

**Medically Attended Influenza Illness and the Risk of Stillbirth: A Population-Based
Retrospective Cohort Study in Ontario, Canada**

Nichole Dai

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School of Epidemiology and Public Health

Faculty of Medicine

University of Ottawa

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ABSTRACT

Background: Influenza illness during pregnancy has been associated with severe maternal adverse outcomes, including stillbirth. Despite recommendations from Canada's National Advisory Committee on Immunization (NACI) for influenza vaccination during pregnancy, coverage remains suboptimal, with only 45% of pregnant individuals vaccinated. Existing studies demonstrate inconsistent evidence regarding the association between maternal influenza and adverse outcomes, particularly for seasonal influenza and stillbirth.

Methods: We conducted a population-based retrospective cohort study using administrative health data housed at ICES in Ontario, Canada, between April 1, 2006, and March 31, 2020. Adjusted hazard ratios for stillbirth were estimated using an extended Cox proportional hazards model, accounting for time-varying exposure to medically attended influenza illness and adjusted for confounders. Two subgroup analyses were conducted: (1) exploring the acute infection of influenza using risk windows and (2) examining the effects of infection in high-risk individuals with pre-existing maternal medical conditions.

Results: We identified 1,646,864 pregnancies, of which 8227 (0.50%) resulted in stillbirths. 16,286 (0.99%) pregnant individuals were diagnosed with medically attended influenza illness during pregnancy. There was a significant association between influenza illness during pregnancy and stillbirth when the seasonal epidemics and the 2009/2010 H1N1 pandemic were pooled for analysis (adjusted HR [95% CI]: 1.30 [1.03,1.62]). When analyzed separately, there was a significant association during seasonal epidemics with the highest hazard when medically attended influenza was diagnosed in the second trimester (adjusted HR [95% CI]: 1.52 [1.09,2.22]) but no association was observed for pandemic influenza. The risk of stillbirth was highest during the two weeks after medically attended influenza infection, with an adjusted HR

of 3.70 [95% CI 2.19, 6.25], 2.69 [95% CI 1.73, 4.17] during the four weeks following infection, and 1.96 [95% CI 1.29, 2.97] during the six weeks following infection. In the high-risk population with pre-existing conditions, there was a higher risk of medically attended influenza illness during pregnancy and stillbirth, but the association was not statistically significant (adjusted HR [95% CI]: 1.48 [0.96,2.67]).

Conclusion: The findings of our study demonstrate that there is a significant association between medically attended influenza illness during pregnancy and the risk of stillbirth, especially during seasonal epidemics. Importantly, it highlights the need to strengthen vaccination efforts to protect pregnant individuals from obstetrical complications and adverse perinatal outcomes associated with influenza illness.

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LIST OF ABBREVIATIONS

aHR	Adjusted hazard ratio
ARI	Acute respiratory infection
CAN-Marg	Canadian Marginalization Index
CCI	Canadian Classification of Health Interventions
CI	Confidence interval
CIHI	Canadian Institute for Health Information
DAD	Discharge Abstract Database
DIN	Drugs Information Number Database
EPM	Evaluation, Planning or Management
FFS	Fee-for-service
HA	Hemagglutinin
HR	Hazard ratio
ICD	International Classification of Diseases
ICES	Institute for Clinical Evaluative Sciences
ICPC	International Classification of Primary Care
IKN	ICES key number
IPDB	ICES Physician Database
LCI	Laboratory-confirmed influenza
LMP	Last menstrual period
MA	Medically attended
MOMBABY	ICES-Derived Linked Delivering Mother and Newborns Database

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NA	Neuraminidase
NACI	Canada's National Advisory Committee on Immunization
NACRS	National Ambulatory Care Reporting System
OHIP	Ontario Health Insurance Plan Claims Database
OMHRS	Ontario Mental Health Reporting System
ONMARG	Ontario Marginalization Index
PCCF	Postal Code Conversion File
PHAC	Public Health Agency of Canada
PHIPA	Personal Health Information Protection Act
RAE	Research Analytic Environment
REB	Research Ethics Board
RPDB	Registered Persons Database
SDS	Same Day Surgery Database
SGA	Small for gestational age

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PREFACE

Nichole Dai was responsible for collecting all the approvals to conduct this research. Under the joint supervision of Dr. Mark Walker, Dr. Steven Hawken, and thesis committee member Dr. Deshayne Fell, Nichole Dai designed the study, performed the data analysis, interpreted the study findings, disseminated the results, and drafted the final thesis paper. The study cohort was cut by Asnake Yohannes Dumicho at ICES. All supervisors and thesis committee members provided feedback on the final paper.

CHAPTER 1. INTRODUCTION

1.1 Background

Influenza is a contagious viral infection that affects the human respiratory tract. From several global pandemics over the past century—including the 1918 influenza pandemic and the H1N1 influenza pandemic in 2009—research has shown that influenza infection during pregnancy has been associated with severe maternal illness and several adverse perinatal outcomes, such as stillbirth.^{1,2} The pathophysiologic mechanism of how influenza illness impacts pregnant people and their fetuses, however, remains unclear. Due to these increased risks, Canada’s National Advisory Committee on Immunization (NACI) has continued to recommend that all pregnant people receive the inactivated influenza vaccine during each pregnancy; however, coverage remains sub-optimal.^{3,4} A survey conducted by the Public Health Agency of Canada (PHAC) concluded that less than half (45%) of mothers were vaccinated against influenza while they were pregnant during recent influenza seasons.⁴

Currently, few comparative observational studies have assessed the association between influenza during pregnancy and stillbirth.^{1,2,5–7} Despite this collection of literature, the results remain inconclusive and there are few of high quality. There are also very few population-based studies within the Canadian context.

1.2 Research objectives

The objective of this master’s thesis was to assess the risk of stillbirth in pregnant individuals who experienced medically attended influenza illness during pregnancy compared to those who did not.

1.3 Thesis Organization

This thesis is presented in a monograph format and is organized into Chapters 1-6. Chapter 1 presents the overview of the topic and the research objectives. Chapter 2 is a review of the literature that currently exists on influenza illness, including its clinical features and epidemiology, both in the global and Canadian context. The effects of influenza illness during pregnancy are further explored, including obstetrical complications and the risk of adverse perinatal outcomes. Chapter 3 discusses the study's methodology, including the study population, data sources, exposure and outcome measurement, and statistical analysis. Chapter 4 summarizes the findings of the study, including the final study sample and the results of the research objective. Chapter 5 interprets the study findings and compares them to the current literature. The strengths and weaknesses of our study, and the clinical and research implications, are also discussed. Finally, Chapter 6 concludes the thesis and provides a summary of the study findings.

CHAPTER 2. LITERATURE REVIEW

2.1 Influenza illness

2.1.1 Transmission and clinical features

Influenza illness, commonly known as ‘the flu’, is a highly contagious viral infection of the human respiratory tract caused by the negative-strand RNA virus of the Orthomyxoviridae family.⁸ There are four main types of influenza viruses: influenza types A and B are primarily responsible for seasonal influenza illnesses in humans, influenza type C causes more minor infections in humans only and is usually not responsible for seasonal epidemics, and influenza D mainly affects cattle with some spillover into humans.^{8,9} The virus spreads indirectly through the droplets of infected individuals when they cough, sneeze, or talk.¹⁰ It can also be spread directly through contact with contaminated surfaces, such as tables or doorknobs, and then by touching the eyes, mouth, or nose.¹⁰ After the virus is transmitted into the respiratory tract, it penetrates the epithelial cells of the human trachea and bronchi, where the host cell is destroyed as viral replication occurs.⁸ After the incubation period, there can be a sudden onset of symptoms such as sore throat, fever, cough, body aches and fatigue; most symptoms typically manifest 1-4 days after infection and last up to a week.⁸ While most symptoms are relatively mild, severe complications, including secondary bacterial pneumonia (e.g., *Haemophilus influenzae* or *Streptococcus pneumoniae*) and death, can occur.⁸ Diagnosis is often made clinically; however, laboratory confirmation is required for a definitive diagnosis.⁸ Most people recover quickly from influenza illness on their own with no treatment necessary, but more severe symptoms may require medical attention and antiviral medication.⁸

2.1.2 Genetic changes

The influenza virus is highly susceptible to antigenic changes. It is made up of eight independent RNA strands, and hemagglutinin (HA) and neuraminidase (NA) proteins on the surface of the viral particle.^{11,12} The HA and NA proteins continuously undergo genetic changes—small changes point mutations in the genetic component of the HA or NA surface proteins can be characterized as antigenic drift.¹¹ While these small mutations, which occur frequently, are recognized by the human immune system and can trigger an immune response resulting in production of anti-influenza antibodies,¹¹ most people have little to no immunity against a novel virus resulting from a genetic reassortment.¹¹ When antigenic drift occurs and the genetic component of the HA or NA surface protein changes, pre-existing antibodies from prior influenza exposure may no longer recognize and bind to the new antigens; therefore, providing no immunity against viral replication and illness.¹¹ This is primarily the reason why an individual can get the illness more than once and why the vaccine composition needs to be updated every influenza season.⁸

Antigenic shift is another method by which the HA and NA proteins undergo genetic changes. This is when there is a significant change in one or both of the HA or NA proteins, potentially resulting in an entirely new subtype of influenza capable of infecting humans (e.g., the influenza A virus that caused the H1N1 pandemic in 1918).^{11,12}

2.2 Influenza epidemiology

2.2.1 Seasonal influenza illness

Most influenza illness occurs seasonally; in Northern Hemisphere settings, an influenza epidemic typically occurs annually in the fall to early spring seasons.^{8,13} Globally, there are an estimated

billion cases of influenza illness every year, and 3-5 million of those are severe illness.¹⁴ Seasonal influenza is also estimated to cause 290,000-650,000 respiratory deaths annually.¹⁴ Influenza A and influenza B are primarily responsible for seasonal influenza illness.¹⁵ Although everyone is susceptible to influenza illness, certain populations are at higher risk of serious illness and complications. This includes children under the age of 5 years, older adults over the age of 65 years, immunocompromised individuals with chronic medical conditions (e.g., heart disease or diabetes), and pregnant people.¹⁴ A 2017 systematic review concluded that the pooled symptomatic attack rate—the proportion of previously disease-free individuals who develop symptomatic illness—for all influenza in unvaccinated populations is 4.4% (95% CI 3.0%, 6.3%) in adults, 12.7% (95% CI 8.5%, 18.6%) in children, and 7.2% (95% CI 3.9%, 28.2%) in older adults, indicating that children are approximately three times more likely, and older adults about twice as likely, as adults to develop symptomatic influenza infection.¹⁶

2.2.2 Pandemic influenza illness

A pandemic can occur when a novel influenza virus emerges (through antigenic shift), to which few people have pre-existing immunity, and rapidly spreads efficiently between humans worldwide. There have been several documented pandemics involving influenza A and its subtypes. The 1918 influenza A/H1N1 pandemic, also known as the “Spanish Flu”, resulted in more than 50 million deaths, with an estimated mortality rate of more than 2.5% compared to the estimated 0.1% in typical influenza epidemics.¹⁷ In the 1918 pandemic, the most impacted age group was adults between 20-40 years of age, accounting for half of all deaths. As there were no vaccines or antiviral drugs available at that time, wearing gauze masks and implementing physical distancing measures were the only methods available to help stop the spread of the

disease.¹⁸ An influenza A/H2N2 (Asian Flu) global pandemic occurred in 1957 with approximately one million deaths.¹⁸ In 2009, another strain of influenza A caused another global pandemic, known as the “Swine Flu”. This pandemic resulted in the death of over 12,500 people worldwide, including 428 deaths in Canada.^{19,20} Children and young adults were mostly affected by this pandemic, suggesting that the older population had some immunity from exposure to related influenza A strains in previous pandemics/epidemics.¹⁹ The pregnant population has been disproportionately affected by pandemic influenza illness. During the 2009 A/H1N1 pandemic, pregnant people represented 5% of all deaths despite representing less than 1% of the population.^{21,22} Additionally, the mortality rate in pregnant people was high in the 1918 and 1957 influenza pandemics.^{21,23} In 1918, 27% of 1350 reported cases of influenza among pregnant people with pandemic influenza illness died.²⁴ In the 1957 pandemic, 20% of pregnancy-related deaths were associated with influenza.²⁴

