appendix: List of drug names and DINs utilized to define immunocompromising conditions

DIN	Drug Name	Route of Administration	Strength
00616192	ETOPOSIDE	CAP	50MG
00523410	ETOPOSIDE	IV SOL	20MG/ML
02080036	ETOPOSIDE	IV SOL	20MG/ML
02241182	ETOPOSIDE	IV SOL	20MG/ML
02231622	IRINOTECAN HCL	IV SOL	20MG/ML
02258218	IRINOTECAN HCL	IV SOL	20MG/ML
00015431	VINBLASTINE SULFATE	IV PWS	1MG/ML
00611182	VINCRISTINE SULFATE	IV SOL	1MG/ML
02143305	VINCRISTINE SULFATE	IV SOL	1MG/ML
00004618	BUSULFAN	TAB	2MG
00297763	CARMUSTINE	IV PWS	100MG
09851399	CARMUSTINE	TOP SOL	NOT AVLE
00004626	CHLORAMBUCIL	TAB	2MG
00344915	CYCLOPHOSPHAMIDE	INJ PWS	2GM
00013544	CYCLOPHOSPHAMIDE	IV PWS	200MG
00013552	CYCLOPHOSPHAMIDE	IV PWS	200MG
02241797	CYCLOPHOSPHAMIDE	IV PWS	200MG
02241799	CYCLOPHOSPHAMIDE	IV PWS	1000MG
00013749	CYCLOPHOSPHAMIDE	TAB	50MG
00262676	CYCLOPHOSPHAMIDE	TAB	25MG
00344877	CYCLOPHOSPHAMIDE	TAB	25MG
00344885	CYCLOPHOSPHAMIDE	TAB	50MG
02241795	CYCLOPHOSPHAMIDE	TAB	25MG
02241796	CYCLOPHOSPHAMIDE	TAB	50MG
02063794	ESTRAMUSTINE DISODIUM PHOSPHATE	CAP	140MG
00780278	ESTRAMUSTINE PHOSPHATE	CAP	140MG
00360414	LOMUSTINE	CAP	100MG
00360422	LOMUSTINE	CAP	40MG
00360430	LOMUSTINE	CAP	10MG
00016063	MECHLORETHAMINE	IV PWS	10MG
00004715	MELPHALAN	TAB	2MG
02312794	TEMOZOLOMIDE	CAP	140MG
02312816	TEMOZOLOMIDE	CAP	180MG
02395274	TEMOZOLOMIDE	CAP	20MG
02395282	TEMOZOLOMIDE	CAP	100MG
02395290	TEMOZOLOMIDE	CAP	140MG
02395312	TEMOZOLOMIDE	CAP	250MG
02443473	TEMOZOLOMIDE	CAP	5MG
02443481	TEMOZOLOMIDE	CAP	20MG

DIN	Drug Name	Route of Administration	Strength
02443511	TEMOZOLOMIDE	CAP	100MG
02443538	TEMOZOLOMIDE	CAP	140MG
02443554	TEMOZOLOMIDE	CAP	250MG
02241093	TEMOZOLOMIDE	CAP	5MG
02241094	TEMOZOLOMIDE	CAP	20MG
02241095	TEMOZOLOMIDE	CAP	100MG
02241096	TEMOZOLOMIDE	CAP	250MG
02441160	TEMOZOLOMIDE	CAPSULE	5MG
00237035	THIOTEPA	INJ PWS	15MG/ML
02421917	CAPECITABINE	FC TAB	150MG
02421925	CAPECITABINE	FC TAB	500MG
02426757	CAPECITABINE	FC TAB	150MG
02426765	CAPECITABINE	FC TAB	500MG
02400022	CAPECITABINE	TAB	150MG
02400030	CAPECITABINE	TAB	500MG
02238453	CAPECITABINE	TAB	150MG
02238454	CAPECITABINE	TAB	500MG
02022117	CLADRIBINE	IV SOL	1MG
00194727	CYTARABINE	INJ PWS	500MG
00386715	CYTARABINE	INJ PWS	100MG
02167867	CYTARABINE	INJ PWS	100MG
00646296	CYTARABINE	IV PWS	1GM
00646318	CYTARABINE	IV PWS	2GM
02246226	FLUDARABINE PHOSPHATE	TAB	10MG
00012882	FLUOROURACIL	IV SOL	
00330582	FLUOROURACIL	TOP CRM	5%
00465283	HYDROXYUREA	CAP	500MG
02242920	HYDROXYUREA	CAP	500MG
02247937	HYDROXYUREA	CAP	500MG
00004723	MERCAPTOPURINE	TAB	50MG
02415275	MERCAPTOPURINE	TABLET	50MG
09857520	METHOTREXATE	INJ SOL	50MG/2ML
02182777	METHOTREXATE	INJ SOL	25MG/ML
02182955	METHOTREXATE	INJ SOL	25MG/ML
00014915	METHOTREXATE	TAB	2.5MG
02170698	METHOTREXATE	TAB	2.5MG
02182750	METHOTREXATE	TAB	10MG
02182963	METHOTREXATE	TAB	2.5MG
02244798	METHOTREXATE	TAB	2.5MG
02398427	METHOTREXATE	VIAL	25MG/ML
00321397	METHOTREXATE DISODIUM	INJ SOL	2.5MG/ML
00321400	METHOTREXATE DISODIUM	INJ SOL	2.5MG/ML

DIN	Drug Name	Route of Administration	Strength
02170663	METHOTREXATE DISODIUM	INJ SOL	50MG/2ML
02170671	METHOTREXATE DISODIUM	INJ SOL	2.5MG/ML
02182947	METHOTREXATE SODIUM	INJ SOL	10MG/ML
00614335	METHOTREXATE SODIUM	IV SOL	10MG/ML
00874132	METHOTREXATE SODIUM	TAB	2.5MG
02171767	METHOTREXATE SODIUM	TAB	2.5MG
00282081	THIOGUANINE	TAB	40MG
02384256	CRIZOTINIB	CAP	200MG
02384264	CRIZOTINIB	CAP	250MG
02409607	DABRAFENIB	CAP	50MG
02409615	DABRAFENIB	CAP	75MG
02320193	DASATINIB	TAB	100MG
02293129	DASATINIB	TAB	20MG
02293137	DASATINIB	TAB	50MG
02293145	DASATINIB	TAB	70MG
02269007	ERLOTINIB HCL	TAB	25MG
02269015	ERLOTINIB HCL	TAB	100MG
02269023	ERLOTINIB HCL	TAB	150MG
02377705	ERLOTINIB HCL	TABLET	100MG
02377713	ERLOTINIB HCL	TABLET	150MG
02434407	IBRUTINIB	CAP	140MG
09857447	IMATINIB MESYLATE	TAB	100MG
02388006	RUXOLITINIB	TAB	5MG
02388014	RUXOLITINIB	TAB	15MG
02388022	RUXOLITINIB	TAB	20MG
02409658	TRAMETINIB RECOMBINANT	TAB	2MG
01926438	ASPARAGINASE	INJ PWS	10MU
02389649	AXITINIB	TAB	5MG
02389630	AXITINIB	TAB FC	1MG
02262452	BORTEZOMIB	IV PWS	3.5MG
00521183	DACARBAZINE	IV PWS	200MG/VIAL
02154854	DACARBAZINE	IV PWS	200MG
02248676	GEFITINIB	TAB	250MG
02244725	IMATINIB MESYLATE	CAP	100MG
02399806	IMATINIB MESYLATE	FC TAB	100MG
02355337	IMATINIB MESYLATE	TAB	100MG
02355345	IMATINIB MESYLATE	TAB	400MG
02397285	IMATINIB MESYLATE	TAB	100MG
02397293	IMATINIB MESYLATE	TAB	400MG
02399814	IMATINIB MESYLATE	TAB	400MG
02431114	IMATINIB MESYLATE	TAB	100MG
02431122	IMATINIB MESYLATE	TAB	400MG

DIN	Drug Name	Route of Administration	Strength
09857448	IMATINIB MESYLATE	TAB	400MG
02253275	IMATINIB MESYLATE	TAB	100MG
02253283	IMATINIB MESYLATE	TAB	400MG
02326442	LAPATINIB DITOSYLATE	TAB	250MG
02315874	NILOTINIB	CAP	200MG
02368250	NILOTINIB	CAP	150MG
02352303	PAZOPANIB HCL	TAB	200MG
00012750	PROCARBAZINE HCL	CAP	50MG
02403390	REGORAFENIB	TAB	40MG
02284227	SORAFENIB TOSYLATE	TAB	200MG
02280795	SUNITINIB MALATE	CAP	12.5MG
02280809	SUNITINIB MALATE	CAP	25MG
02280817	SUNITINIB MALATE	CAP	50MG
02258595	ADALIMUMAB	INJ-SC SOL	40MG
09854785	ADALIMUMAB	INJ-SC SOL	40MG
09857294	ADALIMUMAB	INJ-SC SOL	40MG
09857326	ADALIMUMAB	INJ-SC SOL	40MG
09857327	ADALIMUMAB	INJ-SC SOL	40MG
02130181	ALDESLEUKIN	IV PWS	1.3MG
02331675	CERTOLIZUMAB PEGOL	INJ-SC SOL	200MG/ML
09857394	ETANERCEPT RECOMBINANT	INJ SOL	50MG/ML
02242903	ETANERCEPT RECOMBINANT	INJ-SC PWS	25MG
02274728	ETANERCEPT RECOMBINANT	INJ-SC SOL	50MG/ML
09857322	ETANERCEPT RECOMBINANT	INJ-SC SOL	50MG/ML
02233014	GLATIRAMER	INJ-SC PWS	20MG
02245619	GLATIRAMER	INJ-SC SOL	20MG/ML
02324776	GOLIMUMAB RECOMBINANT	INJ-SC SOL	50MG/0.5ML
02324784	GOLIMUMAB RECOMBINANT	INJ-SC SOL	50MG/0.5ML
02244016	INFLIXIMAB	IV PWS	100MG
09852956	INFLIXIMAB	IV PWS	100MG
02419475	INFLIXIMAB	PWD VIAL	100MG
02239832	INTERFERON	INJ-SC SOL	0.03MG/ML
09852751	INTERFERON	OPH SOL	1MU/ML
02223384	INTERFERON ALFA 2B	INJ PWS	3MMU
02223392	INTERFERON ALFA 2B	INJ PWS	5MMU
02223406	INTERFERON ALFA 2B	INJ PWS	10MMU
02231651	INTERFERON ALFA 2B	INJ PWS	18MMU
00889067	INTERFERON ALFA 2B	INJ SOL	10MMU/2ML
02223414	INTERFERON ALFA 2B	INJ SOL	10MMU/2ML
02238674	INTERFERON ALFA 2B	INJ SOL	3MMU/0.5ML
02238675	INTERFERON ALFA 2B	INJ SOL	5MMU/0.5ML
09853995	INTERFERON ALFA 2B	INJ SOL	10MU/VIAL