2.3 Prevention

Vaccination is the most effective strategy to prevent influenza-associated illness.⁸ Because of the regular antigenic changes of the virus, the influenza vaccine is updated each year to try to match the vaccine to the predicted strain that will be circulating.⁸ There are several different forms of influenza vaccine depending on the type of vaccine platform and the formulation. The various types of vaccine platforms are inactivated, recombinant, and live attenuated, and the different types of formulation for influenza vaccine are trivalent and quadrivalent.²⁵

2.3.1 Prevention in pregnancy

As the pregnant population is a group known to be at higher risk of severe complications from influenza illness, vaccination is strongly recommended; and the efficacy/effectiveness in protecting pregnant individuals against laboratory-confirmed influenza (LCI) has been demonstrated in clinical trials (pooled risk ratio (RR) 0.5, 95% CI 0.3-0.7) and case-control studies (pooled odds ratio (OR) 0.4, 95% CI 0.2-0.6).²⁶ In a pooled analysis of three randomized controlled trials with 10,002 women and 9800 liveborn infants, the pooled efficacy of maternal vaccination to prevent infant PCR-confirmed influenza up to six months of age was 35% (95% CI 19-47).²⁷ The vaccine efficacy against PCR-confirmed influenza was 50% (95% CI 32-63) in mothers from enrollment during pregnancy to the end of follow-up at six months postpartum.²⁷ Vaccination during pregnancy can reduce influenza complications among pregnant people and newborn children.²⁸ There have been no significant harmful effects of trivalent or quadrivalent seasonal influenza vaccination during pregnancy on birth outcomes.²⁸

2.4 Influenza illness in pregnancy

The pregnant population is at an increased risk of developing severe complications from the influenza infection. This is thought to be due to physiological changes in the cardiac, respiratory, and immune systems during pregnancy.²¹ From the 1918 influenza pandemic and the H1N1 influenza pandemic in 2009, extensive research has shown that influenza infection during pregnancy has been associated with severe maternal illness and several adverse perinatal outcomes, including stillbirth and preterm birth.^{2,29} A 13-year population-based cohort study published in 2007 found that 25.2% of pregnant women visited their family physician due to a respiratory illness in the influenza season and 0.4% were hospitalized due to the same reason.³⁰ A

systematic review done in 2013 showed that although pregnancy did not increase the risk of death for pandemic influenza, pregnant people were at higher risk for hospital admission, and individuals in the third trimester had an increase in all-cause mortality (1.22, 1.01-1.48, $I^2=0\%$, $n=5$) when compared to individuals in the first or second trimester.³¹ There has been minimal research investigating the risk of adverse pregnancy and perinatal outcomes for seasonal influenza compared with pandemic influenza.³¹ Studies have found that maternal influenza illness during the 2009 H1N1 pandemic was associated with an increase in perinatal mortality, including miscarriage and stillbirths.^{32,33} The pathophysiologic mechanism of the influenza illness and how it affects mothers and their fetuses; however, remains unclear.³⁴ Clinically, the symptoms of influenza infection in pregnant individuals are similar to those who are not pregnant, with pneumonia as a major complication in cases of severe illness.³⁵ Due to these increased risks that influenza illness poses on pregnant people, Canada's National Advisory Committee on Immunization (NACI) currently recommends all pregnant people receive inactivated influenza vaccine during each pregnancy,³ but coverage remains sub-optimal.⁴ A study done by the Public Health Agency of Canada (PHAC) concluded that less than half (45%) of mothers were vaccinated against influenza while they were pregnant during the influenza season.⁴

Few observational studies have assessed the association between influenza during pregnancy and stillbirth. A systematic review published in 2017 concluded that there are limited studies that have studied the adverse birth outcomes following maternal influenza disease.² The low quality of evidence, inconsistency of results, and influenza potentially ascertained differently resulted in difficulty in drawing conclusions.² However, several studies have suggested that preterm birth is associated with severe 2009 H1N1 influenza but no evidence for seasonal or moderate 2009

H1N1 influenza.² Due to the insufficient mortality events in most studies studying fetal death outcomes, overall conclusions were difficult to draw with regard to stillbirth.² In 2017, another systematic review investigating influenza A virus infection during pregnancy and the association with adverse pregnancy outcomes concluded there were no significant associations between influenza A virus infection and preterm birth.⁵ However, infection with influenza A virus was linked to a nearly 2.4-fold increase in stillbirths compared to pregnant individuals without influenza-virus infections (P=0.04, RR=2.36, 95% CI: 1.05-5.31).⁵ However, there was evidence that it was associated with pre-existing maternal conditions such as asthma, hypertension, and diabetes.³⁶ In 2020, a Norwegian study using individual-level data from population-based, national registries concluded that H1N1 pandemic influenza in the first trimester was associated with an increase in the risk of fetal death in pregnancy with an adjusted hazard ratio of 2.28 (95% CI 1.45-3.59).²⁹ Seasonal influenza illness during pregnancy, however, did not increase the risk of fetal death.²⁹ In 2022, a 16-year retrospective, population-based cohort study from New Zealand concluded that pregnant women who were hospitalized for acute respiratory illness (ARI) during influenza season were at greater risk of preterm birth (adjusted HR [95% CI]: 1.50 [1.39, 1.61]) and low birthweight (adjusted HR [95% CI]: 1.64 [1.51, 1.79]) than pregnancies without hospitalizations.⁶ In contrast, there were no significant associations between maternal hospitalizations and fetal death (adjusted HR [95% CI]: 0.96 [0.69, 1.34]).⁶ Interestingly, several studies have reported large reductions in the risk of stillbirth and preterm birth following influenza vaccination in pregnancy,^{37,38} suggesting the possibility that vaccination may have reduced influenza-associated occurrences of these adverse outcomes. While most studies conclude that there is a higher risk of adverse outcomes associated with pandemic influenza illness during pregnancy, one study concluded that the clinical burden of the H1N1 infection

during pregnancy is low, indicating some inconsistency within the literature.⁷ It is important to further evaluate and quantify the potential impact of influenza during pregnancy, to better inform patients, care providers, and public health.

Table 2-1. Studies assessing the occurrence of stillbirth and preterm birth following maternal influenza illness during pregnancy.

Reference	Location	Study design	Study population and size	Birth outcomes	Results
Fell et al. (2017)	Canada	Systematic review and meta-analysis	21 comparative studies	Preterm birth, SGA birth, fetal death	Severe pandemic influenza illness was associated with preterm birth. Inconclusive overall results were drawn for stillbirth.
He et al. (2017)	China	Systematic review and meta-analysis	8 retrospective cohort studies, 2 case-control studies	Stillbirth, low birth weight	No association between maternal influenza A virus infection and preterm birth. There was an association between influenza A virus infection during pregnancy and stillbirth.
Gunnes et al. (2020)	Norway	Registry-based cohort study	8341 maternal seasonal influenza during pregnancy, 3581 maternal pandemic	Fetal death	No association between maternal seasonal influenza during pregnancy and

			influenza during pregnancy (n=414,896)		fetal death. The risk of fetal death was higher following maternal pandemic influenza during pregnancy.
Duque et al. (2022)	New Zealand	Retrospective population-based cohort study	5095 maternal acute respiratory illness hospitalization during influenza season (n=822,391)	Fetal death, preterm birth, low birth weight	Maternal hospitalizations during influenza season were associated with increased risk of preterm birth. No association between hospitalizations and fetal death.
Gérardin et al. (2010)	France	Prospective register-based cohort study	139 pregnant women with pandemic influenza, 131 pregnant women with non-pandemic influenza-like illness, 440 uninfected pregnant women, 108 nonpregnant women with indistinct influenza-like illness (n=818)	Stillbirth, preterm birth	No significant associations between pandemic influenza and stillbirth and preterm birth.

*SGA birth = small-for-gestational-age birth

2.5 Stillbirth

Stillbirth is defined as fetal loss after 20 weeks of gestational age, with a rate of 0.4-0.6% in Ontario in 2021.³⁹ In 2022, 8.9 per 1000 total newborns were stillborn in Canada, and around 13.9 stillbirths per 1000 total births worldwide.^{40,41} Despite the high frequency, the cause of stillbirth is often unknown or is a combination of multiple causes.⁴² Before 24 weeks of pregnancy, the most common possible cause of stillbirth is pregnancy and labour complications such as multiple pregnancy (twins, triplets), preterm labour, and/or separation of the placenta from the uterus.⁴² The leading cause of stillbirth after 24 weeks of pregnancy is due to problems with the placenta, such as insufficient blood flow.⁴² Other causes can include fetal genetic problems and birth defects, including neural tube defects, anencephaly, high blood pressure disorders, and medical conditions such as diabetes.⁴² Maternal infectious diseases are also associated with stillbirth.⁴³ A review of the literature in the last 10 years investigating the association of maternal infection and stillbirth in low-resource settings found that there was a 2-fold risk of stillbirth when infected with malaria and syphilis.⁴³ The economic and psychosocial consequences of stillbirth are also understudied. Economically, the burden of stillbirth is substantial.⁴⁴ One systematic review investigating the economic burden of stillbirth in high-income countries concluded that the cost of every stillbirth can range from \$6934 to \$9220.⁴⁴ Economic costs include direct and indirect medical costs during the antepartum, intrapartum, and postpartum periods, and hospital resource utilization. The psychosocial implications on parents and healthcare providers are extensive, resulting from the adverse effects of grief, anxiety, fear, and guilt.⁴⁵ Stillbirth remains an understudied adverse perinatal outcome due to its low incidence, inconsistent definitions and classification systems and its history of it to receive less focus compared to other adverse perinatal outcomes, such as preterm birth or low birth weight.

2.6 Rationale for this thesis

The majority of existing research has evaluated adverse perinatal outcomes following influenza infection during pregnancy during the 2009 A/H1N1 pandemic time period. However, there is limited evidence on the risk of stillbirth following influenza illness during pregnancy, particularly seasonal influenza illness. This master's study aims to generate new evidence on the risk of stillbirth following medically attended influenza during pregnancy, investigating both the 2009 A/H1N1 pandemic as well as seasonal epidemic periods.

CHAPTER 3. METHODOLOGY

3.1 Study design

This project was a population-based retrospective cohort study. A cohort of all births at 20 weeks of gestation or greater, and weighing 500 grams or more, between April 1, 2006, and March 31, 2020, in Ontario, Canada, was created using several individually linked data sources housed at ICES (formerly known as the Institute for Clinical Evaluative Sciences).

3.2 Study population and size

The study cohort was created using the maternal-fetal delivery records in the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) and MOMBABY, a database of linked maternal-newborn records derived from the CIHI-DAD. We excluded individuals who had multiple births, such as twins and higher order births. We also excluded non-Ontario residents and individuals who did not have continuous OHIP eligibility to ensure we had complete exposure and outcome information. Further, individuals with missing gestational weeks at delivery, and individuals who were under 12 years old or greater than 50 years old at the delivery date were excluded. Pregnancies with gestational weeks at delivery under 20 weeks and invalid infant sex were also excluded. Furthermore, pregnancies with conception before November 11, 2005, and pregnancies with conception after June 11, 2019, were excluded to ensure that all pregnancies with a minimum of 20 gestational weeks were captured in the study cohort.⁴⁶

Individuals with a healthcare encounter for influenza illness in the same influenza season, but before pregnancy, were excluded. Individuals who were not continuously eligible to receive Ontario healthcare during the year preceding pregnancy and throughout pregnancy were also excluded. Lastly, maternal and infant records with any covariate missing were excluded.