DIN	Drug Name	Route of Administration	Strength
09854045	INTERFERON ALFA 2B	INJ SOL	3MMU/0.5ML
09854053	INTERFERON ALFA 2B	INJ SOL	5MMU/0.5ML
00705896	INTERFERON ALFA 2B	INJ-SC SOL	3MMU
00705918	INTERFERON ALFA 2B	INJ-SC SOL	5MMU
00705926	INTERFERON ALFA 2B	INJ-SC SOL	10MMU
02240693	INTERFERON ALFA 2B	INJ-SC SOL	18MMU/1.2ML
02240694	INTERFERON ALFA 2B	INJ-SC SOL	30MMU/1.2ML
02240695	INTERFERON ALFA 2B	INJ-SC SOL	60MMU/1.2ML
01911988	INTERFERON ALFA-2A	INJ PWS	3000MU/ML
01911996	INTERFERON ALFA-2A	INJ PWS	9000MU/ML
01912003	INTERFERON ALFA-2A	INJ PWS	6000MU/ML
00812471	INTERFERON ALFA-2A	INJ PWS	6000MU/ML
00812498	INTERFERON ALFA-2A	INJ SOL	6000MU/ML
00812501	INTERFERON ALFA-2A	INJ SOL	3000MU/ML
02217015	INTERFERON ALFA-2A	INJ SOL	3000MU/ML
02217031	INTERFERON ALFA-2A	INJ SOL	6000MU/ML
02217058	INTERFERON ALFA-2A	INJ SOL	9000MU/ML
02217066	INTERFERON ALFA-2A	INJ SOL	18000MU/ML
02019914	INTERFERON ALFA-2A	INJ SOL	9000MU/ML
01959069	INTERFERON ALPHA-N1	INJ SOL	10MU
01959077	INTERFERON ALPHA-N1	INJ SOL	3MU
00709042	INTERFERON ALPHA-N1	INJ SOL	3MU
00709050	INTERFERON ALPHA-N1	INJ SOL	10MU
02169649	INTERFERON BETA	INJ-SC PWS	0.3MG
02237317	INTERFERON BETA 1A	INJ PWS	11MCG
02237318	INTERFERON BETA 1A	INJ PWS	44MCG
02237770	INTERFERON BETA 1A	INJ-IM PWS	30MCG/1.1ML
02269201	INTERFERON BETA 1A	INJ-IM SOL	30MCG/0.5ML
02318253	INTERFERON BETA 1A	INJ-SC SOL	66MCG/1.5ML
02318261	INTERFERON BETA 1A	INJ-SC SOL	132MCG/1.5ML
02237319	INTERFERON BETA 1A	INJ-SC SOL	22MCG/0.5ML
02237320	INTERFERON BETA 1A	INJ-SC SOL	44MCG/0.5ML
09857395	INTERFERON BETA-1A	PREF AUTOINJ PEN	30MCG/0.5ML
02337819	INTERFERON BETA-1B RECOMBINANT	INJ-SC PWS	0.3MG
00846368	LEVAMISOLE HCL	TAB	50MG
02234217	LEVAMISOLE HCL	TAB	50MG
09857505	PEGINTERFERON ALFA 2A RECOMBINANT	INJ-SC SOL	180MCG/0.5ML
02248077	PEGINTERFERON ALFA 2A RECOMBINANT	INJ-SC SOL	180MCG/0.5ML
02248078	PEGINTERFERON ALFA 2A RECOMBINANT	INJ-SC SOL	180MCG/ML

DIN	Drug Name	Route of Administration	Strength
00258482	BLEOMYCIN SULFATE	INJ PWS	15U
00163899	DAUNORUBICIN HCL	INJ PD	20MG
01926683	DAUNORUBICIN HCL	IV PWS	20MG
00353078	DOXORUBICIN HCL	IV PWS	50MG
00357391	DOXORUBICIN HCL	IV PWS	10MG
00640050	EPIRUBICIN HCL	INJ PWS	10MG
00640069	EPIRUBICIN HCL	IV PWS	50MG
00381799	MITOMYCIN	IV PWS	5MG
00463221	MITOTANE	TAB	500MG
02415992	AFLIBERCEPT	VIAL	40MG/ML
02273993	ALEMTUZUMAB	IV SOL	10MG/ML
02290960	ALEMTUZUMAB	IV SOL	30MG/ML
02270994	BEVACIZUMAB	IV SOL	25MG/ML
09857407	RITUXIMAB	IV SOL	10MG/ML
02241927	RITUXIMAB	IV SOL	10MG/ML

Appendix: ICD-9 codes and ICD-10 codes utilized to define acute respiratory illness in physician, ER and hospital encounters.

Description	ICD-9 Code	ICD-10 Code
Viral infection, unspecified site	079	B34
Viral agents as the cause of diseases classified to other chapters	--	B97 (but not B973 or B977)
Acute nasopharyngitis (common cold)	460	J00
Acute sinusitis	461	J01
Acute pharyngitis	462	J02
Acute tonsillitis	463	J03
Acute laryngitis, tracheitis, epiglottitis, croup	464	J04, J05
Acute upper respiratory infections of multiple or unspecified sites	465	J06
Influenza due to identified novel influenza A virus	488	J09
Influenza	487	J10, J11
Pneumonia, organism unspecified	486	--
Viral pneumonia	480	J12
Bacterial pneumonia	481, 482	J13, J14, J15
Pneumonia due to other specified organism	483	J16
Pneumonia in infectious diseases classified elsewhere	484	J17
Bronchopneumonia, organism unspecified	485	J18
Acute bronchitis and bronchiolitis	466	J20, J21
Unspecified diseases respiratory system	519	J22, J39.8, J39.9
Bronchitis, not specified as acute or chronic	490	J40
Acute respiratory distress syndrome	518.82	J80
Pulmonary edema	518.4	J81
Pleural effusion	510.9, 511.0, 511.1, 511.89	J86.9, J90, R09.1
Respiratory failure	518.81	J96.0, J96.9
Atelectasis	--	J98.10
Pulmonary collapse	518.0	J98.19
Other respiratory disorders	786.00, 786.09	J98.0, J98.4, J98.8, J98.9
Hemoptysis	786.30	R04.2
Cough	786.2	R05
Shortness of breath (dyspnea)	786.02, 786.05, 786.09	R06.0
Stridor	786.1	R06.1
Wheezing	786.07	R06.2
Tachypnea	786.06	R06.4

Description	ICD-9 Code	ICD-10 Code
Chest pain on breathing	786.52	R07.1
Hypoxemia	799.02	R09.0
Respiratory arrest	799.1	R09.2
Abnormal sputum	786.4	R09.3
Nasal congestion	478.19	R09.81
Abnormal chest sounds	786.7	R09.89
Fever	780.60	R50
Chills (without fever)	780.64	R68.0
Sepsis, shock	669.11, 669.12, 669.14, 785.50, 785.52, 995.91, 995.92	A41.9, R57.9

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Using population-wide administrative and laboratory data to estimate type- and subtype-specific influenza vaccine effectiveness: a surveillance protocol

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TITLE

Using population-wide administrative and laboratory data to estimate type- and subtype-specific influenza vaccine effectiveness: a surveillance protocol

Allison N Scott[1,2,3]

Sarah A Buchan[4,5,6]

Jeffrey C Kwong[4,5,6,7,8]

Steven J Drews[9,10]

Kimberley A Simmonds[1,11]

Lawrence W Svenson[1,11, 12, 13]

Affiliations

[1]Ministry of Health, Government of Alberta, Edmonton, AB, Canada

[2]PolicyWise for Children & Families, Edmonton, AB, Canada

[3]Department of Public Health, Concordia University of Edmonton, AB, Canada

[4]ICES, Toronto, ON, Canada

[5]Public Health Ontario, Toronto, ON, Canada

[6]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

[7]Department of Family & Community Medicine, University of Toronto, Toronto, ON, Canada

[8]University Health Network, Toronto, ON, Canada

[9]The Alberta Provincial Laboratory for Public Health, Edmonton, AB, Canada

[10]Department of Laboratory Medicine & Pathology, University of Alberta, Edmonton, AB, Canada

[11] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

[12] School of Public Health, University of Alberta, Edmonton, AB, Canada

[13] Division of Preventive Medicine, University of Alberta, Edmonton, AB, Canada

Corresponding Author:

Allison N. Scott, Ph.D.

PolicyWise for Children & Families

1000, 9925-109 Street NW

Edmonton, Alberta, Canada T5K 2J8

Email Addresses

Allison N Scott	AScott@policywise.com
Sarah A Buchan	Sarah.Buchan@oahpp.ca
Jeffrey C Kwong	jeff.kwong@utoronto.ca
Steven J Drews	steven.drews@blood.ca
Kimberley A Simmonds	kimberley.simmonds@gov.ab.ca
Lawrence W Svenson	larry.svenson@gov.ab.ca

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ABSTRACT

Introduction

The appropriateness of using routinely collected laboratory data combined with administrative data for estimating influenza vaccine effectiveness (VE) is still being explored. This paper outlines a protocol to estimate influenza VE using linked laboratory and administrative data which could act as a companion to estimates derived from other methods.

Methods and Analysis

We will use the test-negative design to estimate VE for each influenza type/subtype and season. Province-wide individual-level records of positive and negative influenza tests at the Provincial Laboratory for Public Health in Alberta will be linked, by unique personal health numbers, to administrative databases and vaccination records held at the Ministry of Health in Alberta to determine covariates and influenza vaccination status, respectively. Covariates of interests include age, sex, immunocompromising chronic conditions, and healthcare setting. Cases will be defined based on an individual's first positive influenza test during the season, and potential controls will be defined based on an individual's first negative influenza test during the season. One control for each case will be randomly selected based on the week the specimen was collected. We will estimate vaccine effectiveness using multivariable logistic regression.

Ethics and Dissemination

Ethics approval was obtained from the University of Alberta's Health Research Ethics Board – Health Panel under study ID Pro00075997. Results will be disseminated by public health officials in Alberta.

Key Words

Influenza

Vaccine effectiveness

Case Control

Test-negative

Administrative data

Population-level

Laboratory data

Vaccination database

ARTICLE SUMMARY

Strengths and limitations of this study

- A strength of this protocol is that it provides near real time estimation of vaccine effectiveness to assist public health in allocating resources and determining the appropriate policies and public messaging during the influenza season.
- Vaccine effectiveness estimates use a test negative design, taking advantage of linked administrative health records for the entire population.
- While many confounders are included in the vaccine effectiveness estimates, not all known confounders can be measured using administrative health data.

INTRODUCTION

Influenza is a respiratory viral disease associated with significant morbidity and mortality globally. Infections range from relatively mild presentations (e.g. cough, sore throat) to severe lower respiratory tract infections (e.g. pneumonia). Severe cases may be associated with hospitalization, intensive care admission, and death; young children, the elderly, and individuals with chronic conditions are at highest risk of severe outcomes[1]. In Canada, rates of laboratory-confirmed influenza infections are, on average, approximately 200 cases per 100,000 population, with approximately 50% of cases occurring in patients aged ≤18 years [2]. The causative agents, influenza A (subtypes H3N2 and H1N1pdm(09)) and influenza B (Yamagata and Victoria lineages), are under strong selective pressure to mutate genetically; significant genetic changes can occur in relatively short periods of time (i.e. <1 year) [3].

Influenza prevention relies, in part, on annual vaccination campaigns. Selection of viral strains for inclusion in the vaccine occurs approximately 9 months prior to the onset of the influenza season; by the time the vaccines are administered, the predominant circulating strains may have mutated to the point such that the effectiveness of the vaccine has diminished or has become completely ineffective [4,5].

Influenza VE is commonly estimated using the test-negative design, a variation of the case-control design where cases and controls are selected from a pool of individuals who have been tested for influenza [6–10]. Several research groups use sentinel physician networks to recruit patients: influenza testing is performed on patients who meet a case definition for influenza-like illness, and cases and controls are selected from that pool [6–8]. While this has become an established method, there are some limitations to using sentinel physicians. As the physicians are often volunteers, there can be bias in the geographic distribution, leading to clustering of sampling in certain areas and not others. This can lead to inaccuracies as predominant circulating influenza strains vary geographically [7,11]. Immunization information is commonly self-reported, potentially leading to recall and social desirability biases [12]; volunteer physicians may be more likely to have strong views on influenza immunization, potentially making it more difficult for the patient to admit to not being immunized. Finally, as these studies are labour-intensive for clinic staff, physician recruitment is often

low, resulting in small sample sizes and wide confidence intervals. Estimates are, therefore, typically available after the peak of the influenza season, decreasing their usefulness for public health messaging and resource and operational planning [6–8,11].

Using administrative data and routinely collected clinical specimens for estimating VE is currently under debate [13]. VE estimates generated using linked health administrative and laboratory data in the province Ontario have been shown to be comparable to previously published estimates[14]. There has been one published estimate of Alberta-specific vaccine effectiveness using a sentinel surveillance system[11]; however, because of the small sample size the confidence interval was large, ranging from 8% to 72%. Estimating VE in a large jurisdiction with near-real-time data on all influenza laboratory testing and influenza vaccination in the population has the potential to provide more precise and timely VE estimates than has previously been possible. We present a protocol to estimate influenza VE using individually-linked laboratory and administrative data.

METHODS AND ANALYSIS

Study Setting:

Alberta is a province in Canada with a publicly-funded universal health care system; each of the 4.25 million residents is assigned a unique personal health number (PHN) at birth or upon immigration to the province [15]. The PHN is recorded each time a person accesses the healthcare system, allowing for deterministic linkage across multiple administrative data sets held by the Ministry of Health.

In 2009, influenza vaccination became universally available to all Albertans aged ≥6 months, regardless of comorbidities or other risk conditions [16]. Influenza vaccines are available at no cost to the patient at public health clinics, pharmacies, physician offices, long-term care facilities, university health centers, and workplaces. Annual vaccine campaigns begin in October, with approximately 60% of all influenza vaccinations given by the end of the second week of the campaign. While the peak of influenza activity has

varied widely since 2010, the median influenza peak in Alberta is in mid-January, approximately three months after vaccination campaigns begin.

Laboratory methods for influenza A and B detection and influenza A subtyping

All influenza testing in Alberta is performed at a single diagnostic lab, the Provincial Laboratory for Public Health (ProvLab) and stored in a single laboratory information system, along with test and patient identifiers. Clinical specimens (e.g. nasopharyngeal swabs, nasopharyngeal aspirates, bronchoalveolar lavages) are processed at ProvLab using previously published protocols. Nucleic acid extraction utilizes the easyMAG extractor and reagents (bioMerieux,St.Laurent,Quebec,Canada)[17]. Nucleic acid from clinical specimens are then tested using a series of respiratory detection assays as described below. Prior to May 2017, a real-time influenza A/B reverse-transcriptase PCR (RT-PCR) was used to diagnose influenza using a protocol previously described [18,19]. After May 2017, ProvLab has been using a Luminex Respiratory Pathogen Panel for the identification of influenza A (including subtype), influenza B, and other respiratory viruses (e.g. coronavirus and parainfluenza) [15]. Results of the laboratory testing were imported into specific laboratory information systems depending on the testing time period.

Study Design:

We will use the test-negative design to estimate VE. We will estimate VE for the 2011/12 – 2019/20 influenza seasons. The results of all respiratory virus tests conducted at ProvLab will be sent to the Ministry of Health for deterministic linkage to health administrative databases, in order to determine eligibility for inclusion in the analysis, influenza vaccination status, and the following covariates: age, sex, socio-economic status, geographic zone of residence, history of immunocompromising comorbidities, healthcare setting (inpatient or outpatient setting), and month at the time of specimen submission. The presence of a diagnostic code for an acute respiratory illness (ARI) at the time of specimen collection will be used in a sensitivity analysis.

Isolates will be considered eligible for inclusion in the analysis if they met all of the following criteria: a valid PHN is recorded, the isolate is not from a resident of a long-term care facility, the isolate was collected at least four weeks after the initiation of the public influenza vaccination program, and the isolate was collected during the influenza season, as determined using the method recommended by the WHO r [20–22].

It is important to ensure that the population has the chance to be exposed to influenza and there is sufficient time for immunity to the vaccine to be developed. Residence in a long-term care facility will be determined via the Alberta Continuing Care Information System (ACCIS), which contains information on admissions and discharges from long-term care facilities [23]. PHN validity will be assessed using the Alberta Health Care Insurance Plan (AHCIP) Adjusted Population Registry, which contains records of all individuals registered for healthcare insurance [23,24].

Individuals can have multiple laboratory tests over the course of their illness; therefore only the first positive influenza test during the influenza season will be used, and potential control samples will be selected from among those who only tested negative for influenza during that influenza season, using the first negative test. Cases and controls tested <14 days after vaccination will be excluded from the analysis.

Influenza vaccination status will be determined from the Influenza Vaccination Registry. The registry combines data from four databases that record influenza vaccination events (see below).

The following administrative data sets will be used in this study.

- Alberta Health Immunization and Adverse Reaction to Immunization system (Imm/ARI) contains records of all publicly funded vaccines administered through public health, including influenza vaccines administered at mass influenza vaccination clinics, public health clinics, and vaccinations administered by public health nurses in long-term care facilities. Data submission is mandatory and guidelines exist to support complete and accurate vaccination records with descriptions of each, including notes [25,26].

- The Supplemental Enhanced Service Event (SESE) database captures physician claims for billing purposes; International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes, procedure codes (Canadian Classification of Procedures), codes indicating location of service delivery, and a number of other administrative elements used to support the payment for each patient encounter [24,27,28].
- Alberta Blue Cross (ABC) administers the pharmacist component of the universal vaccination program. Pharmacists administering influenza vaccines through this program submit claims to ABC for each vaccine provided; they are required to submit patient information such as PHN, date of service, name, and address.
- The Pharmaceutical Information Network (PIN) database records dispensed pharmacological products, regardless of payer, including the rare instances when an influenza vaccine is purchased rather than administered through the public program (e.g. purchased by travelers prior to the launch of the public campaign). PIN captures approximately 95% of all dispensed events in the province [23].
- Provincial Vaccine Registry combines influenza vaccinations given in the province and recorded in four source databases (PIN, ABC, SESE and Imm/ARI).
- Alberta Health Care Insurance Plan (AHCIP) Population Registry contains demographic variables, age, sex, socio-economic status, and geographic zone of residence. Neighbourhood-level socio-economic status is derived from census dissemination area income quintiles using postal code.
- Morbidity and Ambulatory Care Abstracting Reporting (MACAR) system contains ICD-10-CA diagnostic codes, procedure codes, the date of admission, and date of discharge for every visit to hospitals, emergency rooms, and outpatient clinics.

The quality of administrative datasets in Alberta has been extensively reviewed [29–31].

Individuals will be considered inpatients if they have at least one physician claim for inpatient services on the same day as specimen collection or if specimen collection occurred during an inpatient stay; all others

will be considered outpatients. Individuals with an immunocompromising condition will be defined as those who have a diagnosis of HIV, who received an organ transplant, or received oral corticosteroids (for ≥30 days), antineoplastic agents, or another immunocompromising drug from a community pharmacist in the past 6 months. (Appendix 1 and 2) [32]. HIV diagnosis and ARI will be determined through physician claims and MACAR. Organ transplantation will be determined using MACAR, and immunocompromising drug dispensations will be identified through PIN.

Statistical Analysis

We will use multivariable logistic regression to estimate influenza vaccine effectiveness as (1 – adjusted OR) x 100%. We will estimate VE separately by influenza season and influenza subtype (i.e., A(H3N2), A(H1N1)pdm09, and influenza B) [33]. When there is a large enough sample size in a particular season to provide adequate power, VE will be estimated for specific age groups such as children under the age of 5 and seniors over the age of 65. The following covariates will be included in the adjusted model, regardless of statistical significance: age, sex, socio-economic status, geographic zone of residence, history of immunocompromising comorbidities, healthcare setting (inpatient or outpatient setting), and month of specimen submission within the influenza season. SAS version 9.4 will be used for all statistical analysis (SAS Institute Inc, Cary, NC). VE estimates will be compared to published estimates of VE [6,7,11,13,34,35] .

As shedding of influenza virus continues for approximately 4-5 days after symptom onset, bias can result if specimens that are collected too long after symptom onset are used [36]. Most studies use a threshold of 7 days [37]. To test the robustness of the findings, a sensitivity analysis will be performed; controls will be restricted to those specimens positive for a different respiratory virus (i.e. coronavirus, human respiratory syncytial virus) (As suggested by Sullivan et al 2016).

A potential limitation to this study is that the samples utilized here are clinical isolates taken through the course of normal patient care, and are not from a standard case definition as is utilized in some other studies [12]. To test the robustness of the findings, the analysis will be repeated using only cases and controls that

were given a diagnosis code for ARI on the same day as specimen collection, as per the SESE database or MACAR. Appendix 3 lists the ICD-9 and ICD-10 codes used to define ARIs.

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not involved in the design of the study, including the development of the research question, outcomes measures, recruitment to or conduct of the study. The results of the study will be disseminated to the public as deemed appropriate by public health officials.

DISCUSSION

This protocol describes the estimation of seasonal influenza VE using specimens collected for routine influenza diagnostics as well as administrative data and vaccination records.

A key strength of this approach is the large sample size. This approach allows calculation of near real-time, precise influenza VE estimates weeks prior to the influenza season peak, creating an early warning system for public health if, as in the 2014-2015 season, the vaccine is found to have exceedingly low effectiveness. Early notification of VE can assist public health in determining policies, messaging, and allocation of resources (antiviral agents, staffing emergency departments) to counter a potentially more severe influenza season [37,38]. The large sample size also allows for stratified analyses of VE based on product, age group, or region.

Whereas sentinel physician networks rely primarily on self-reported measures of influenza vaccination [34], a significant strength of this study is the use of the near-real-time influenza vaccination registry that contains individual-level, linkable data for most influenza vaccinations administered in the province. Use of this registry reduces the likelihood of recall error and information biases such as social desirability bias and reduces non-differential misclassification, which would bias the odds ratio towards the null, thus underestimating VE [12].

Finally, we are certain to capture the results of all respiratory virus testing in the province, as all respiratory virus testing is centralized at ProvLab and there is limited use of point-of-care testing.

There are some limitations to this methodology compared to the traditional method of VE estimation using sentinel physician networks, because a standardized clinical case definition cannot be applied to determine study eligibility. A sensitivity analysis restricting to healthcare encounters with a diagnosis code for ARI will be used as a proxy for a standard case definition.

While the inclusion of confounders is important for VE estimate adjustment, not all known confounders can be measured using administrative data. Frailty has been demonstrated to be a potential confounder of VE [39–41]. Frailty cannot be included in the multivariable model because no validated indices of frailty generated from standard administrative data exist at this time. However, this may not affect the results significantly as a previous study indicated that inclusion of frailty in the multivariate model increased VE estimates only slightly [42].

Laboratory requisitions in Alberta do not contain illness onset date. Ideally this would be used to ensure that the negative laboratory test results were representative of an acute infectious period and that test-negative specimens were not collected after viral shedding had ceased. Sullivan et al 2016 have indicated this bias may be accounted for by selecting influenza test-negative controls that were positive for another respiratory virus. Requiring controls to be positive for another virus excludes individuals who are tested long after their acute infectious period. However, a recent systematic review found no differences when using different groups of controls [43].

Comparison of the VE results using administrative data to previously published studies, specifically sentinel surveillance for the same seasons (2011/12 – 2018/19) will help to identify further areas of refinement. This approach could successfully allow for the generation of early influenza VE estimates which could facilitate tailoring of public health messaging and assist in public health operations planning for the peak of the influenza season.