The final study size was reached after all administrative and eligibility criteria exclusions were applied.

3.3 Data sources

The ICES Data Repository contains records of publicly funded administrative health services provided for the Ontario population eligible for universal health coverage.⁴⁷ The repository has records for 13 million people so far since 1986.⁴⁷ The datasets are record-level, coded and linkable to other health datasets.⁴⁷ **Appendix A** contains the complete list of variables and their associated data source.

3.3.1 Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD)

The CIHI-DAD contains information related to acute-care hospitalizations in Ontario, including sociodemographic data, diagnoses, procedures, treatments, transfers, and deaths.⁴⁸ Clinical information related to the hospitalizations is documented using standard diagnostic ICD-10-CA codes (the Canadian modification of ICD-10), procedural or interventional CCI codes (Canadian Classification of Health Interventions).⁴⁹ For this study, we utilized this database to create cohorts by providing maternal delivery records between April 1, 2006, and March 31, 2020. ICES maintains and updates this database quarterly.⁵⁰ We also used CIHI-DAD to extract the ICD-10 codes needed to define the exposure (**Table 2-1**).

3.3.2 Drugs Information Number Database (DIN)

The Drugs Information Number database (DIN) contains information on drugs administered in Ontario for controlled substances and for individuals who are registered under OHIP. ICES updates the DIN database quarterly.⁵⁰ We used this database for covariate selection, specifically diabetes in pre-existing maternal medical conditions.

3.3.3 ICES Physician Database (IPDB)

ICES designs the ICES Physician Database (IPDB), which contains information about practicing physicians in Ontario, such as demographic information about each physician, practice location, physician specialty, and services provided. ICES maintains and updates the IPDB every year.⁵⁰ We used this database for covariate selection, specifically heart disease in pre-existing maternal conditions (list of variables in **Appendix A**).

3.3.4 ICES-Derived Linked Delivering Mother and Newborns Database (MOMBABY)

The MOMBABY database contains characteristics of maternal and newborn hospital inpatient admission records from CIHI-DAD, including information on gestational age, maternal age, pre-existing maternal medical conditions, obstetrical complications, birth weight, and the baby's sex.⁵¹ MOMBABY links together mother and offspring by maternal and infant IKN, facilitating analysis of mother and infants.⁵¹ ICES maintains and updates the database annually.⁵⁰ For this study, the MOMBABY database was used for cohort creation and covariate selection (list of variables in **Appendix A**).

3.3.5 Canadian Institute for Health Information National Ambulatory Care Reporting System (CIHI-NACRS)

The Canadian Institute for Health Information National Ambulatory Care Reporting System (CIHI-NACRS) contains information related to hospital-based and community-based ambulatory care in Ontario, such as day surgeries, outpatient and community-based clinics, and emergency departments.⁵² CIHI-NACRS also collects demographic, administrative, clinical and service-specific data for emergency departments.⁵² Similar to CIHI-DAD, ICES maintains and updates CIHI-NACRS every calendar quarter.⁵⁰ We used this database to extract ICD-10 codes for the influenza illness exposure definition (**Table 2-1**).

3.3.6 Ontario Health Insurance Plan Claims Database (OHIP)

The Ontario Health Insurance Plan Claims Database (OHIP) contains claims for reimbursement by Ontario physicians for inpatient and outpatient services, paid for by the Ontario Health Insurance Plan. This database captures claims submitted to OHIP by all eligible health care providers, including physicians, practice groups, laboratories, and providers located outside of Ontario. Health care providers are to submit fee-for-service (FFS) billings and shadow billings for their non-FFS services to OHIP. When a vaccine is administered to a patient, a specific fee code is used, which helps define our exposure. All records in the database have an identifier that allows linkage to other ICES-held datasets. ICES maintains and updates this database every month.⁵⁰ We used the OHIP database to extract ICD-9 codes for the influenza illness exposure definition (**Table 2-1**) as well as the 2009-2010 H1N1 pandemic vaccination data.

3.3.7 Canadian Institute for Health Information Ontario Mental Health Reporting System (CIHI-OMHRS)

The Canadian Institute for Health Information Ontario Mental Health Reporting System Metadata (CIHI-OMHRS) contains admissions to hospital beds designated for mental health care. It records the most responsible diagnosis for each admission. ICES maintains and updates this database every three months.⁵⁰ We used the CIHI-OMHRS for covariate selection, specifically heart disease in pre-existing maternal medical conditions (list of variables in **Appendix A**).

3.3.8 Ontario Marginalization Index (ONMARG)

The Ontario Marginalization Index (ONMARG), derived from the Canadian Marginalization Index (CAN-Marg), is a tool to understand the inequities in health and social determinants of health in specific populations or geographic areas across Ontario.⁵⁴ This is based on postal code and Census area information. Four dimensions of combined census data are used in this index:

material resources, households and dwellings, age and labour force, and racialized and newcomer populations.⁵⁴ Material resources encompass indicators that measure access to and attainment of basic material needs, including housing, food, clothing, and education, as well as unemployment rates and percentages of individuals without a high school degree.⁵⁴ The households and dwellings dimension includes indicators that measure the types and density of residential accommodations, such as the percentage living alone and the percentage of dwellings not owned.⁵⁴ The age and labour force dimension refers to the impacts of disability and dependence, including indicators such as the percentage of seniors and the percentage not participating in the labour force.⁵⁴ Finally, the racialized and newcomer populations dimension identifies the proportion of newcomers and/or non-white, non-Indigenous populations and relates to the impact of racialization.⁵⁴ This dimension includes indicators such as the percentage of recent immigrants (those who have been in the country for the last 5 years).⁵⁴ Factor scores relating to each of the four dimensions are divided into quintiles, where quintile one is the area that is least marginalized and quintile five is the most marginalized area.⁵⁴

3.3.9 Postal Code Conversion File (PCCF)

Statistics Canada's Postal Code Conversion File (PCCF) contains information on postal codes and links them to standard geographic areas such as dissemination areas, census tracts, and census subdivisions.⁵⁵ ICES designed a derived macro to link the PCCF to other geographic identifiers, such as census-based neighbourhood income quintiles and rurality. ICES updates the macro every five years and is updated according to the collected census data.⁵⁰ We used the PCCF database to obtain covariate information such as neighbourhood income quintile and rural residence.

3.3.10 ICES Registered Persons Database (RPDB)

The Registered Persons Database (RPDB) contains basic demographic information on all Ontario residents eligible for publicly funded health care in the province (i.e., registered under the Ontario Health Insurance Plan), such as date of birth, sex, postal code and death date (if applicable).⁵⁶ The Ontario Ministry of Health directly supplies the data for this database, and ICES updates the database monthly.⁵⁰ We used the RPDB for cohort creation (list of variables in **Appendix A**).

3.3.11 Same Day Surgery Database (SDS)

The Same Day Surgery (SDS) database contains records of ambulatory care visits associated with inpatient surgical procedures or emergency department services. ICES maintains and updates the database every year.⁵⁰ We used the SDS database for covariate selection, specifically the pre-existing maternal medical conditions (list of variables in **Appendix A**).

3.4 Data linkage, data access, and privacy

Data linkage is an essential tool, as it enables the combination of information from individuals across multiple administrative databases. ICES is a designated entity that is authorized to conduct analyses on the management and effectiveness of health systems.⁵⁷ ICES implements numerous policies to ensure that personal information is kept private and confidential under the privacy law, Ontario's Personal Health Information Protection Act (PHIPA).⁵⁷ Each database must be requested with justification based on the project's specific needs. A unique encrypted ICES key number (IKN) is assigned to each patient, which allows ICES researchers to individually link patients across ICES data holdings via the IKN identifier.

Furthermore, calendar dates were preprocessed by the ICES analyst, and we had no access to information about calendar dates, such as the date of delivery or the first day of the last

menstrual period (LMP). Instead, the ICES analyst had access to all the calendar dates and calculated gestational age “day zero” using the baby’s date of birth and gestational age at birth. Every health care encounter during pregnancy, such as an influenza exposure diagnosis, was assigned a number corresponding to the gestational age after day zero.

According to section 45 of PHIPA, this project did not require Research Ethics Board (REB) approval as it was for Evaluation, Planning or Management (EPM) of all or part of the health system and/or health services.⁵⁷

3.5 Missing data

We excluded maternal-newborn records if there was missing information on gestational age, as that information was essential for the outcome definition. Maternal records with missing covariates regarding prenatal care adequacy, marginalization indices, neighbourhood median family income, rural residence, Ontario health regions, and mode of delivery were excluded.

Missing data were not imputed as the cumulative missingness across all covariates was ~3%. A complete case analysis was conducted as imputation would have had a minimal impact.

3.6 Exposure measurement

Medically attended influenza illness during pregnancy was ascertained from the International Classification of Diseases (ICD) diagnostic codes for influenza assigned during hospitalizations (CIHI-DAD), emergency department visits (CIHI-NACRS), and out-patient (OHIP) healthcare encounters during pregnancy and during the defined influenza seasons (determined from provincial surveillance). This was a proxy for medically attended influenza illness. If an outpatient healthcare visit has an ICD code for influenza, and an OHIP fee code indicating immunization (G590, G591, Q130, Q590, Q690, Q691) in the same visit, the visit was not considered indicative of an influenza illness.³⁶ Pregnant individuals without these codes during

pregnancy were considered to have no medically attended influenza illness. An individual was only considered medically attended influenza-exposed if their influenza diagnosis during pregnancy occurred within an influenza season. The ICD codes that were used to identify healthcare encounters for influenza are shown in **Table 3-1** and **Table 3-2** below.

Table 3-1. ICD influenza codes for the CIHI-DAD and CIHI-NACRS databases

ICD-10-CA Code	Definition ⁵⁸
J09	Influenza due to identified zoonotic or pandemic influenza virus
J10	Influenza due to identified seasonal influenza virus
J11	Influenza, virus not identified

Table 3-2. ICD influenza codes for the OHIP database

Modified ICD-9 Code	Definition ⁵⁹
487	Influenza

Seasonal influenza seasons were defined as November 1 to March 31 of every year except for the pandemic season. Between May 17, 2009, and February 6, 2010, any medically attended influenza illness diagnosis was considered pandemic H1N1 influenza illness.³⁶

Three additional variables characterizing the influenza season were derived for all pregnancies for potential use in sensitivity analyses, stratified analyses, and adjustment for temporal confounding. The first variable indicated which pregnancy overlapped with the influenza season; this variable indicated whether any part of an influenza season occurred during the interval between the LMP and the date of delivery for each pregnancy. The second variable indicated

which influenza seasons the pregnancy overlapped, whether it was a seasonal or a pandemic influenza season. The third variable indicated the quarter of the year in which the pregnancy started to account for seasonality (i.e., January-March, April-June, July-September, October-December).

3.7 Outcome measurement

Stillbirth was defined as fetal loss after 20 completed weeks of gestation and was identified using database-specific codes in the maternal delivery record of the MOMBABY, derived from ICD-10 codes.