ETHICS

Ethics approval was obtained from the University of Alberta's Health Research Ethics Board – Health Panel under study ID Pro00075997.

LIST OF ABBREVIATIONS

ABC – Alberta Blue Cross

ACCIS – Alberta Continuing Care Information System

AHCIP – Alberta Health Care Insurance Plan Adjusted Population Registry

CCI – Canadian Classification of Health Interventions

CCP – Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures

ICD-9 – International Classification of Diseases, Ninth Revision

ICD-10 – International Classification of Diseases, Tenth Revision

Imm/ARI – Alberta Health Immunization and Adverse Reaction to Immunization system

MACAR – Morbidity and Ambulatory Care Abstracting Reporting

PHN – Personal Health Number

PIN – Pharmaceutical Information Network

ProvLab – Alberta Provincial Laboratory for Public Health

RT-PCR – Reverse Transcriptase Polymerase Chain Reaction

SESE – Supplemental Enhance Service Event

VE – Vaccine Effectiveness

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was obtained from the University of Alberta's Health Research Ethics Board – Health Panel under study ID Pro00075997.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

Not applicable

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

Not applicable

AUTHOR STATEMENT

ANS and SJD conceived of and designed the protocol and drafted and revised the manuscript. KS and LS planned the original approach, providing guidance on available administrative database resources. SAB and JCK made substantial contributions to the design and critically revised the manuscript.

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Supplementary File - Using population-wide administrative and laboratory data to estimate type- and subtype-specific influenza vaccine effectiveness: a surveillance protocol

Appendix: List of CCP, CCI, and CMG codes utilized to define individuals who have had an organ transplant

CCP Code	Description
495	Heart Transplantation
455	Lung Transplant
456	Combined Heart-Lung Transplantation
624	Liver Transplant
675	Transplant of Kidney
648	Transplant of Pancreas

CCI Code	Description
1HY85	Transplant, Heart With Lung(S)
1HZ85	Transplant, Heart Nec
1GT85	Transplant, Lung Nec
1GR85	Transplant, Lobe of Lung
1OA85	Transplant, Liver
1PC85	Transplant, Kidney
1OJ85	Transplant, Pancreas
1OK85	Transplant, Pancreas With Duodenum
1NK85	Transplant, Small Intestine
1NP85	Transplant, Small And Large Intestine

CMG 1992 To 2005	
175	Heart or Lung Transplant
253	Major Intestinal And Rectal Procedures
310	Liver Transplant
311	Major Pancreatic Procedures
500	Kidney Transplant

CMG 2007 To 2016	
110	Lung Transplant
160	Heart Transplant
220	Major Upper Gastrointestinal Reconstruction/Excision
270	Liver/Pancreas/Duodenum Transplant
450	Kidney Transplant

Appendix: List of drug names and DINs utilized to define immunocompromising conditions

DIN	Drug Name	Route of Administration	Strength
00616192	ETOPOSIDE	CAP	50MG
00523410	ETOPOSIDE	IV SOL	20MG/ML
02080036	ETOPOSIDE	IV SOL	20MG/ML
02241182	ETOPOSIDE	IV SOL	20MG/ML
02231622	IRINOTECAN HCL	IV SOL	20MG/ML
02258218	IRINOTECAN HCL	IV SOL	20MG/ML
00015431	VINBLASTINE SULFATE	IV PWS	1MG/ML
00611182	VINCRISTINE SULFATE	IV SOL	1MG/ML
02143305	VINCRISTINE SULFATE	IV SOL	1MG/ML
00004618	BUSULFAN	TAB	2MG
00297763	CARMUSTINE	IV PWS	100MG
09851399	CARMUSTINE	TOP SOL	NOT AVLE
00004626	CHLORAMBUCIL	TAB	2MG
00344915	CYCLOPHOSPHAMIDE	INJ PWS	2GM
00013544	CYCLOPHOSPHAMIDE	IV PWS	200MG
00013552	CYCLOPHOSPHAMIDE	IV PWS	200MG
02241797	CYCLOPHOSPHAMIDE	IV PWS	200MG
02241799	CYCLOPHOSPHAMIDE	IV PWS	1000MG
00013749	CYCLOPHOSPHAMIDE	TAB	50MG
00262676	CYCLOPHOSPHAMIDE	TAB	25MG
00344877	CYCLOPHOSPHAMIDE	TAB	25MG
00344885	CYCLOPHOSPHAMIDE	TAB	50MG
02241795	CYCLOPHOSPHAMIDE	TAB	25MG
02241796	CYCLOPHOSPHAMIDE	TAB	50MG
02063794	ESTRAMUSTINE DISODIUM PHOSPHATE	CAP	140MG
00780278	ESTRAMUSTINE PHOSPHATE	CAP	140MG
00360414	LOMUSTINE	CAP	100MG
00360422	LOMUSTINE	CAP	40MG
00360430	LOMUSTINE	CAP	10MG
00016063	MECHLORETHAMINE	IV PWS	10MG
00004715	MELPHALAN	TAB	2MG
02312794	TEMOZOLOMIDE	CAP	140MG
02312816	TEMOZOLOMIDE	CAP	180MG
02395274	TEMOZOLOMIDE	CAP	20MG
02395282	TEMOZOLOMIDE	CAP	100MG
02395290	TEMOZOLOMIDE	CAP	140MG
02395312	TEMOZOLOMIDE	CAP	250MG
02443473	TEMOZOLOMIDE	CAP	5MG
02443481	TEMOZOLOMIDE	CAP	20MG

DIN	Drug Name	Route of Administration	Strength
02443511	TEMOZOLOMIDE	CAP	100MG
02443538	TEMOZOLOMIDE	CAP	140MG
02443554	TEMOZOLOMIDE	CAP	250MG
02241093	TEMOZOLOMIDE	CAP	5MG
02241094	TEMOZOLOMIDE	CAP	20MG
02241095	TEMOZOLOMIDE	CAP	100MG
02241096	TEMOZOLOMIDE	CAP	250MG
02441160	TEMOZOLOMIDE	CAPSULE	5MG
00237035	THIOTEPA	INJ PWS	15MG/ML
02421917	CAPECITABINE	FC TAB	150MG
02421925	CAPECITABINE	FC TAB	500MG
02426757	CAPECITABINE	FC TAB	150MG
02426765	CAPECITABINE	FC TAB	500MG
02400022	CAPECITABINE	TAB	150MG
02400030	CAPECITABINE	TAB	500MG
02238453	CAPECITABINE	TAB	150MG
02238454	CAPECITABINE	TAB	500MG
02022117	CLADRIBINE	IV SOL	1MG
00194727	CYTARABINE	INJ PWS	500MG
00386715	CYTARABINE	INJ PWS	100MG
02167867	CYTARABINE	INJ PWS	100MG
00646296	CYTARABINE	IV PWS	1GM
00646318	CYTARABINE	IV PWS	2GM
02246226	FLUDARABINE PHOSPHATE	TAB	10MG
00012882	FLUOROURACIL	IV SOL	
00330582	FLUOROURACIL	TOP CRM	5%
00465283	HYDROXYUREA	CAP	500MG
02242920	HYDROXYUREA	CAP	500MG
02247937	HYDROXYUREA	CAP	500MG
00004723	MERCAPTOPURINE	TAB	50MG
02415275	MERCAPTOPURINE	TABLET	50MG
09857520	METHOTREXATE	INJ SOL	50MG/2ML
02182777	METHOTREXATE	INJ SOL	25MG/ML
02182955	METHOTREXATE	INJ SOL	25MG/ML
00014915	METHOTREXATE	TAB	2.5MG
02170698	METHOTREXATE	TAB	2.5MG
02182750	METHOTREXATE	TAB	10MG
02182963	METHOTREXATE	TAB	2.5MG
02244798	METHOTREXATE	TAB	2.5MG
02398427	METHOTREXATE	VIAL	25MG/ML
00321397	METHOTREXATE DISODIUM	INJ SOL	2.5MG/ML
00321400	METHOTREXATE DISODIUM	INJ SOL	2.5MG/ML

DIN	Drug Name	Route of Administration	Strength
02170663	METHOTREXATE DISODIUM	INJ SOL	50MG/2ML
02170671	METHOTREXATE DISODIUM	INJ SOL	2.5MG/ML
02182947	METHOTREXATE SODIUM	INJ SOL	10MG/ML
00614335	METHOTREXATE SODIUM	IV SOL	10MG/ML
00874132	METHOTREXATE SODIUM	TAB	2.5MG
02171767	METHOTREXATE SODIUM	TAB	2.5MG
00282081	THIOGUANINE	TAB	40MG
02384256	CRIZOTINIB	CAP	200MG
02384264	CRIZOTINIB	CAP	250MG
02409607	DABRAFENIB	CAP	50MG
02409615	DABRAFENIB	CAP	75MG
02320193	DASATINIB	TAB	100MG
02293129	DASATINIB	TAB	20MG
02293137	DASATINIB	TAB	50MG
02293145	DASATINIB	TAB	70MG
02269007	ERLOTINIB HCL	TAB	25MG
02269015	ERLOTINIB HCL	TAB	100MG
02269023	ERLOTINIB HCL	TAB	150MG
02377705	ERLOTINIB HCL	TABLET	100MG
02377713	ERLOTINIB HCL	TABLET	150MG
02434407	IBRUTINIB	CAP	140MG
09857447	IMATINIB MESYLATE	TAB	100MG
02388006	RUXOLITINIB	TAB	5MG
02388014	RUXOLITINIB	TAB	15MG
02388022	RUXOLITINIB	TAB	20MG
02409658	TRAMETINIB RECOMBINANT	TAB	2MG
01926438	ASPARAGINASE	INJ PWS	10MU
02389649	AXITINIB	TAB	5MG
02389630	AXITINIB	TAB FC	1MG
02262452	BORTEZOMIB	IV PWS	3.5MG
00521183	DACARBAZINE	IV PWS	200MG/VIAL
02154854	DACARBAZINE	IV PWS	200MG
02248676	GEFITINIB	TAB	250MG
02244725	IMATINIB MESYLATE	CAP	100MG
02399806	IMATINIB MESYLATE	FC TAB	100MG
02355337	IMATINIB MESYLATE	TAB	100MG
02355345	IMATINIB MESYLATE	TAB	400MG
02397285	IMATINIB MESYLATE	TAB	100MG
02397293	IMATINIB MESYLATE	TAB	400MG
02399814	IMATINIB MESYLATE	TAB	400MG
02431114	IMATINIB MESYLATE	TAB	100MG
02431122	IMATINIB MESYLATE	TAB	400MG

DIN	Drug Name	Route of Administration	Strength
09857448	IMATINIB MESYLATE	TAB	400MG
02253275	IMATINIB MESYLATE	TAB	100MG
02253283	IMATINIB MESYLATE	TAB	400MG
02326442	LAPATINIB DITOSYLATE	TAB	250MG
02315874	NILOTINIB	CAP	200MG
02368250	NILOTINIB	CAP	150MG
02352303	PAZOPANIB HCL	TAB	200MG
00012750	PROCARBAZINE HCL	CAP	50MG
02403390	REGORAFENIB	TAB	40MG
02284227	SORAFENIB TOSYLATE	TAB	200MG
02280795	SUNITINIB MALATE	CAP	12.5MG
02280809	SUNITINIB MALATE	CAP	25MG
02280817	SUNITINIB MALATE	CAP	50MG
02258595	ADALIMUMAB	INJ-SC SOL	40MG
09854785	ADALIMUMAB	INJ-SC SOL	40MG
09857294	ADALIMUMAB	INJ-SC SOL	40MG
09857326	ADALIMUMAB	INJ-SC SOL	40MG
09857327	ADALIMUMAB	INJ-SC SOL	40MG
02130181	ALDESLEUKIN	IV PWS	1.3MG
02331675	CERTOLIZUMAB PEGOL	INJ-SC SOL	200MG/ML
09857394	ETANERCEPT RECOMBINANT	INJ SOL	50MG/ML
02242903	ETANERCEPT RECOMBINANT	INJ-SC PWS	25MG
02274728	ETANERCEPT RECOMBINANT	INJ-SC SOL	50MG/ML
09857322	ETANERCEPT RECOMBINANT	INJ-SC SOL	50MG/ML
02233014	GLATIRAMER	INJ-SC PWS	20MG
02245619	GLATIRAMER	INJ-SC SOL	20MG/ML
02324776	GOLIMUMAB RECOMBINANT	INJ-SC SOL	50MG/0.5ML
02324784	GOLIMUMAB RECOMBINANT	INJ-SC SOL	50MG/0.5ML
02244016	INFLIXIMAB	IV PWS	100MG
09852956	INFLIXIMAB	IV PWS	100MG
02419475	INFLIXIMAB	PWD VIAL	100MG
02239832	INTERFERON	INJ-SC SOL	0.03MG/ML
09852751	INTERFERON	OPH SOL	1MU/ML
02223384	INTERFERON ALFA 2B	INJ PWS	3MMU
02223392	INTERFERON ALFA 2B	INJ PWS	5MMU
02223406	INTERFERON ALFA 2B	INJ PWS	10MMU
02231651	INTERFERON ALFA 2B	INJ PWS	18MMU
00889067	INTERFERON ALFA 2B	INJ SOL	10MMU/2ML
02223414	INTERFERON ALFA 2B	INJ SOL	10MMU/2ML
02238674	INTERFERON ALFA 2B	INJ SOL	3MMU/0.5ML
02238675	INTERFERON ALFA 2B	INJ SOL	5MMU/0.5ML
09853995	INTERFERON ALFA 2B	INJ SOL	10MU/VIAL

DIN	Drug Name	Route of Administration	Strength
09854045	INTERFERON ALFA 2B	INJ SOL	3MMU/0.5ML
09854053	INTERFERON ALFA 2B	INJ SOL	5MMU/0.5ML
00705896	INTERFERON ALFA 2B	INJ-SC SOL	3MMU
00705918	INTERFERON ALFA 2B	INJ-SC SOL	5MMU
00705926	INTERFERON ALFA 2B	INJ-SC SOL	10MMU
02240693	INTERFERON ALFA 2B	INJ-SC SOL	18MMU/1.2ML
02240694	INTERFERON ALFA 2B	INJ-SC SOL	30MMU/1.2ML
02240695	INTERFERON ALFA 2B	INJ-SC SOL	60MMU/1.2ML
01911988	INTERFERON ALFA-2A	INJ PWS	3000MU/ML
01911996	INTERFERON ALFA-2A	INJ PWS	9000MU/ML
01912003	INTERFERON ALFA-2A	INJ PWS	6000MU/ML
00812471	INTERFERON ALFA-2A	INJ PWS	6000MU/ML
00812498	INTERFERON ALFA-2A	INJ SOL	6000MU/ML
00812501	INTERFERON ALFA-2A	INJ SOL	3000MU/ML
02217015	INTERFERON ALFA-2A	INJ SOL	3000MU/ML
02217031	INTERFERON ALFA-2A	INJ SOL	6000MU/ML
02217058	INTERFERON ALFA-2A	INJ SOL	9000MU/ML
02217066	INTERFERON ALFA-2A	INJ SOL	18000MU/ML
02019914	INTERFERON ALFA-2A	INJ SOL	9000MU/ML
01959069	INTERFERON ALPHA-N1	INJ SOL	10MU
01959077	INTERFERON ALPHA-N1	INJ SOL	3MU
00709042	INTERFERON ALPHA-N1	INJ SOL	3MU
00709050	INTERFERON ALPHA-N1	INJ SOL	10MU
02169649	INTERFERON BETA	INJ-SC PWS	0.3MG
02237317	INTERFERON BETA 1A	INJ PWS	11MCG
02237318	INTERFERON BETA 1A	INJ PWS	44MCG
02237770	INTERFERON BETA 1A	INJ-IM PWS	30MCG/1.1ML
02269201	INTERFERON BETA 1A	INJ-IM SOL	30MCG/0.5ML
02318253	INTERFERON BETA 1A	INJ-SC SOL	66MCG/1.5ML
02318261	INTERFERON BETA 1A	INJ-SC SOL	132MCG/1.5ML
02237319	INTERFERON BETA 1A	INJ-SC SOL	22MCG/0.5ML
02237320	INTERFERON BETA 1A	INJ-SC SOL	44MCG/0.5ML
09857395	INTERFERON BETA-1A	PREF AUTOINJ PEN	30MCG/0.5ML
02337819	INTERFERON BETA-1B RECOMBINANT	INJ-SC PWS	0.3MG
00846368	LEVAMISOLE HCL	TAB	50MG
02234217	LEVAMISOLE HCL	TAB	50MG
09857505	PEGINTERFERON ALFA 2A RECOMBINANT	INJ-SC SOL	180MCG/0.5ML
02248077	PEGINTERFERON ALFA 2A RECOMBINANT	INJ-SC SOL	180MCG/0.5ML
02248078	PEGINTERFERON ALFA 2A RECOMBINANT	INJ-SC SOL	180MCG/ML

DIN	Drug Name	Route of Administration	Strength
00258482	BLEOMYCIN SULFATE	INJ PWS	15U
00163899	DAUNORUBICIN HCL	INJ PD	20MG
01926683	DAUNORUBICIN HCL	IV PWS	20MG
00353078	DOXORUBICIN HCL	IV PWS	50MG
00357391	DOXORUBICIN HCL	IV PWS	10MG
00640050	EPIRUBICIN HCL	INJ PWS	10MG
00640069	EPIRUBICIN HCL	IV PWS	50MG
00381799	MITOMYCIN	IV PWS	5MG
00463221	MITOTANE	TAB	500MG
02415992	AFLIBERCEPT	VIAL	40MG/ML
02273993	ALEMTUZUMAB	IV SOL	10MG/ML
02290960	ALEMTUZUMAB	IV SOL	30MG/ML
02270994	BEVACIZUMAB	IV SOL	25MG/ML
09857407	RITUXIMAB	IV SOL	10MG/ML
02241927	RITUXIMAB	IV SOL	10MG/ML

Appendix: ICD-9 codes and ICD-10 codes utilized to define acute respiratory illness in physician, ER and hospital encounters.

Description	ICD-9 Code	ICD-10 Code
Viral infection, unspecified site	079	B34
Viral agents as the cause of diseases classified to other chapters	--	B97 (but not B973 or B977)
Acute nasopharyngitis (common cold)	460	J00
Acute sinusitis	461	J01
Acute pharyngitis	462	J02
Acute tonsillitis	463	J03
Acute laryngitis, tracheitis, epiglottitis, croup	464	J04, J05
Acute upper respiratory infections of multiple or unspecified sites	465	J06
Influenza due to identified novel influenza A virus	488	J09
Influenza	487	J10, J11
Pneumonia, organism unspecified	486	--
Viral pneumonia	480	J12
Bacterial pneumonia	481, 482	J13, J14, J15
Pneumonia due to other specified organism	483	J16
Pneumonia in infectious diseases classified elsewhere	484	J17
Bronchopneumonia, organism unspecified	485	J18
Acute bronchitis and bronchiolitis	466	J20, J21
Unspecified diseases respiratory system	519	J22, J39.8, J39.9
Bronchitis, not specified as acute or chronic	490	J40
Acute respiratory distress syndrome	518.82	J80
Pulmonary edema	518.4	J81
Pleural effusion	510.9, 511.0, 511.1, 511.89	J86.9, J90, R09.1
Respiratory failure	518.81	J96.0, J96.9
Atelectasis	--	J98.10
Pulmonary collapse	518.0	J98.19
Other respiratory disorders	786.00, 786.09	J98.0, J98.4, J98.8, J98.9
Hemoptysis	786.30	R04.2
Cough	786.2	R05
Shortness of breath (dyspnea)	786.02, 786.05, 786.09	R06.0
Stridor	786.1	R06.1
Wheezing	786.07	R06.2
Tachypnea	786.06	R06.4

Description	ICD-9 Code	ICD-10 Code
Chest pain on breathing	786.52	R07.1
Hypoxemia	799.02	R09.0
Respiratory arrest	799.1	R09.2
Abnormal sputum	786.4	R09.3
Nasal congestion	478.19	R09.81
Abnormal chest sounds	786.7	R09.89
Fever	780.60	R50
Chills (without fever)	780.64	R68.0
Sepsis, shock	669.11, 669.12, 669.14, 785.50, 785.52, 995.91, 995.92	A41.9, R57.9

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TITLE

Using population-wide administrative and laboratory data to estimate type- and subtype-specific influenza vaccine effectiveness: a surveillance protocol

Allison N Scott[1,2,3]

Sarah A Buchan[4,5,6]

Jeffrey C Kwong[4,5,6,7,8]

Steven J Drews[9,10]

Kimberley A Simmonds[1,11]

Lawrence W Svenson[1,11, 12, 13]

Affiliations

[1]Ministry of Health, Government of Alberta, Edmonton, AB, Canada

[2]PolicyWise for Children & Families, Edmonton, AB, Canada

[3]Department of Public Health, Concordia University of Edmonton, AB, Canada

[4]ICES, Toronto, ON, Canada

[5]Public Health Ontario, Toronto, ON, Canada

[6]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

[7]Department of Family & Community Medicine, University of Toronto, Toronto, ON, Canada

[8]University Health Network, Toronto, ON, Canada

[9]The Alberta Provincial Laboratory for Public Health, Edmonton, AB, Canada

[10]Department of Laboratory Medicine & Pathology, University of Alberta, Edmonton, AB, Canada

[11] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

[12] School of Public Health, University of Alberta, Edmonton, AB, Canada

[13] Division of Preventive Medicine, University of Alberta, Edmonton, AB, Canada

Corresponding Author:

Allison N. Scott, Ph.D.

PolicyWise for Children & Families

1000, 9925-109 Street NW

Edmonton, Alberta, Canada T5K 2J8

Email Addresses

Allison N Scott	AScott@policywise.com
Sarah A Buchan	Sarah.Buchan@oahpp.ca
Jeffrey C Kwong	jeff.kwong@utoronto.ca
Steven J Drews	steven.drews@blood.ca
Kimberley A Simmonds	kimberley.simmonds@gov.ab.ca
Lawrence W Svenson	larry.svenson@gov.ab.ca

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ABSTRACT

Introduction

The appropriateness of using routinely collected laboratory data combined with administrative data for estimating influenza vaccine effectiveness (VE) is still being explored. This paper outlines a protocol to estimate influenza VE using linked laboratory and administrative data which could act as a companion to estimates derived from other methods.

Methods and Analysis

We will use the test-negative design to estimate VE for each influenza type/subtype and season. Province-wide individual-level records of positive and negative influenza tests at the Provincial Laboratory for Public Health in Alberta will be linked, by unique personal health numbers, to administrative databases and vaccination records held at the Ministry of Health in Alberta to determine covariates and influenza vaccination status, respectively. Covariates of interests include age, sex, immunocompromising chronic conditions, and healthcare setting. Cases will be defined based on an individual's first positive influenza test during the season, and potential controls will be defined based on an individual's first negative influenza test during the season. One control for each case will be randomly selected based on the week the specimen was collected. We will estimate vaccine effectiveness using multivariable logistic regression.