Table 3-3. ICD-10 stillbirth codes

ICD-10-CA Code	Definition ⁵⁸
Z37.1	Single stillbirth
Z37.3	Twins, one liveborn and one stillborn
Z37.4	Twins, both stillborn
Z37.6	Other multiple births, some liveborn
Z37.7	Other multiple births, all stillborn
O36.4	Maternal care for intrauterine death Excl.: missed abortion

3.8 Covariates

A number of covariates were available from the various databases and were considered as potential confounding variables for adjustment in the analyses. These included:

sociodemographic characteristics (i.e., maternal age at delivery, neighbourhood income, Ontario Marginalization Indices, rural residence, Public Health Unit region), pre-existing chronic medical

conditions (diabetes, heart disease, asthma, chronic hypertension), pregnancy characteristics (i.e., parity, delivery mode), obstetrical complications (pregnancy-induced hypertension, preeclampsia, eclampsia, gestational diabetes, placental previa, placental abruption), markers of access to health care (i.e., prenatal care adequacy). Seasonal and pandemic influenza vaccination information was obtained from physician billings (OHIP). **Appendix B** and **Appendix C** contain the full list of diagnostic and procedural codes, and prenatal visit associated OHIP fee codes, respectively.

3.9 Statistical analysis

3.9.1 Descriptive analysis

A descriptive analysis for the baseline characteristics of the study population (overall and stratified by medically attended influenza illness exposure status) was conducted using frequencies for categorical variables.

3.9.2 Cox proportional hazards regression model

We used survival analysis, an analytical approach in which the outcome variable of interest is the time to an event occurring (time-to-event outcomes).⁶⁰ The event (d) was stillbirth and the time (T), also known as survival time, was measured in gestational days and represented the period from the beginning of follow-up (pregnancy onset [i.e., estimated last menstrual period]) until either the event occurred or end of follow-up (end of the pregnancy). For this project, the follow-up time started at pregnancy onset (i.e., estimated last menstrual period) until either a stillbirth occurred, or end of follow-up was reached at the end of the pregnancy. A key component of survival analysis is censoring, where the exact survival time is not known. Censoring can happen when the individual does not experience the event before the study ends, an individual is lost to follow-up during the study period, or an individual withdraws from the study. For our research,

censoring occurred when there was a live birth or when it was the first day of the 43rd week of gestational age. These situations are where the individuals are no longer at risk for the outcome.

In survival analysis, the risk set $R(t_{(f)})$ is a collection of individuals who have survived at least to time $t_{(f)}$. This means that everyone in the $R(t_{(f)})$ has a survival time that is $t_{(f)}$ or longer, regardless of whether the person has failed or is censored.

The survivor function, $S(t)$, is the probability that an individual survives longer than a specific time (t) ; $S(t) = P(T > t)$. Related to the survivor function, the hazard function, $h(t)$, is the instantaneous potential per unit time for the event to occur, given that the individual has survived up to time t ; $h(t) = \lim_{\Delta t \rightarrow 0} \frac{P(t \leq T < t + \Delta t | T \geq t)}{\Delta t}$.

The Cox proportional hazards model, first introduced by Dr. Cox in 1972, is a semi-parametric model used to analyze time-to-event outcomes.⁶¹ Generally, the proportional hazards model can be defined as $h(t|X_i) = h_0(t) \cdot \exp(\beta_1 X_{i1} + \beta_2 X_{i2} + \dots + \beta_p X_{ip})$, where X_1, X_2, \dots, X_p are the predictor variables. The Cox model is semi-parametric as it has a non-parametric component, which is the baseline hazard; $h_0(t)$, and a parametric component which is the log-linear function of covariates; $\exp(\beta_1 X_{i1} + \beta_2 X_{i2} + \dots + \beta_p X_{ip})$. This allows multiple predictors to be included in the model to estimate their relationship with the hazard function, $h(t)$, without specifying the baseline hazard. The baseline hazard is a function of time while the predictors are independent of time.

The hazard ratio (HR) compares the hazard rates in two groups over time. Formally, the formula is $HR = \frac{h(t|X=x_2)}{h(t|X=x_1)} = \frac{h_0(t) \exp(\beta_1 x_2)}{h_0(t) \exp(\beta_1 x_1)}$ which simplifies to $HR = \exp(\beta(x_2 - x_1))$. This sets the two values to be a unit difference, and we interpret the hazard ratio relative to a unit change in X. If

the variable is binary, the hazard ratio would just be $HR = \exp(\beta)$. The two groups we were comparing in this study were the individuals who were exposed to medically attended influenza illness during pregnancy and those who were not exposed.

We used an extended Cox proportional hazards model to estimate the unadjusted and adjusted hazard ratios (aHR) for stillbirth, along with 95% confidence intervals, comparing individuals with and without medically attended influenza illness during pregnancy. Medically attended influenza was treated as a time-varying exposure throughout the pregnancy, beginning from estimated LMP. Individuals initially contributed unexposed follow-up time; for those who experienced influenza during pregnancy, their exposure status changed to exposed on the healthcare visit date associated with an influenza ICD code, as previously described. The extended Cox model allowed us to account for the time-varying exposure. Gestational age in days was used as the underlying time axis. We additionally accounted for calendar time (i.e., influenza season) through the introduction of a covariate in the model. The proportional hazards assumptions were assessed using Schoenfeld residuals and modelling time interactions to ensure that there were no violations.

Seasonal influenza exposure and pandemic influenza exposure were pooled together for the main analysis. Additionally, separate analyses for seasonal and pandemic influenza exposure were conducted as well. The trimester-specific adjusted and unadjusted HRs were estimated for seasonal influenza exposure only.

As a subgroup analysis, in addition to the time-varying exposure definition above, we also considered an alternate exposure window classification in which individuals with medically attended influenza illness in pregnancy were only considered exposed during a risk window after

the date of diagnosis (e.g., 2-week risk window; 4-week risk window; 6-week risk window), after which, exposure status reverted to unexposed for the remainder of the follow-up period.

Finally, we conducted another subgroup analysis of women with pre-existing chronic medical conditions (diabetes, heart disease, asthma, and chronic hypertension). A previous study has shown that pre-existing medical conditions can increase the risk of influenza illness and complications.³⁰

We conducted the analysis using the in-line programming method.

All statistical analyses were conducted using SAS version 9.4 in the secure Research Analytic Environment (RAE) at ICES.

3.9.3 Multivariable adjustment

Multivariable adjustment was used to adjust for potential confounders in the model. Covariates were determined a priori based on substantive knowledge of the literature, as well as ensuring that all covariates met the disjunctive cause criteria recommending that the analysis control for any pre-exposure covariate that is a cause of the exposure, or of the outcome, or both.⁶² Pre-existing literature was also used to help determine the covariates that were chosen to be adjusted in the model.^{29,38} The covariates that were adjusted for in the adjusted models were maternal age, parity, neighbourhood income, pre-existing maternal conditions, rural residence, prenatal care adequacy, obstetrical complications, delivery mode, and calendar quarter to account for seasonality. 2009-2010 H1N1 pandemic vaccination was additionally adjusted for in the pandemic sub-analysis models.

CHAPTER 4. RESULTS

4.1 Characteristics of the study population

Between the study period of April 1, 2006, and March 31, 2020, 1,876,908 birth records were identified in the MOMBABY database. We excluded 66,606 (3.55%) multiple births, 18,271 (0.97%) non-Ontario residents, 42,700 (2.28%) individuals without continuous OHIP eligibility throughout pregnancy, 1321 (0.07%) records with missing gestational weeks at delivery, 221 (0.01%) records of individuals who were <12 years or >50 years of age at delivery, 147 (0.01%) records with gestational age at delivery under 20 weeks and 81 (0.004%) records with invalid fetal sex at delivery. Further to this, we excluded 45,891 (2.45%) pregnancies with onset before November 11, 2005, 7497 (0.40%) pregnancies with onset after June 11, 2019, and 57,482 (3.06%) records with missing information on covariates. After exclusions, the final study sample size was 1,646,892 singleton births, of which 8227 (0.50%) were stillbirths (**Figure 4-1**).

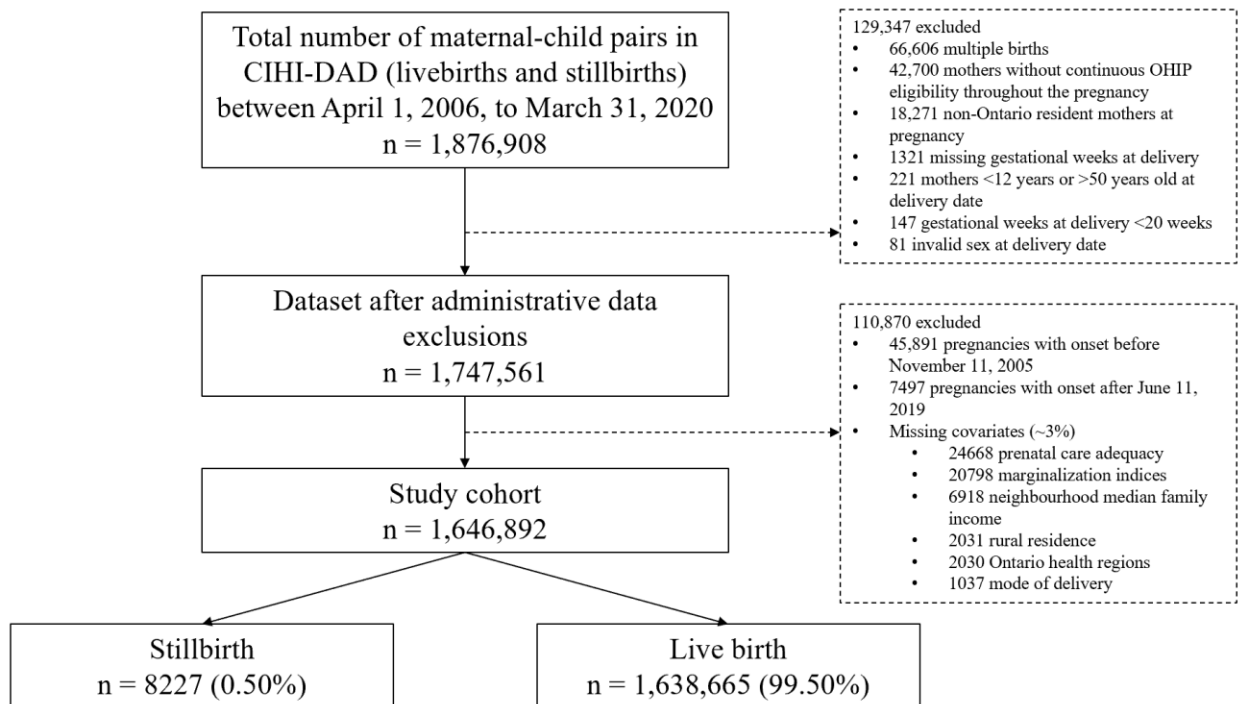


Figure 4-1. Study flow diagram

Table 4-1 provides the study population characteristics. The number of births was similar across all years of the study except for 2006 and 2020, as there were fewer calendar months included in those years in the study. Overall, about half of the population received intermediate prenatal care adequacy (836,589/1,646,892; 50.8%) and 72.1% had a vaginal delivery (1,186,709/1,646,892). Around 19% (311,026/1,646,892) of pregnant individuals had at least one pre-existing medical condition before pregnancy (asthma, chronic hypertension, diabetes, heart disease), with asthma being the most common (246,969/1,646,892; 15.0%). 12% (192,302/1,646,892) of the study population had at least one obstetrical complication, with gestational diabetes (100,942/1,646,892; 6.13%) and pregnancy-induced hypertension (88,729/1,646,892; 5.39%) being the most common. Approximately 9.48% (156,129/1,646,892) of the population resided in a rural area.

4.1 Medically attended influenza illness rates

Table 4-1 also describes the frequency of medically attended influenza illness during pregnancy among all births. From April 1, 2006, to March 31, 2020, 16,286 (0.99%) pregnant individuals were diagnosed with medically attended influenza illness during pregnancy. There was a slight gradient toward increasing rates with increasing intensity of prenatal care (1.28 per 100 individuals with intense prenatal care adequacy vs. 0.72 per 100 among those with no prenatal care). Individuals with pre-existing medical conditions had a slightly higher rate of medically attended influenza illness during pregnancy (1.11 per 100 individuals compared to those who did not have a pre-existing medical condition [0.96 per 100 individuals]). There was no substantial difference in rates of medically attended influenza among individuals with/without obstetrical complications.