Ethics and Dissemination

Ethics approval was obtained from the University of Alberta's Health Research Ethics Board – Health Panel under study ID Pro00075997. Results will be disseminated by public health officials in Alberta.

Key Words

Influenza

Vaccine effectiveness

Case Control

Test-negative

Administrative data

Population-level

Laboratory data

Vaccination database

ARTICLE SUMMARY

Strengths and limitations of this study

- A strength of this protocol is that it provides timely estimation of vaccine effectiveness to assist public health in allocating resources and determining the appropriate policies and public messaging during the influenza season.
- Vaccine effectiveness estimates use a test negative design, taking advantage of linked administrative health records for the entire population.
- While many confounders are included in the vaccine effectiveness estimates, not all known confounders can be measured using administrative health data.

INTRODUCTION

Influenza is a respiratory viral disease associated with significant morbidity and mortality globally. Infections range from relatively mild presentations (e.g. cough, sore throat) to severe lower respiratory tract infections (e.g. pneumonia). Severe cases may be associated with hospitalization, intensive care admission, and death; young children, the elderly, and individuals with chronic conditions are at highest risk of severe outcomes[1]. In Canada, rates of laboratory-confirmed influenza infections are, on average, approximately 200 cases per 100,000 population, with approximately 50% of cases occurring in patients aged ≤18 years [2]. The causative agents, influenza A (subtypes H3N2 and H1N1pdm(09)) and influenza B (Yamagata and Victoria lineages), are under strong selective pressure to mutate genetically; significant genetic changes can occur in relatively short periods of time (i.e. <1 year) [3].

Influenza prevention relies, in part, on annual vaccination campaigns. Selection of viral strains for inclusion in the vaccine occurs approximately 9 months prior to the onset of the influenza season; by the time the vaccines are administered, the predominant circulating strains may have mutated to the point such that the effectiveness of the vaccine has diminished or has become completely ineffective [4,5].

Influenza VE is commonly estimated using the test-negative design, a variation of the case-control design where cases and controls are selected from a pool of individuals who have been tested for influenza [6–10]. Several research groups use sentinel physician networks to recruit patients: influenza testing is performed on patients who meet a case definition for influenza-like illness, and cases and controls are selected from that pool [6–8]. While this has become an established method, there are some limitations to using sentinel physicians. As the physicians are often volunteers, there can be bias in the geographic distribution, leading to clustering of sampling in certain areas and not others. This can lead to inaccuracies as predominant circulating influenza strains vary geographically [7,11]. Immunization information is commonly self-reported, potentially leading to recall and social desirability biases [12]; volunteer physicians may be more likely to have strong views on influenza immunization, potentially making it more difficult for the patient to admit to not being immunized. Finally, as these studies are labour-intensive for clinic staff, physician recruitment is often

low, resulting in small sample sizes and wide confidence intervals. Estimates are, therefore, typically available after the peak of the influenza season, decreasing their usefulness for public health messaging and resource and operational planning [6–8,11].

Using administrative data and routinely collected clinical specimens for estimating VE is currently under debate [13]. VE estimates generated using linked health administrative and laboratory data in the province Ontario have been shown to be comparable to previously published estimates[14]. There has been one published estimate of Alberta-specific vaccine effectiveness using a sentinel surveillance system[11]; however, because of the small sample size the confidence interval was large, ranging from 8% to 72%. Estimating VE in a large jurisdiction with near-real-time data on all influenza laboratory testing and influenza vaccination in the population has the potential to provide more precise and timely VE estimates than has previously been possible. We present a protocol to estimate influenza VE using individually-linked laboratory and administrative data.

METHODS AND ANALYSIS

Study Setting:

Alberta is a province in Canada with a publicly-funded universal health care system; each of the 4.25 million residents is assigned a unique personal health number (PHN) at birth or upon immigration to the province [15]. The PHN is recorded each time a person accesses the healthcare system, allowing for deterministic linkage across multiple administrative data sets held by the Ministry of Health.

In 2009, influenza vaccination became universally available to all Albertans aged ≥6 months, regardless of comorbidities or other risk conditions [16]. Influenza vaccines are available at no cost to the patient at public health clinics, pharmacies, physician offices, long-term care facilities, university health centers, and workplaces. Annual vaccine campaigns begin in October, with approximately 60% of all influenza vaccinations given by the end of the second week of the campaign. While the peak of influenza activity has

varied widely since 2010, the median influenza peak in Alberta is in mid-January, approximately three months after the vaccination campaigns begin.

Laboratory methods for influenza A and B detection and influenza A subtyping

All influenza testing in Alberta is performed at a single diagnostic lab, the Provincial Laboratory for Public Health (ProvLab) and stored in a single laboratory information system, along with test and patient identifiers. Clinical specimens (e.g. nasopharyngeal swabs, nasopharyngeal aspirates, bronchoalveolar lavages) are processed at ProvLab using previously published protocols. Nucleic acid extraction utilizes the easyMAG extractor and reagents (bioMerieux,St.Laurent,Quebec,Canada)[17]. Nucleic acid from clinical specimens are then tested using a series of respiratory detection assays as described below. Prior to May 2017, a real-time influenza A/B reverse-transcriptase PCR (RT-PCR) was used to diagnose influenza using a protocol previously described [18,19]. After May 2017, ProvLab has been using a Luminex Respiratory Pathogen Panel for the identification of influenza A (including subtype), influenza B, and other respiratory viruses (e.g. coronavirus and parainfluenza) [15]. Results of the laboratory testing were imported into specific laboratory information systems depending on the testing time period.

Study Design:

We will use the test-negative design to estimate VE. We will estimate VE for the 2011/12 – 2019/20 influenza seasons. The results of all respiratory virus tests conducted at ProvLab will be sent to the Ministry of Health for deterministic linkage to health administrative databases, in order to determine eligibility for inclusion in the analysis, influenza vaccination status, and the following covariates: age, sex, socio-economic status, geographic zone of residence, history of immunocompromising comorbidities, healthcare setting (inpatient or outpatient setting), and month at the time of specimen submission. The presence of a diagnostic code for an acute respiratory illness (ARI) at the time of specimen collection will be used in a sensitivity analysis.

Isolates will be considered eligible for inclusion in the analysis if they met all of the following criteria: a valid PHN is recorded, the isolate is not from a resident of a long-term care facility, the isolate was collected at least four weeks after the initiation of the public influenza vaccination program, and the isolate was collected during the influenza season, as determined using the method recommended by the WHO [20–22].

It is important to ensure that the population has the chance to be exposed to influenza and there is sufficient time for immunity to the vaccine to be developed. Residence in a long-term care facility will be determined via the Alberta Continuing Care Information System (ACCIS), which contains information on admissions and discharges from long-term care facilities [23]. PHN validity will be assessed using the Alberta Health Care Insurance Plan (AHCIP) Adjusted Population Registry, which contains records of all individuals registered for healthcare insurance [23,24].

Individuals can have multiple laboratory tests over the course of their illness; therefore only the first positive influenza test during the influenza season will be used, and potential control samples will be selected from among those who only tested negative for influenza during that influenza season, using the first negative test. Cases and controls tested <14 days after vaccination will be excluded from the analysis.

Influenza vaccination status will be determined from the Influenza Vaccination Registry. The registry combines data from four databases that record influenza vaccination events (see below).

The following administrative data sets will be used in this study.

- Alberta Health Immunization and Adverse Reaction to Immunization system (Imm/ARI) contains records of all publicly funded vaccines administered through public health, including influenza vaccines administered at mass influenza vaccination clinics, public health clinics, and vaccinations administered by public health nurses in long-term care facilities. Data submission is mandatory and guidelines exist to support complete and accurate vaccination records with descriptions of each, including notes [25,26].

- The Supplemental Enhanced Service Event (SESE) database captures physician claims for billing purposes; International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes, procedure codes (Canadian Classification of Procedures), codes indicating location of service delivery, and a number of other administrative elements used to support the payment for each patient encounter [24,27,28].
- Alberta Blue Cross (ABC) administers the pharmacist component of the universal vaccination program. Pharmacists administering influenza vaccines through this program submit claims to ABC for each vaccine provided; they are required to submit patient information such as PHN, date of service, name, and address.
- The Pharmaceutical Information Network (PIN) database records dispensed pharmacological products, regardless of payer, including the rare instances when an influenza vaccine is purchased rather than administered through the public program (e.g. purchased by travelers prior to the launch of the public campaign). PIN captures approximately 95% of all dispensed events in the province [23].
- Provincial Vaccine Registry combines influenza vaccinations given in the province and recorded in four source databases (PIN, ABC, SESE and Imm/ARI).
- Alberta Health Care Insurance Plan (AHCIP) Population Registry contains demographic variables, age, sex, socio-economic status, and geographic zone of residence. Neighbourhood-level socio-economic status is derived from census dissemination area income quintiles using postal code.
- Morbidity and Ambulatory Care Abstracting Reporting (MACAR) system contains ICD-10-CA diagnostic codes, procedure codes, the date of admission, and date of discharge for every visit to hospitals, emergency rooms, and outpatient clinics.

The quality of administrative datasets in Alberta has been extensively reviewed [29–31].

Individuals will be considered inpatients if they have at least one physician claim for inpatient services on the same day as specimen collection or if specimen collection occurred during an inpatient stay; all others

will be considered outpatients. Individuals with an immunocompromising condition will be defined as those who have a diagnosis of HIV, who received an organ transplant, or received oral corticosteroids (for ≥30 days), antineoplastic agents, or another immunocompromising drug from a community pharmacist in the past 6 months. (Appendix 1 and 2) [32]. HIV diagnosis and ARI will be determined through physician claims and MACAR. Organ transplantation will be determined using MACAR, and immunocompromising drug dispensations will be identified through PIN.

Statistical Analysis

Vaccine effectiveness data will be refreshed and the analysis completed every two weeks until the peak of the influenza season and monthly thereafter. We will use multivariable logistic regression to estimate influenza vaccine effectiveness as (1 – adjusted OR) x 100% and will compare the results to historical values of VE for the predominate subtype. We will estimate VE separately by influenza season and influenza subtype (i.e., A(H3N2), A(H1N1)pdm09, and influenza B) [33]. When there is a large enough sample size in a particular season to provide adequate power, VE will be estimated for specific age groups such as children under the age of 5 and seniors over the age of 65. The following covariates will be included in the adjusted model, regardless of statistical significance: age, sex, socio-economic status, geographic zone of residence, history of immunocompromising comorbidities, healthcare setting (inpatient or outpatient setting), and month of specimen submission within the influenza season. SAS version 9.4 will be used for all statistical analysis (SAS Institute Inc, Cary, NC). VE estimates will be compared to published estimates of VE [6,7,11,13,34,35] .

As shedding of influenza virus continues for approximately 4-5 days after symptom onset, bias can result if specimens that are collected too long after symptom onset are used [36]. Most studies use a threshold of 7 days [37]. To test the robustness of the findings, a sensitivity analysis will be performed; controls will be restricted to those specimens positive for a different respiratory virus (i.e. coronavirus, human respiratory syncytial virus) (As suggested by Sullivan et al 2016).

A potential limitation to this study is that the samples utilized here are clinical isolates taken through the course of normal patient care, and are not from a standard case definition as is utilized in some other studies

[12]. To test the robustness of the findings, the analysis will be repeated using only cases and controls that were given a diagnosis code for ARI on the same day as specimen collection, as per the SESE database or MACAR. Appendix 3 lists the ICD-9 and ICD-10 codes used to define ARIs.

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not involved in the design of the study, including the development of the research question, outcomes measures, recruitment to or conduct of the study. The results of the study will be disseminated to the public as deemed appropriate by public health officials.

DISCUSSION

This protocol describes the estimation of seasonal influenza VE using specimens collected for routine influenza diagnostics as well as administrative data and vaccination records.

A key strength of this approach is the large sample size. This approach allows calculation of timely, precise influenza VE estimates weeks prior to the influenza season peak, creating an early warning system for public health if, as in the 2014-2015 season, the vaccine is found to have exceedingly low effectiveness. Early notification of VE can assist public health in determining policies, messaging, and allocation of resources (antiviral agents, staffing emergency departments) to counter a potentially more severe influenza season [37,38]. The large sample size also allows for stratified analyses of VE based on product, age group, or region.

Whereas sentinel physician networks rely primarily on self-reported measures of influenza vaccination [34], a significant strength of this study is the use of the near-real-time influenza vaccination registry that contains individual-level, linkable data for most influenza vaccinations administered in the province. Use of this registry reduces the likelihood of recall error and information biases such as social desirability bias and

reduces non-differential misclassification, which would bias the odds ratio towards the null, thus underestimating VE [12].

Finally, we are certain to capture the results of all respiratory virus testing in the province, as all respiratory virus testing is centralized at ProvLab and there is limited use of point-of-care testing.

There are some limitations to this methodology compared to the traditional method of VE estimation using sentinel physician networks, because a standardized clinical case definition cannot be applied to determine study eligibility. A sensitivity analysis restricting to healthcare encounters with a diagnosis code for ARI will be used as a proxy for a standard case definition.

While the inclusion of confounders is important for VE estimate adjustment, not all known confounders can be measured using administrative data. Frailty has been demonstrated to be a potential confounder of VE [39–41]. Frailty cannot be included in the multivariable model because no validated indices of frailty generated from standard administrative data exist at this time. However, this may not affect the results significantly as a previous study indicated that inclusion of frailty in the multivariate model increased VE estimates only slightly [42].

Laboratory requisitions in Alberta do not contain illness onset date. Ideally this would be used to ensure that the negative laboratory test results were representative of an acute infectious period and that test-negative specimens were not collected after viral shedding had ceased. Sullivan et al 2016 have indicated this bias may be accounted for by selecting influenza test-negative controls that were positive for another respiratory virus. Requiring controls to be positive for another virus excludes individuals who are tested long after their acute infectious period. However, a recent systematic review found no differences when using different groups of controls [43].

Comparison of the VE results using administrative data to previously published studies, specifically sentinel surveillance for the same seasons (2011/12 – 2018/19) will help to identify further areas of refinement.

This approach could successfully allow for the generation of early influenza VE estimates which could facilitate tailoring of public health messaging and assist in public health operations planning for the peak of the influenza season.

ETHICS

Ethics approval was obtained from the University of Alberta's Health Research Ethics Board – Health Panel under study ID Pro00075997.

LIST OF ABBREVIATIONS

ABC – Alberta Blue Cross

ACCIS – Alberta Continuing Care Information System

AHCIP – Alberta Health Care Insurance Plan Adjusted Population Registry

CCI – Canadian Classification of Health Interventions

CCP – Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures

ICD-9 – International Classification of Diseases, Ninth Revision

ICD-10 – International Classification of Diseases, Tenth Revision

Imm/ARI – Alberta Health Immunization and Adverse Reaction to Immunization system

MACAR – Morbidity and Ambulatory Care Abstracting Reporting

PHN – Personal Health Number

PIN – Pharmaceutical Information Network

ProvLab – Alberta Provincial Laboratory for Public Health

RT-PCR – Reverse Transcriptase Polymerase Chain Reaction

SESE – Supplemental Enhance Service Event

VE – Vaccine Effectiveness

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was obtained from the University of Alberta's Health Research Ethics Board – Health Panel under study ID Pro00075997.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

Not applicable

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

Not applicable

AUTHOR STATEMENT

ANS and SJD conceived of and designed the protocol and drafted and revised the manuscript. KS and LS planned the original approach, providing guidance on available administrative database resources. SAB and JCK made substantial contributions to the design and critically revised the manuscript.

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Supplementary File - Using population-wide administrative and laboratory data to estimate type- and subtype-specific influenza vaccine effectiveness: a surveillance protocol

Appendix: List of CCP, CCI, and CMG codes utilized to define individuals who have had an organ transplant

CCP Code	Description
495	Heart Transplantation
455	Lung Transplant
456	Combined Heart-Lung Transplantation
624	Liver Transplant
675	Transplant of Kidney
648	Transplant of Pancreas

CCI Code	Description
1HY85	Transplant, Heart With Lung(S)
1HZ85	Transplant, Heart Nec
1GT85	Transplant, Lung Nec
1GR85	Transplant, Lobe of Lung
1OA85	Transplant, Liver
1PC85	Transplant, Kidney
1OJ85	Transplant, Pancreas
1OK85	Transplant, Pancreas With Duodenum
1NK85	Transplant, Small Intestine
1NP85	Transplant, Small And Large Intestine

CMG 1992 To 2005	
175	Heart or Lung Transplant
253	Major Intestinal And Rectal Procedures
310	Liver Transplant
311	Major Pancreatic Procedures
500	Kidney Transplant

CMG 2007 To 2016	
110	Lung Transplant
160	Heart Transplant
220	Major Upper Gastrointestinal Reconstruction/Excision
270	Liver/Pancreas/Duodenum Transplant
450	Kidney Transplant

Appendix: List of drug names and DINs utilized to define immunocompromising conditions

DIN	Drug Name	Route of Administration	Strength
00616192	ETOPOSIDE	CAP	50MG
00523410	ETOPOSIDE	IV SOL	20MG/ML
02080036	ETOPOSIDE	IV SOL	20MG/ML
02241182	ETOPOSIDE	IV SOL	20MG/ML
02231622	IRINOTECAN HCL	IV SOL	20MG/ML
02258218	IRINOTECAN HCL	IV SOL	20MG/ML
00015431	VINBLASTINE SULFATE	IV PWS	1MG/ML
00611182	VINCRISTINE SULFATE	IV SOL	1MG/ML
02143305	VINCRISTINE SULFATE	IV SOL	1MG/ML
00004618	BUSULFAN	TAB	2MG
00297763	CARMUSTINE	IV PWS	100MG
09851399	CARMUSTINE	TOP SOL	NOT AVLE
00004626	CHLORAMBUCIL	TAB	2MG
00344915	CYCLOPHOSPHAMIDE	INJ PWS	2GM
00013544	CYCLOPHOSPHAMIDE	IV PWS	200MG
00013552	CYCLOPHOSPHAMIDE	IV PWS	200MG
02241797	CYCLOPHOSPHAMIDE	IV PWS	200MG
02241799	CYCLOPHOSPHAMIDE	IV PWS	1000MG
00013749	CYCLOPHOSPHAMIDE	TAB	50MG
00262676	CYCLOPHOSPHAMIDE	TAB	25MG
00344877	CYCLOPHOSPHAMIDE	TAB	25MG
00344885	CYCLOPHOSPHAMIDE	TAB	50MG
02241795	CYCLOPHOSPHAMIDE	TAB	25MG
02241796	CYCLOPHOSPHAMIDE	TAB	50MG
02063794	ESTRAMUSTINE DISODIUM PHOSPHATE	CAP	140MG
00780278	ESTRAMUSTINE PHOSPHATE	CAP	140MG
00360414	LOMUSTINE	CAP	100MG
00360422	LOMUSTINE	CAP	40MG
00360430	LOMUSTINE	CAP	10MG
00016063	MECHLORETHAMINE	IV PWS	10MG
00004715	MELPHALAN	TAB	2MG
02312794	TEMOZOLOMIDE	CAP	140MG
02312816	TEMOZOLOMIDE	CAP	180MG
02395274	TEMOZOLOMIDE	CAP	20MG
02395282	TEMOZOLOMIDE	CAP	100MG
02395290	TEMOZOLOMIDE	CAP	140MG
02395312	TEMOZOLOMIDE	CAP	250MG
02443473	TEMOZOLOMIDE	CAP	5MG
02443481	TEMOZOLOMIDE	CAP	20MG

DIN	Drug Name	Route of Administration	Strength
02443511	TEMOZOLOMIDE	CAP	100MG
02443538	TEMOZOLOMIDE	CAP	140MG
02443554	TEMOZOLOMIDE	CAP	250MG
02241093	TEMOZOLOMIDE	CAP	5MG
02241094	TEMOZOLOMIDE	CAP	20MG
02241095	TEMOZOLOMIDE	CAP	100MG
02241096	TEMOZOLOMIDE	CAP	250MG
02441160	TEMOZOLOMIDE	CAPSULE	5MG
00237035	THIOTEPA	INJ PWS	15MG/ML
02421917	CAPECITABINE	FC TAB	150MG
02421925	CAPECITABINE	FC TAB	500MG
02426757	CAPECITABINE	FC TAB	150MG
02426765	CAPECITABINE	FC TAB	500MG
02400022	CAPECITABINE	TAB	150MG
02400030	CAPECITABINE	TAB	500MG
02238453	CAPECITABINE	TAB	150MG
02238454	CAPECITABINE	TAB	500MG
02022117	CLADRIBINE	IV SOL	1MG
00194727	CYTARABINE	INJ PWS	500MG
00386715	CYTARABINE	INJ PWS	100MG
02167867	CYTARABINE	INJ PWS	100MG
00646296	CYTARABINE	IV PWS	1GM
00646318	CYTARABINE	IV PWS	2GM
02246226	FLUDARABINE PHOSPHATE	TAB	10MG
00012882	FLUOROURACIL	IV SOL	
00330582	FLUOROURACIL	TOP CRM	5%
00465283	HYDROXYUREA	CAP	500MG
02242920	HYDROXYUREA	CAP	500MG
02247937	HYDROXYUREA	CAP	500MG
00004723	MERCAPTOPURINE	TAB	50MG
02415275	MERCAPTOPURINE	TABLET	50MG
09857520	METHOTREXATE	INJ SOL	50MG/2ML
02182777	METHOTREXATE	INJ SOL	25MG/ML
02182955	METHOTREXATE	INJ SOL	25MG/ML
00014915	METHOTREXATE	TAB	2.5MG
02170698	METHOTREXATE	TAB	2.5MG
02182750	METHOTREXATE	TAB	10MG
02182963	METHOTREXATE	TAB	2.5MG
02244798	METHOTREXATE	TAB	2.5MG
02398427	METHOTREXATE	VIAL	25MG/ML
00321397	METHOTREXATE DISODIUM	INJ SOL	2.5MG/ML
00321400	METHOTREXATE DISODIUM	INJ SOL	2.5MG/ML