Table 4-1. Characteristics of the study population and frequency of medically attended influenza illness during pregnancy among all births, Ontario, Canada, 2006-2020

Characteristics	All births		Medically attended influenza illness during pregnancy		
	N	% ^a	N	% ^a	Rate per 100 ^b
Total	1,646,892	100	16286	100	0.99
Year of birth					
2006 ^c	48461	2.94	325	2.00	0.67
2007	123647	7.51	827	5.08	0.67
2008	123953	7.53	836	5.13	0.67
2009	124235	7.54	1360	8.35	1.09
2010	122517	7.44	2570	15.8	2.10
2011	122048	7.41	1181	7.25	0.97
2012	122892	7.46	932	5.72	0.76
2013	120620	7.32	1286	7.90	1.07
2014	120701	7.33	1164	7.15	0.96
2015	119904	7.28	1127	6.92	0.94
2016	120000	7.29	1113	6.83	0.93
2017	119520	7.26	910	5.59	0.76
2018	118949	7.22	1275	7.83	1.07
2019	118749	7.21	1153	7.08	0.97
2020 ^d	20696	1.26	227	1.39	1.10
Gestational length (completed weeks)					
20-27	9595	0.58	66	0.41	0.69
28-36	100649	6.11	1034	6.35	1.03
37+	1536648	93.3	15186	93.2	0.99
Maternal age at delivery (years)					
<20	43401	2.64	476	2.92	1.10
20-24	186345	11.3	2025	12.4	1.09
25-29	447115	27.1	4508	27.7	1.01
30-34	591640	35.9	5635	34.6	0.95
35+	378391	23.0	3642	22.4	0.96
Parity					
0 (nulliparous)	717520	43.6	6192	38.0	0.86
≥1 (multiparous)	929372	56.4	10094	62.0	1.09
Prenatal care adequacy					
Intensive	20876	1.27	267	1.64	1.28
Adequate	464004	28.2	4721	29.0	1.02
Intermediate	836589	50.8	8612	52.9	1.03
Inadequate	225131	13.7	1967	12.1	0.87
No care	100292	6.09	719	4.41	0.72
Pre-existing maternal medical conditions^e					

No	1335866	81.1	12829	78.8	0.96
Yes	311026	18.9	3457	21.2	1.11
Type of pre-existing maternal medical condition^f					
Asthma	246969	15.0	2808	81.2	1.14
Chronic hypertension	38009	2.31	377	10.9	0.99
Diabetes	27395	1.66	311	9.00	1.14
Heart disease	19684	1.20	209	6.05	1.06
Obstetrical complications^g					
No	1454590	88.3	14385	88.3	0.99
Yes	192302	11.7	1901	11.7	0.99
Type of obstetrical complication^h					
Pregnancy-induced hypertension, preeclampsia, eclampsia	88729	5.39	840	44.2	0.95
Gestational diabetes	100942	6.13	1043	54.9	1.03
Placental previa	12328	0.75	128	6.73	1.04
Placental abruption	1439	0.09	8	0.421	0.56
Mode of delivery					
Vaginal	1186709	72.1	11493	70.6	0.97
Cesarean	460183	27.9	4793	29.4	1.04
Neighbourhood median family income quintiles					
1 (lowest)	353478	21.5	3815	23.4	1.08
2	330442	20.1	3374	20.7	1.02
3	342782	20.8	3336	20.5	0.97
4	347260	21.1	3342	20.5	0.96
5 (highest)	272930	16.6	2419	14.9	0.89
Rural residence					
No	1490763	90.5	14911	91.6	1.00
Yes	156129	9.48	1375	8.44	0.88
Marginalization indices					
Material resources					
1 (low marginalization)	321354	19.5	2840	17.4	0.88
2	318284	19.3	2963	18.2	0.93
3	313543	19.0	3095	19.0	0.99
4	313509	19.0	3283	20.2	1.05

5 (high marginalization)	380202	23.1	4105	25.2	1.08
Households and dwellings					
1 (low marginalization)	365926	22.2	3805	23.4	1.04
2	312186	19.0	2913	17.9	0.93
3	296666	18.0	2886	17.7	0.97
4	310865	18.9	3072	18.9	0.99
5 (high marginalization)	361249	21.9	3610	22.2	1.00
Age and labour force					
1 (low marginalization)	552953	33.6	5730	35.2	1.04
2	352627	21.4	3490	21.4	0.99
3	282931	17.2	2762	17.0	0.98
4	245870	14.9	2283	14.0	0.93
5 (high marginalization)	212511	12.9	2021	12.4	0.95
Racialized and newcomer populations					
1 (low marginalization)	221155	13.4	1983	12.2	0.90
2	245583	14.9	2230	13.7	0.91
3	277189	16.8	2646	16.3	0.95
4	347790	21.1	3304	20.3	0.95
5 (high marginalization)	555175	33.7	6123	37.6	1.10
Ontario health regions					
West region	381737	23.2	3791	23.3	0.99
Central region	501316	30.4	5461	33.5	1.09
East region	325021	19.7	2706	16.6	0.83
Toronto region	341513	20.7	3339	20.5	0.98
North East region	61046	3.71	688	4.22	1.13
North West region	36259	2.20	311	1.91	0.86

^a Column percentage.

^b Row percentage.

^c Encompasses the months April – December. Excluding pregnancies with onset before November 11, 2005.

^d Encompasses the months January – March. Excluding pregnancies with onset after June 11, 2019.

^e Pre-existing maternal medical conditions included: asthma, chronic hypertension, diabetes or heart disease.

^f Pre-existing maternal medical conditions categories are not mutually exclusive.

^g Obstetrical complications included: pregnancy-induced hypertension, preeclampsia, eclampsia, gestational diabetes, placenta previa, and placental abruption.

^h Obstetrical complications categories are not mutually exclusive.

The rate of medically attended influenza illness during pregnancy per 100 deliveries is shown in **Figure 4-2**. During the 2009-2010 H1N1 influenza pandemic season, the rate was 1.59% and for all other seasonal influenza epidemics, the rate ranged from 0.67-1.10%.

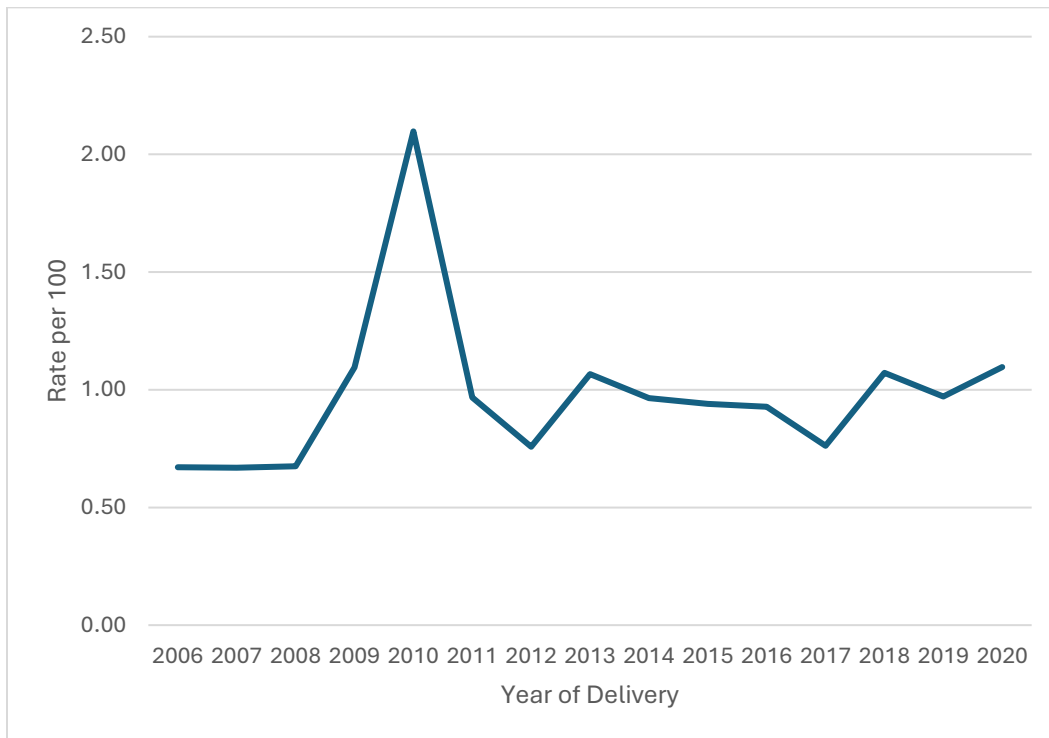


Figure 4-2. Rate of medically attended influenza illness during pregnancy (per 100 deliveries).

4.2 Stillbirth

The overall rate of stillbirth was 5.00 per 1000 births (8227/1,646,892) from April 1, 2006, to March 31, 2020. The number of stillbirths was highest between 20-27 gestational weeks

(3657/8227; 44.5%), followed by 28-36 gestational weeks (2528/8227; 30.7%) and finally 37+ gestational weeks (2042/8227; 24.8%). The highest rates of stillbirth were among mothers who were under 20 years of age at delivery (6.22 per 1000 births) or over 35 years of age (6.12 per 1000 births) in our study population. The highest rates of stillbirth occurred in pregnancies in the “no care” category of prenatal care adequacy (8.07 per 1000 births), and the lowest rates occurred in the “intensive” category of prenatal care adequacy (2.35 per 1000 births). Mothers who had a pre-existing maternal condition had a slightly higher rate of stillbirth (5.81 per 1000 births) compared to those who did not (4.81 per 1000 births). Within the pre-existing conditions, individuals who had diabetes and/or chronic hypertension had the highest rates, 13.3 per 1000 births and 9.68 per 1000 births, respectively. Individuals in the low marginalization quintiles for the marginalization indices had the lowest rates of stillbirth compared to individuals who were in the higher marginalization quintiles.

Table 4-2. Risk of stillbirth by characteristics of the study population, Ontario, Canada, 2006-2020

Characteristics	All births		Stillbirth		
	N	% ^a	N	% ^a	Rate per 1000 ^b
Total	1,646,892	100	8227	100	5.00
Year of birth					
2006 ^c	48461	2.94	393	4.78	8.11
2007	123647	7.51	656	7.97	5.31
2008	123953	7.53	603	7.33	4.86
2009	124235	7.54	631	7.67	5.08
2010	122517	7.44	616	7.49	5.03
2011	122048	7.41	669	8.13	5.48
2012	122892	7.46	584	7.10	4.75
2013	120620	7.32	572	6.95	4.74
2014	120701	7.33	586	7.12	4.85
2015	119904	7.28	584	7.10	4.87
2016	120000	7.29	596	7.24	4.97
2017	119520	7.26	602	7.32	5.04
2018	118949	7.22	557	6.77	4.68
2019	118749	7.21	546	6.64	4.60