DIN	Drug Name	Route of Administration	Strength
02170663	METHOTREXATE DISODIUM	INJ SOL	50MG/2ML
02170671	METHOTREXATE DISODIUM	INJ SOL	2.5MG/ML
02182947	METHOTREXATE SODIUM	INJ SOL	10MG/ML
00614335	METHOTREXATE SODIUM	IV SOL	10MG/ML
00874132	METHOTREXATE SODIUM	TAB	2.5MG
02171767	METHOTREXATE SODIUM	TAB	2.5MG
00282081	THIOGUANINE	TAB	40MG
02384256	CRIZOTINIB	CAP	200MG
02384264	CRIZOTINIB	CAP	250MG
02409607	DABRAFENIB	CAP	50MG
02409615	DABRAFENIB	CAP	75MG
02320193	DASATINIB	TAB	100MG
02293129	DASATINIB	TAB	20MG
02293137	DASATINIB	TAB	50MG
02293145	DASATINIB	TAB	70MG
02269007	ERLOTINIB HCL	TAB	25MG
02269015	ERLOTINIB HCL	TAB	100MG
02269023	ERLOTINIB HCL	TAB	150MG
02377705	ERLOTINIB HCL	TABLET	100MG
02377713	ERLOTINIB HCL	TABLET	150MG
02434407	IBRUTINIB	CAP	140MG
09857447	IMATINIB MESYLATE	TAB	100MG
02388006	RUXOLITINIB	TAB	5MG
02388014	RUXOLITINIB	TAB	15MG
02388022	RUXOLITINIB	TAB	20MG
02409658	TRAMETINIB RECOMBINANT	TAB	2MG
01926438	ASPARAGINASE	INJ PWS	10MU
02389649	AXITINIB	TAB	5MG
02389630	AXITINIB	TAB FC	1MG
02262452	BORTEZOMIB	IV PWS	3.5MG
00521183	DACARBAZINE	IV PWS	200MG/VIAL
02154854	DACARBAZINE	IV PWS	200MG
02248676	GEFITINIB	TAB	250MG
02244725	IMATINIB MESYLATE	CAP	100MG
02399806	IMATINIB MESYLATE	FC TAB	100MG
02355337	IMATINIB MESYLATE	TAB	100MG
02355345	IMATINIB MESYLATE	TAB	400MG
02397285	IMATINIB MESYLATE	TAB	100MG
02397293	IMATINIB MESYLATE	TAB	400MG
02399814	IMATINIB MESYLATE	TAB	400MG
02431114	IMATINIB MESYLATE	TAB	100MG
02431122	IMATINIB MESYLATE	TAB	400MG

DIN	Drug Name	Route of Administration	Strength
09857448	IMATINIB MESYLATE	TAB	400MG
02253275	IMATINIB MESYLATE	TAB	100MG
02253283	IMATINIB MESYLATE	TAB	400MG
02326442	LAPATINIB DITOSYLATE	TAB	250MG
02315874	NILOTINIB	CAP	200MG
02368250	NILOTINIB	CAP	150MG
02352303	PAZOPANIB HCL	TAB	200MG
00012750	PROCARBAZINE HCL	CAP	50MG
02403390	REGORAFENIB	TAB	40MG
02284227	SORAFENIB TOSYLATE	TAB	200MG
02280795	SUNITINIB MALATE	CAP	12.5MG
02280809	SUNITINIB MALATE	CAP	25MG
02280817	SUNITINIB MALATE	CAP	50MG
02258595	ADALIMUMAB	INJ-SC SOL	40MG
09854785	ADALIMUMAB	INJ-SC SOL	40MG
09857294	ADALIMUMAB	INJ-SC SOL	40MG
09857326	ADALIMUMAB	INJ-SC SOL	40MG
09857327	ADALIMUMAB	INJ-SC SOL	40MG
02130181	ALDESLEUKIN	IV PWS	1.3MG
02331675	CERTOLIZUMAB PEGOL	INJ-SC SOL	200MG/ML
09857394	ETANERCEPT RECOMBINANT	INJ SOL	50MG/ML
02242903	ETANERCEPT RECOMBINANT	INJ-SC PWS	25MG
02274728	ETANERCEPT RECOMBINANT	INJ-SC SOL	50MG/ML
09857322	ETANERCEPT RECOMBINANT	INJ-SC SOL	50MG/ML
02233014	GLATIRAMER	INJ-SC PWS	20MG
02245619	GLATIRAMER	INJ-SC SOL	20MG/ML
02324776	GOLIMUMAB RECOMBINANT	INJ-SC SOL	50MG/0.5ML
02324784	GOLIMUMAB RECOMBINANT	INJ-SC SOL	50MG/0.5ML
02244016	INFLIXIMAB	IV PWS	100MG
09852956	INFLIXIMAB	IV PWS	100MG
02419475	INFLIXIMAB	PWD VIAL	100MG
02239832	INTERFERON	INJ-SC SOL	0.03MG/ML
09852751	INTERFERON	OPH SOL	1MU/ML
02223384	INTERFERON ALFA 2B	INJ PWS	3MMU
02223392	INTERFERON ALFA 2B	INJ PWS	5MMU
02223406	INTERFERON ALFA 2B	INJ PWS	10MMU
02231651	INTERFERON ALFA 2B	INJ PWS	18MMU
00889067	INTERFERON ALFA 2B	INJ SOL	10MMU/2ML
02223414	INTERFERON ALFA 2B	INJ SOL	10MMU/2ML
02238674	INTERFERON ALFA 2B	INJ SOL	3MMU/0.5ML
02238675	INTERFERON ALFA 2B	INJ SOL	5MMU/0.5ML
09853995	INTERFERON ALFA 2B	INJ SOL	10MU/VIAL

DIN	Drug Name	Route of Administration	Strength
09854045	INTERFERON ALFA 2B	INJ SOL	3MMU/0.5ML
09854053	INTERFERON ALFA 2B	INJ SOL	5MMU/0.5ML
00705896	INTERFERON ALFA 2B	INJ-SC SOL	3MMU
00705918	INTERFERON ALFA 2B	INJ-SC SOL	5MMU
00705926	INTERFERON ALFA 2B	INJ-SC SOL	10MMU
02240693	INTERFERON ALFA 2B	INJ-SC SOL	18MMU/1.2ML
02240694	INTERFERON ALFA 2B	INJ-SC SOL	30MMU/1.2ML
02240695	INTERFERON ALFA 2B	INJ-SC SOL	60MMU/1.2ML
01911988	INTERFERON ALFA-2A	INJ PWS	3000MU/ML
01911996	INTERFERON ALFA-2A	INJ PWS	9000MU/ML
01912003	INTERFERON ALFA-2A	INJ PWS	6000MU/ML
00812471	INTERFERON ALFA-2A	INJ PWS	6000MU/ML
00812498	INTERFERON ALFA-2A	INJ SOL	6000MU/ML
00812501	INTERFERON ALFA-2A	INJ SOL	3000MU/ML
02217015	INTERFERON ALFA-2A	INJ SOL	3000MU/ML
02217031	INTERFERON ALFA-2A	INJ SOL	6000MU/ML
02217058	INTERFERON ALFA-2A	INJ SOL	9000MU/ML
02217066	INTERFERON ALFA-2A	INJ SOL	18000MU/ML
02019914	INTERFERON ALFA-2A	INJ SOL	9000MU/ML
01959069	INTERFERON ALPHA-N1	INJ SOL	10MU
01959077	INTERFERON ALPHA-N1	INJ SOL	3MU
00709042	INTERFERON ALPHA-N1	INJ SOL	3MU
00709050	INTERFERON ALPHA-N1	INJ SOL	10MU
02169649	INTERFERON BETA	INJ-SC PWS	0.3MG
02237317	INTERFERON BETA 1A	INJ PWS	11MCG
02237318	INTERFERON BETA 1A	INJ PWS	44MCG
02237770	INTERFERON BETA 1A	INJ-IM PWS	30MCG/1.1ML
02269201	INTERFERON BETA 1A	INJ-IM SOL	30MCG/0.5ML
02318253	INTERFERON BETA 1A	INJ-SC SOL	66MCG/1.5ML
02318261	INTERFERON BETA 1A	INJ-SC SOL	132MCG/1.5ML
02237319	INTERFERON BETA 1A	INJ-SC SOL	22MCG/0.5ML
02237320	INTERFERON BETA 1A	INJ-SC SOL	44MCG/0.5ML
09857395	INTERFERON BETA-1A	PREF AUTOINJ PEN	30MCG/0.5ML
02337819	INTERFERON BETA-1B RECOMBINANT	INJ-SC PWS	0.3MG
00846368	LEVAMISOLE HCL	TAB	50MG
02234217	LEVAMISOLE HCL	TAB	50MG
09857505	PEGINTERFERON ALFA 2A RECOMBINANT	INJ-SC SOL	180MCG/0.5ML
02248077	PEGINTERFERON ALFA 2A RECOMBINANT	INJ-SC SOL	180MCG/0.5ML
02248078	PEGINTERFERON ALFA 2A RECOMBINANT	INJ-SC SOL	180MCG/ML

DIN	Drug Name	Route of Administration	Strength
00258482	BLEOMYCIN SULFATE	INJ PWS	15U
00163899	DAUNORUBICIN HCL	INJ PD	20MG
01926683	DAUNORUBICIN HCL	IV PWS	20MG
00353078	DOXORUBICIN HCL	IV PWS	50MG
00357391	DOXORUBICIN HCL	IV PWS	10MG
00640050	EPIRUBICIN HCL	INJ PWS	10MG
00640069	EPIRUBICIN HCL	IV PWS	50MG
00381799	MITOMYCIN	IV PWS	5MG
00463221	MITOTANE	TAB	500MG
02415992	AFLIBERCEPT	VIAL	40MG/ML
02273993	ALEMTUZUMAB	IV SOL	10MG/ML
02290960	ALEMTUZUMAB	IV SOL	30MG/ML
02270994	BEVACIZUMAB	IV SOL	25MG/ML
09857407	RITUXIMAB	IV SOL	10MG/ML
02241927	RITUXIMAB	IV SOL	10MG/ML

Appendix: ICD-9 codes and ICD-10 codes utilized to define acute respiratory illness in physician, ER and hospital encounters.

Description	ICD-9 Code	ICD-10 Code
Viral infection, unspecified site	079	B34
Viral agents as the cause of diseases classified to other chapters	--	B97 (but not B973 or B977)
Acute nasopharyngitis (common cold)	460	J00
Acute sinusitis	461	J01
Acute pharyngitis	462	J02
Acute tonsillitis	463	J03
Acute laryngitis, tracheitis, epiglottitis, croup	464	J04, J05
Acute upper respiratory infections of multiple or unspecified sites	465	J06
Influenza due to identified novel influenza A virus	488	J09
Influenza	487	J10, J11
Pneumonia, organism unspecified	486	--
Viral pneumonia	480	J12
Bacterial pneumonia	481, 482	J13, J14, J15
Pneumonia due to other specified organism	483	J16
Pneumonia in infectious diseases classified elsewhere	484	J17
Bronchopneumonia, organism unspecified	485	J18
Acute bronchitis and bronchiolitis	466	J20, J21
Unspecified diseases respiratory system	519	J22, J39.8, J39.9
Bronchitis, not specified as acute or chronic	490	J40
Acute respiratory distress syndrome	518.82	J80
Pulmonary edema	518.4	J81
Pleural effusion	510.9, 511.0, 511.1, 511.89	J86.9, J90, R09.1
Respiratory failure	518.81	J96.0, J96.9
Atelectasis	--	J98.10
Pulmonary collapse	518.0	J98.19
Other respiratory disorders	786.00, 786.09	J98.0, J98.4, J98.8, J98.9
Hemoptysis	786.30	R04.2
Cough	786.2	R05
Shortness of breath (dyspnea)	786.02, 786.05, 786.09	R06.0
Stridor	786.1	R06.1
Wheezing	786.07	R06.2
Tachypnea	786.06	R06.4

Description	ICD-9 Code	ICD-10 Code
Chest pain on breathing	786.52	R07.1
Hypoxemia	799.02	R09.0
Respiratory arrest	799.1	R09.2
Abnormal sputum	786.4	R09.3
Nasal congestion	478.19	R09.81
Abnormal chest sounds	786.7	R09.89
Fever	780.60	R50
Chills (without fever)	780.64	R68.0
Sepsis, shock	669.11, 669.12, 669.14, 785.50, 785.52, 995.91, 995.92	A41.9, R57.9