2020 ^d	20696	1.26	32	0.389	1.55
Gestational length^e (completed weeks)					
20-27	9595	0.58	3657	44.5	
28-36	100649	6.11	2528	30.7	
37+	1536648	93.3	2042	24.8	
Maternal age at delivery (years)					
<20	43401	2.64	270	3.28	6.22
20-24	186345	11.3	971	11.8	5.21
25-29	447115	27.1	1957	23.8	4.38
30-34	591640	35.9	2714	33.0	4.59
35+	378391	23.0	2315	28.1	6.12
Parity					
0 (nulliparous)	717520	43.6	3935	47.8	5.48
≥1 (multiparous)	929372	56.4	4292	52.2	4.62
Prenatal care adequacy					
Intensive	20876	1.27	49	0.596	2.35
Adequate	464004	28.2	2868	34.9	6.18
Intermediate	836589	50.8	3570	43.4	4.27
Inadequate	225131	13.7	931	11.3	4.14
No care	100292	6.09	809	9.83	8.07
Pre-existing maternal medical conditions^f					
No	1335866	81.1	6421	78.0	4.81
Yes	311026	18.9	1806	22.0	5.81
Type of pre-existing maternal medical condition^g					
Asthma	246969	15.0	1235	15.0	5.00
Chronic hypertension	38009	2.31	368	4.47	9.68
Diabetes	27395	1.66	363	4.41	13.3
Heart disease	19684	1.20	95	1.15	4.83
Obstetrical complications^h					
No	1454590	88.3	7218	87.7	4.96
Yes	192302	11.7	1009	12.3	5.25
Type of obstetrical complicationⁱ					
Pregnancy-induced hypertension, preeclampsia, eclampsia	88729	5.39	525	6.38	5.92
Gestational diabetes	100942	6.13	309	3.76	3.06
Placental previa	12328	0.75	128	1.56	10.4
Placental abruption	1439	0.09	127	1.54	88.3
Mode of delivery					
Vaginal	1186709	72.1	7327	89.1	6.17
Cesarean	460183	27.9	900	10.9	1.96

Neighbourhood median family income quintiles

1 (lowest)	353478	21.5	2284	27.8	6.46
2	330442	20.1	1769	21.5	5.35
3	342782	20.8	1687	20.5	4.92
4	347260	21.1	1474	17.9	4.24
5 (highest)	272930	16.6	1013	12.3	3.71

Rural residence

No	1490763	90.5	7477	90.9	5.02
Yes	156129	9.48	750	9.12	4.80

Marginalization indices**Material resources**

1 (low marginalization)	321354	19.5	1231	15.0	3.83
2	318284	19.3	1359	16.5	4.27
3	313543	19.0	1478	18.0	4.71
4	313509	19.0	1671	20.3	5.33
5 (high marginalization)	380202	23.1	2488	30.2	6.54

Households and dwellings

1 (low marginalization)	365926	22.2	1736	21.1	4.74
2	312186	19.0	1361	16.5	4.36
3	296666	18.0	1415	17.2	4.77
4	310865	18.9	1634	19.9	5.26
5 (high marginalization)	361249	21.9	2081	25.3	5.76

Age and labour force

1 (low marginalization)	552953	33.6	2708	32.9	4.90
2	352627	21.4	1785	21.7	5.06
3	282931	17.2	1416	17.2	5.00
4	245870	14.9	1214	14.8	4.94
5 (high marginalization)	212511	12.9	1104	13.4	5.20

Racialized and newcomer populations

1 (low marginalization)	221155	13.4	1076	13.1	4.87
2	245583	14.9	1096	13.3	4.46
3	277189	16.8	1201	14.6	4.33
4	347790	21.1	1615	19.6	4.64
5 (high marginalization)	555175	33.7	3239	39.4	5.83

Ontario health regions

West region	381737	23.2	1792	21.8	4.69
Central region	501316	30.4	2536	30.8	5.06
East region	325021	19.7	1509	18.3	4.64
Toronto region	341513	20.7	1881	22.9	5.51
North East region	61046	3.71	305	3.71	5.00
North West region	36259	2.20	204	2.48	5.63

Maternal influenza during pregnancy

No	1630606	99.0	8145	99.0	5.00
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Yes	16286	0.99	82	1.00	5.03
Trimester 1					
No	1640790	99.6	8197	99.6	5.00
Yes	6102	0.37	30	0.36	4.92
Trimester 2					
No	1640756	99.6	8187	99.5	4.99
Yes	6136	0.37	40	0.49	6.52
Trimester 3					
No	1642844	99.8	8215	99.9	5.00
Yes	4048	0.25	12	0.15	2.96
Seasonal maternal influenza during pregnancy					
No	1634192	99.2	8158	99.2	4.99
Yes	12700	0.77	69	0.84	5.43
Trimester 1					
No	1642072	99.7	8201	99.7	4.99
Yes	4820	0.29	26	0.32	5.39
Trimester 2					
No	1642208	99.7	8195	99.6	4.99
Yes	4684	0.28	32	0.39	6.83
Trimester 3					
No	1643696	99.8	8216	99.9	5.00
Yes	3196	0.19	11	0.13	3.44
Pandemic maternal influenza during pregnancy					
No	1643306	99.8	8214	99.8	5.00
Yes	3586	0.22	13	0.16	3.63
H1N1 vaccination					
No	1515720	92.0	7826	95.1	5.16
Yes	131172	7.96	401	4.87	3.06

^a Column percentage.

^b Row percentage.

^c Encompasses the months April – December. Excluding pregnancies with onset before November 11, 2005.

^d Encompasses the months January – March. Excluding pregnancies with onset after June 11, 2019.

^e Rates of stillbirth for gestational age are not shown due to different calculations required.

^f Pre-existing maternal medical conditions included: asthma, chronic hypertension, diabetes or heart disease.

^g Only amongst individuals who answered yes to having a diagnosed pre-existing maternal medical condition(s). Pre-existing maternal medical conditions categories are not mutually exclusive.

^h Obstetrical complications included: pregnancy-induced hypertension, preeclampsia, eclampsia, gestational diabetes, placenta previa, and placental abruption.

ⁱ Obstetrical complications categories are not mutually exclusive.

4.3 Risk of stillbirth after influenza exposure during pregnancy

The number of stillbirths was 7704 among 1,645,552 who were at risk of seasonal or pandemic medically attended influenza illness during pregnancy, and 82 out of 16,286 individuals with medically attended influenza during pregnancy experienced a stillbirth. The rate of stillbirth among those with documented medically attended influenza illness during pregnancy was 5.03 per 1000 births, compared to 4.68 per 1000 births among those without documented medically attended influenza illness. In the multivariable analysis, there was a significantly increased risk of stillbirth associated with medically attended influenza during pregnancy (adjusted HR [95% CI]: 1.30 [1.03, 1.62]) (**Table 3-3**). When looking at seasonal medically attended influenza illness alone, 12,700 individuals experienced medically attended influenza illness during pregnancy out of 1,461,886 individuals who were at risk, and 69 stillbirths occurred. There was a significant association between individuals who were exposed and the risk of stillbirth (adjusted HR [95% CI]: 1.35 [1.06, 1.73]) compared to individuals who were not exposed.

When timing of medically attended influenza was stratified by trimester, the risk was highest when exposed in the second trimester (adjusted HR [95% CI]: 1.52 [1.09, 2.22]); no significantly increased risk was observed for exposure in the first trimester (adjusted HR [95% CI]: 1.14 [0.773, 1.67]) or third trimester (adjusted HR [95% CI]: 0.72 [0.400, 1.30]). During the 2009-2010 H1N1 pandemic, 3586 pregnant individuals were exposed out of 183,666 individuals who

were at risk, and 13 stillbirths occurred. There was no evidence of increased risk of stillbirth following medically attended pandemic H1N1 influenza (adjusted HR [95% CI]: 1.02 [0.589, 1.77]). Trimester-specific hazard ratios could not be modelled for the 2009-2010 H1N1 pandemic as the incidence was too low when stratified into trimesters.

Table 4-3. Association between medically attended influenza illness during pregnancy and stillbirth

	Number of birth records	Number of stillbirths	Incidence rate of stillbirth per 1000	Crude HR (95% CI)	Adjusted HR (95% CI) ¹
Total	1645552	7704	4.68	---	---
MA influenza illness during pregnancy (seasonal and pandemic)					
No	1629266	7622	4.68	Reference 1.23	Reference 1.30
Yes	16286	82	5.03	(0.99, 1.54)	(1.03, 1.62)
Seasonal MA influenza illness during pregnancy					
No	1449186	6824	4.71	Reference 1.38	Reference 1.35
Yes	12700	69	5.43	(1.08, 1.76)	(1.06, 1.73)
Yes, in the first trimester	4820	26	5.39	1.16 (0.79, 1.70)	1.14 (0.77, 1.67)
Yes, in the second trimester	4684	32	6.83	1.54 (1.10, 2.15)	1.52 (1.09, 2.22)
Yes, in the third trimester	3196	11	3.44	0.71 (0.39, 1.29)	0.72 (0.40, 1.30)
Pandemic MA influenza illness during pregnancy					
No	180080	798	4.43	Reference 1.05	Reference 1.02
Yes	3586	13	3.63	(0.61, 1.81)	(0.59, 1.77)

¹Adjustment for maternal age, parity, neighbourhood income, pre-existing maternal conditions, rural residence, prenatal care adequacy, obstetrical complications, delivery mode and calendar quarter to account for seasonality. Additionally, the adjusted model for pandemic influenza illness was adjusted for H1N1 vaccination.

4.4 Exposure window subgroup analyses

To examine the acute risk of influenza illness following exposure, we conducted subgroup analyses of 2, 4, and 6-week risk windows where the exposure status of individuals who experience medically attended influenza during pregnancy reverted to unexposed after the specific risk window (**Table 4-4**). Our models showed that the risk of stillbirth was highest during the two weeks following infection (adjusted HR [95% CI]: 3.70 [2.19, 6.25]), then during the four weeks following infection (adjusted HR [95% CI]: 2.69 [1.73, 4.17]), and finally during the six weeks following infection (adjusted HR [95% CI]: 1.96 [1.29, 2.97]). The seasonal epidemics and the 2009-2010 H1N1 pandemic were combined for all models.

Table 4-4. Risk of stillbirth following medically attended influenza illness during pregnancy by exposure windows

Exposure window	Influenza infection	Crude HR (95% CI)	Adjusted HR (95% CI) ¹
2 weeks	Unexposed	Reference	Reference
	Exposed	3.68 (2.18, 6.22)	3.70 (2.19, 6.25)
4 weeks	Unexposed	Reference	Reference
	Exposed	2.68 (1.73, 4.16)	2.69 (1.73, 4.17)
6 weeks	Unexposed	Reference	Reference
	Exposed	1.95 (1.28, 2.96)	1.96 (1.29, 2.97)

¹Adjustment for maternal age, parity, neighbourhood income, pre-existing maternal conditions, rural residence, prenatal care adequacy, obstetrical complications, delivery mode and calendar quarter to account for seasonality.

4.5 High-risk subgroup analysis

Table 4-5 presents the association of medically attended influenza illness during pregnancy and the risk of stillbirth in the high-risk population. These were individuals who had pre-existing maternal conditions such as asthma, chronic hypertension, diabetes, and heart disease. There were 310,728 pregnant individuals in this sub-population, and 1692 births were stillbirths. When investigating the seasonal epidemics and the pandemic combined, the adjusted hazard ratio was

1.48 (95% CI 0.58 to 2.67). The adjusted hazard ratio was 1.32 (95% CI 0.79 to 2.19) and 1.96 (95% CI 0.88 to 4.40) in seasonal epidemics and pandemic only, respectively.

Table 4-5. Association between medically attended influenza illness during pregnancy and stillbirth in pregnant individuals with pre-existing maternal conditions

	Number of birth records	Number of stillbirths	Incidence rate of stillbirth per 1000	Crude HR (95% CI)	Adjusted HR (95% CI) ¹
Total	310728	1692	5.45	---	---
MA influenza illness during pregnancy (seasonal and pandemic)					
No	307271	1671	5.44	Reference 1.44	Reference 1.48
Yes	3457	21	6.07	(0.94, 2.22)	(0.96, 2.67)
Seasonal MA influenza illness during pregnancy					
No	275328	1496	5.43	Reference 1.33	Reference 1.32
Yes	2679	15	5.60	(0.80, 2.21)	(0.79, 2.19)
Pandemic MA influenza illness during pregnancy					
No	31943	175	5.48	Reference 1.84	Reference 1.96
Yes	778	6	7.71	(0.82, 4.14)	(0.88, 4.40)

¹Adjustment for maternal age, parity, neighbourhood income, pre-existing maternal conditions, rural residence, prenatal care adequacy, obstetrical complications, delivery mode and calendar quarter to account for seasonality. Additionally, the adjusted model for pandemic influenza illness was adjusted for H1N1 vaccination as well.

CHAPTER 5. DISCUSSION

Influenza is a highly contagious respiratory illness that primarily affects the upper respiratory tract and can result in significant morbidity across populations. The pregnant population is a subgroup that is disproportionately affected by the disease, as physiological and immunological changes during pregnancy can increase susceptibility to severe influenza illness.²¹ Infections have been associated with severe obstetrical complications and adverse perinatal outcomes, such as preterm birth, low birth weight, and stillbirth.^{2,5}

Influenza vaccination is an effective method to immunize against influenza illness. It is safe to administer during pregnancy, with strong evidence demonstrating reductions in both maternal morbidity and adverse neonatal outcomes.^{26,28,63} However, despite vaccination recommendations by the NACI, the rate of vaccination remains sub-optimal in Canada.^{3,4}

There have been several epidemiological studies examining influenza illness exposure during pregnancy and adverse perinatal outcomes; however, many were limited in quality, and their findings were often inconclusive.^{1,2,5-7} Additionally, there has been limited research investigating the relationship between influenza illness during pregnancy and the risk of stillbirth, specifically seasonal influenza exposure.

Using a large population-based registry, this master's thesis aimed to generate new evidence on the risk of stillbirth following medically attended influenza during pregnancy, investigating the burden of both seasonal and pandemic periods.

5.1 Statement of principal findings

Our pooled analyses demonstrated an increased risk of stillbirth following influenza exposure during pregnancy. This finding was consistent during the seasonal epidemics when seasonal and

pandemic influenza exposures were analyzed separately. There was a strong association with stillbirth when medically attended influenza illness was diagnosed in the second trimester. When risk windows were assessed to explore the acute effects of influenza illness during pregnancy, we found a significant association with stillbirth. The greatest risk was during the two-week risk window immediately following infection, followed by the four-week risk window, and the lowest during the six-week risk window. Among high-risk pregnant individuals, although not statistically significant, there was a higher risk of medically attended influenza illness during pregnancy and stillbirth during the seasonal epidemics and the 2009/2010 H1N1 pandemic.

5.2 Interpretation of study findings

5.2.1 Seasonal epidemics and 2009/2010 H1N1 pandemic associations

Overall, our study found that there was a significant association between influenza illness during pregnancy and the risk of stillbirth in our combined analysis of seasonal and pandemic periods (adjusted HR [95% CI]: 1.30 [1.03, 1.62]). To our knowledge, there were no studies that investigated the relationship between influenza illness during pregnancy and stillbirth in Canada. In contrast, a New Zealand 16-year retrospective cohort study spanning from 2003-2018 found no associations between hospitalizations for influenza-associated maternal acute respiratory infection (ARI) and fetal death (adjusted HR [95% CI]: 0.96 [0.69, 1.34]), but maternal vaccination was associated with reduced risk of fetal death (adjusted HR [95% CI]: 0.50 [0.44, 0.57]).⁶ Seasonal epidemics and the 2009/2010 H1N1 pandemic were analyzed together in the New Zealand study. There might not have been enough power to detect a significant effect in the sample size (n=822,391), especially when there were only 5095 (5095/822,391; 0.62%) influenza-associated maternal ARI hospitalizations.⁶ Their result was limited to only severe

clinical illness from pregnant individuals who were hospitalized, as they were unable to conduct the same analysis for individuals seeking care for ARI in ambulatory settings. It was interesting that the study found no associations between influenza illness and stillbirth when only serious clinical illnesses were explored. A possible explanation for this is that when only hospitalizations are considered in the New Zealand study, it may result in an even smaller number of influenza exposures and the stillbirth outcome. In contrast, our study included all medically attended influenza cases, which allowed us to detect associations that both moderate and severe infections may drive. Another possible explanation is that because the pregnant individuals are already hospitalized, they may receive closer monitoring and medical interventions, which may mitigate the risk of stillbirth. The definition of fetal death was also not explicitly stated in the study, and, therefore, it is difficult to know whether this also differed from our study.

When looking at seasonal influenza infection alone, there was still a significant association with stillbirth (adjusted HR [95% CI]: 1.35 [1.06, 1.73]) in our study. This was inconsistent with a registry-based cohort study conducted in Norway that explored this relationship and found there was no association between seasonal influenza illness during pregnancy and fetal death (adjusted HR [95% CI]: 0.90 [0.64 to 1.27]).¹ Fetal death was defined as any fetal loss after 12 completed weeks of pregnancy.¹ A possible explanation for this discrepancy may be that the effect estimate is less reliable due to the small number of fetal death events (n=2510) in the study sample (n=417,406).¹ The random error could have caused the point estimate (0.90) to fluctuate above or below 1. They were also able to adjust for maternal use of nutritional supplements before and/or during pregnancy and maternal smoking at the beginning of pregnancy, whereas we did not have access to those variables.

There was no significant association between pandemic medically attended influenza illness and stillbirth in our study (adjusted HR [95% CI]: 1.02 [0.589, 1.77]). In contrast to our results, the risk of fetal death was higher following maternal pandemic influenza during pregnancy in the Norwegian study (adjusted HR [96% CI]: 1.75 [1.21, 2.54]).¹ In 2011, another UK national cohort study concluded that following the 2009/2010 H1N1 pandemic influenza, there was an increased odds of stillbirth (adjusted OR [95%CI]: 4.2 [1.4, 12.4]).⁶⁴ This may be due to the small number of stillbirth cases in our study during the pandemic season. Out of 3586 individuals who were exposed to pandemic influenza during pregnancy, there were only 13 cases of stillbirth (0.36%), whereas in the Norwegian and UK studies, the incidence rates of fetal death and stillbirth in the exposed cohort were higher, 0.78% and 3%, respectively.^{1,64} There may also be a possibility of exposure misclassification bias, as our exposure definition was based on ICD-10-CA codes and not laboratory-confirmed cases. Since physicians input these codes, there could have been a possibility that individuals with other respiratory pathogens that co-circulated during the influenza season were captured in the exposed cohort. Additionally, in many cases, diagnostic codes are abstracted by health records administrative staff from physicians' clinical notes, which could contribute to the potential for misclassification. The UK study only included laboratory-confirmed influenza cases that were hospitalized. While the Norwegian study considered both the International Classification of Primary Care (ICPC) R80 diagnosis and laboratory-confirmed diagnosis, assigned in any clinical setting, there could be discrepancies in the diagnostic criteria for the R80 code and the ICD-10-CA codes we used. Another Norwegian study found that the risk of fetal death was increased among pregnant individuals with a clinical diagnosis of influenza (adjusted HR [95% CI]: 1.91 [1.07, 3.41]).⁶⁵ Their definition of fetal death was any recorded miscarriage or stillbirth after 12 completed weeks of pregnancy, which was different

from our outcome definition. Another systematic review and meta-analysis of prospective and retrospective observational studies conducted in 2017 demonstrated that pregnant individuals with influenza A virus infection had a higher risk of stillbirth.⁵ This review consisted of four studies where the outcome of interest was stillbirth.^{7,64,66,67} The meta-analysis demonstrated that individuals with pandemic influenza A virus infection were associated with a 2.36 times (95% CI 1.05 to 5.31) higher risk of stillbirths than individuals who were not infected with the pandemic influenza A virus.⁵

5.2.2 Seasonal trimester-specific associations

When the model was stratified by trimester for seasonal influenza illness during pregnancy, we found a significant association between influenza illness during pregnancy and stillbirth, but no association with seasonal influenza illness in the first or third trimesters. To our knowledge, only one other study stratified by trimesters of influenza illness exposure during pregnancy while investigating the risk of stillbirth. The Norwegian study showed similar results for the first trimester (adjusted HR [95% CI]: 1.13 [0.73, 1.76]).¹ For our study, we were able to separate the analysis for the second and the third trimesters. The adjusted HR for the third trimester was comparable to the Norwegian study estimate for influenza illness during the second/third trimesters combined (adjusted HR [95% CI]: 0.69 [0.40, 1.19]).¹

The association seemed to be strongest when influenza was diagnosed in the second trimester compared to the first or third trimester in our study. In contrast, the Norwegian study found the strongest association when influenza was diagnosed in the first trimester.¹ It is possible that this is due to earlier ascertainment of fetal death in the Norwegian study (from 12 weeks) whereas we were only able to identify fetal deaths from 20 weeks of gestation in our study due to availability of data in Ontario.

5.2.3 Risk windows

To our knowledge, this was the first study to evaluate the acute risk of medically attended influenza illness during pregnancy and its association with stillbirth. The hazard was highest during the first two weeks following infection, then declined during the four-week and six-week exposure windows. This pattern was similarly observed in a Scandinavian study that examined the risk of stillbirth following maternal infection with SARS-CoV-2 during pregnancy.⁶⁸ In their exposure window analysis, the risk of stillbirth was also highest during two weeks following infection (adjusted HR [95%CI]: 5.48 [3.11, 9.63]), then during the four weeks following infection (adjusted HR [95%CI]: 4.38 [2.41, 7.98]), and finally during the six weeks following infection (adjusted HR [95%CI]: 3.71 [1.81, 7.59]).⁶⁸ In line with these findings, another study demonstrated that the incidence ratio for acute myocardial infarction was highest during days 1-3 after influenza infection (incidence ratio [95% CI]: 6.30 [3.25, 12.2]) and decreased during days 4-7 after infection (incidence ratio [95% CI]: 5.78 [3.17, 10.5]).⁶⁹ Collectively, these results suggested that influenza imposed the most significant risk immediately following infection, with risk diminishing over time.

5.2.4 High-risk population

It had been well established that individuals with pre-existing medical conditions were at an increased risk of complications and hospitalizations following exposure to influenza infection. In a study conducted in Nova Scotia investigating hospital admissions following respiratory illness among pregnant women, women with comorbidities had a higher rate of hospital admissions compared to women without comorbidities.⁷⁰ However, there seems to be conflicting conclusions drawn when examining the association of medically attended influenza illness during pregnancy

and the risk of adverse perinatal outcomes such as stillbirth, preterm birth, or small for gestational age (SGA). A large, population-based study found that pregnant women with a pre-existing condition had an increased risk of SGA when diagnosed with seasonal influenza virus infection and the H1N1 pandemic infection, but no significant association with preterm birth.⁷¹ In contrast, a population-based cohort study in Ontario showed there was a significant association between pandemic influenza exposure and preterm birth among high-risk pregnant people.³⁶ Our study was the first to investigate the risk of stillbirth following medically attended influenza illness exposure during pregnancy in high-risk individuals with pre-existing medical conditions. These pre-existing medical conditions were asthma, chronic hypertension, diabetes, and heart disease. Our study found there was a higher risk of medically attended influenza illness during pregnancy and stillbirth; however, the association was not statistically significant in both the seasonal epidemics and the 2009/2010 H1N1 pandemic. Although it was apparent that the incidence rate of stillbirth in the high-risk population was higher, 5.45 stillbirth per 1000 births, compared to the general study population, 4.68 per 1000, the incidence may still have been too small to have enough power to detect a significant effect in the population.

5.3 Strengths and limitations

There were several strengths in our study. Firstly, to our knowledge, this was the first population-based cohort study in Ontario to investigate the association between stillbirth and medically attended influenza illness during pregnancy. As previously mentioned, there have been several studies exploring the exposure of influenza illness during pregnancy and the risk of adverse perinatal outcomes; however, most studies studied preterm birth and low birth weight.

Additionally, the effects of the 2009/2010 H1N1 pandemic have been extensively studied, but the

impact of the seasonal epidemics has not. Another strength was the use of multiple, linked, province-wide health administrative datasets housed at ICES. With the high quality of data, we were able to have access to detailed information about each pregnancy and birth. This allowed for efficient analysis of the association between the exposure and outcome while accounting for multiple potential confounding variables. The large sample size was another strength in our study. After all administrative exclusions, the sample size was 1,646,892. An advantage of this was that the study was able to provide stronger and more reliable results as they have smaller margins of error (narrower confidence intervals). Furthermore, our study utilized an extended Cox model. This model allowed us to incorporate the time-varying exposure, thus mitigating immortal time bias.

Despite these strengths, our study had some limitations as well. First, the rate of influenza illness during pregnancy was only 0.99% for the entire study population, limiting study power. Another limitation was the possibility of information bias from misclassification of the exposure. As we only used administrative databases, there was the possibility that the ICD codes could be coded incorrectly in the database. Many cases of influenza illness may also not be documented, as symptoms are very similar to those of the common cold. To increase the reliability of the influenza measure in our study, we only considered ICD codes as truly representing influenza illness when they were documented during the predefined influenza seasons. Our analyses were also limited to individuals who had OHIP, as we were only able to capture information on pregnant individuals who had OHIP; however, this would be very low and unlikely to have contributed to selection bias. We also had limited ability to evaluate the proportional hazards assumption due to the small number of exposed cases of stillbirth.

5.4 Clinical and research implications

Although the prevalence of both stillbirth and influenza illness during pregnancy was low relative to our large study population size, this study contributed new information regarding this relationship. Importantly, this study reinforced that influenza prevention during pregnancy remains a public health priority, given the increased risk of stillbirth we observed among individuals who experienced medically attended influenza illness during pregnancy.

Strengthening vaccination efforts within maternity services and through antenatal care providers can help protect pregnant individuals from obstetrical complications and adverse perinatal outcomes related to influenza during pregnancy.

As previously mentioned, there have been no studies conducted in Ontario that investigated the relationship between medically attended influenza illness during pregnancy and the risk of stillbirth. This study explored seasonal epidemics and the 2009/2010 H1N1 pandemic, trimester-specific effects of medically attended influenza illness, risk windows, and analyzed high-risk individuals. It was also evident from the literature review that further research is needed, especially in the Canadian setting, as the majority of studies were conducted over a decade ago, with the most recent systematic reviews dating back to 2017. Due to the inconsistent results our study demonstrated when compared to the existing literature, conclusions regarding this association were hard to draw.

Perhaps future research can incorporate an even larger, multi-province cohort study. Pooling data across provinces can increase statistical power, especially given the low incidence rates of influenza exposure and the stillbirth outcome. Future studies can also consider only incorporating laboratory-confirmed influenza cases. This will help further reduce exposure misclassification by ensuring that only true influenza infections are captured. Finally, it would be

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interesting to stratify the severity of the influenza infection to distinguish whether severe cases primarily drive adverse outcomes or whether mild cases contribute as well.

CHAPTER 6. CONCLUSION

In conclusion, the findings of this thesis present information on the impact of influenza illness during pregnancy on obstetrical outcomes, specifically stillbirth. Additionally, we also investigate the effects of acute risk windows and the risk of stillbirth following infection in high-risk populations. Our findings demonstrate that there is a significant association between influenza illness during pregnancy and stillbirth, especially during seasonal epidemics. We were able to fill some gaps in the Canadian setting, but with inconsistent conclusions, more research is needed in this field.

REFERENCES

1. Gunnes N et al. Seasonal and pandemic influenza during pregnancy and risk of fetal death: A Norwegian registry-based cohort study. *European Journal of Epidemiology*. 2020 [accessed 2023 Dec 3];35(4):371. /pmc/articles/PMC7192880/.
<https://doi.org/10.1007/S10654-020-00600-Z>
2. Fell DB et al. Maternal influenza and birth outcomes: systematic review of comparative studies. *BJOG : an international journal of obstetrics and gynaecology*. 2017 [accessed 2023 Nov 8];124(1):48–59. <https://pubmed.ncbi.nlm.nih.gov/27264387/>.
<https://doi.org/10.1111/1471-0528.14143>
3. Immunization in pregnancy and breastfeeding: Canadian Immunization Guide - Canada.ca. [accessed 2023 Oct 28]. <https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-4-immunization-pregnancy-breastfeeding.html>
4. Results from the 2019 Survey of Vaccination During Pregnancy - Canada.ca. [accessed 2023 Oct 30]. <https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/survey-vaccination-during-pregnancy/full-report-2019.html>
5. He J et al. A Systematic Review and Meta-Analysis of Influenza A Virus Infection During Pregnancy Associated with an Increased Risk for Stillbirth and Low Birth Weight. *Kidney Blood Press Res*. 2017 [accessed 2024 Oct 19];42:232–243. www.karger.com/kbr.
<https://doi.org/10.1159/000477221>
6. Duque J, Howe AS, Azziz-Baumgartner E, Petousis-Harris H. Multi-decade national cohort identifies adverse pregnancy and birth outcomes associated with acute respiratory illness hospitalisations during the influenza season. *Influenza and Other Respiratory Viruses*. 2023 [accessed 2025 Jan 19];17(1):e13063.
<https://onlinelibrary.wiley.com/doi/full/10.1111/irv.13063>.
<https://doi.org/10.1111/IRV.13063>
7. Gérardin P et al. Low Clinical Burden of 2009 Pandemic Influenza A (H1N1) Infection during Pregnancy on the Island of La Réunion. *PLoS ONE*. 2010 [accessed 2024 Jun 2];5(5). /pmc/articles/PMC2878351/. <https://doi.org/10.1371/JOURNAL.PONE.0010896>
8. Chapter 12: Influenza | Pink Book | CDC. [accessed 2025 May 1].
<https://www.cdc.gov/pinkbook/hcp/table-of-contents/chapter-12-influenza.html>
9. Liu R et al. Influenza D Virus. *Current opinion in virology*. 2020 [accessed 2025 Jun 19];44:154. <https://pmc.ncbi.nlm.nih.gov/articles/PMC7755673/>.
<https://doi.org/10.1016/J.COVIRO.2020.08.004>

10. How Flu Spreads | Influenza (Flu) | CDC. [accessed 2024 Oct 7]. <https://www.cdc.gov/flu/spread/index.html>
11. How Flu Viruses Can Change: “Drift” and “Shift” | Influenza (Flu) | CDC. [accessed 2024 Oct 8]. <https://www.cdc.gov/flu/php/viruses/change.html>
12. Labella AM, Merel SE. Influenza. *Medical Clinics of North America*. 2013 [accessed 2024 Oct 7];97(4):621–645. <https://doi.org/10.1016/J.MCNA.2013.03.001>
13. Keilman LJ. Seasonal Influenza (Flu). *Nursing Clinics of North America*. 2019 [accessed 2024 Oct 7];54(2):227–243. <https://doi.org/10.1016/J.CNUR.2019.02.009>
14. Influenza (Seasonal). [accessed 2024 Oct 7]. [https://www.who.int/news-room/fact-sheets/detail/influenza-\(seasonal\)](https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal))
15. Schmidt K et al. Influenza and Other Respiratory Infections: National Influenza Annual Report, Canada, 2022–2023: Canada’s first fall epidemic since the 2019–2020 season. *Canada Communicable Disease Report*. 2023 [accessed 2024 Oct 7];49(10):413. [/pmc/articles/PMC10927280/](https://doi.org/10.14745/CCDR.V49I10A02). <https://doi.org/10.14745/CCDR.V49I10A02>
16. Somes MP, Turner RM, Dwyer LJ, Newall AT. Estimating the annual attack rate of seasonal influenza among unvaccinated individuals: A systematic review and meta-analysis. *Vaccine*. 2018 [accessed 2024 Oct 8];36(23):3199–3207. <https://doi.org/10.1016/J.VACCINE.2018.04.063>
17. Threats I of M (US) F on M et al. *The Story of Influenza*. 2005 [accessed 2024 Oct 8]. <https://www.ncbi.nlm.nih.gov/books/NBK22148/>
18. *The History of Influenza*. [accessed 2024 Oct 21]. <https://www.flu.com/Articles/2022/The-History-of-Influenza>
19. Al Hajjar S, McIntosh K. The first influenza pandemic of the 21st century. *Annals of Saudi Medicine*. 2010 [accessed 2024 Oct 21];30(1):1. [https://pmc.ncbi.nlm.nih.gov/articles/PMC2850175/](https://doi.org/10.4103/0256-4947.59365). <https://doi.org/10.4103/0256-4947.59365>
20. H1N1 Flu of 2009 in Canada | *The Canadian Encyclopedia*. [accessed 2024 Oct 21]. <https://www.thecanadianencyclopedia.ca/en/article/h1n1-flu-of-2009-in-canada>
21. Champion EW, Kourtis AP, Read JS, Jamieson DJ. Pregnancy and Infection. *n engl j med*. 2014 [accessed 2024 Oct 19];367(5):2211–2219. <https://doi.org/10.1056/NEJMra1213566>
22. Siston AM et al. Pandemic 2009 Influenza A(H1N1) Virus Illness Among Pregnant Women in the United States. *JAMA*. 2010 [accessed 2024 Oct 21];303(15):1517–1525.

<https://jamanetwork.com/journals/jama/fullarticle/185713>.

<https://doi.org/10.1001/JAMA.2010.479>

23. Macias AE, Precioso AR, Falsey AR. The Global Influenza Initiative recommendations for the vaccination of pregnant women against seasonal influenza. *Influenza and other Respiratory Viruses*. 2015 [accessed 2024 Oct 19];9(S1):31–37.

<https://doi.org/10.1111/IRV.12320>

24. Rasmussen SA, Jamieson DJ, Bresee JS. Pandemic Influenza and Pregnant Women - Volume 14, Number 1—January 2008 - *Emerging Infectious Diseases* journal - CDC.

Emerging Infectious Diseases. 2008 [accessed 2024 Oct 21];14(1):95–100.

https://wwwnc.cdc.gov/eid/article/14/1/07-0667_article.

<https://doi.org/10.3201/EID1401.070667>

25. Influenza vaccines: Canadian Immunization Guide - Canada.ca. [accessed 2024 Oct 18]. <https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-10-influenza-vaccine.html>

26. Ho T, Quach T, Mallis NA, Cordero JF. Influenza Vaccine Efficacy and Effectiveness in Pregnant Women: Systematic Review and Meta-analysis. *Maternal and Child Health Journal*. 2020 [accessed 2024 Oct 18];24:229–240. <https://doi.org/10.1007/s10995-019-02844-y>. <https://doi.org/10.1007/s10995-019-02844-y>

27. Omer SB et al. Efficacy, duration of protection, birth outcomes, and infant growth associated with influenza vaccination in pregnancy: a pooled analysis of three randomised controlled trials. *The Lancet Respiratory Medicine*. 2020 [accessed 2025 Sep 14];8(6):597–608. <https://pubmed.ncbi.nlm.nih.gov/32526188/>. [https://doi.org/10.1016/S2213-2600\(19\)30479-5](https://doi.org/10.1016/S2213-2600(19)30479-5)

28. Wolfe DM et al. Safety of influenza vaccination during pregnancy: a systematic review. *BMJ Open*. 2023 [accessed 2024 Oct 7];13(9):e066182. <https://bmjopen.bmj.com/content/13/9/e066182>. <https://doi.org/10.1136/BMJOPEN-2022-066182>

29. Gunnes N et al. Seasonal and pandemic influenza during pregnancy and risk of fetal death: A Norwegian registry-based cohort study. *European journal of epidemiology*. 2020 [accessed 2023 Oct 30];35(4):371–379. <https://pubmed.ncbi.nlm.nih.gov/31950373/>. <https://doi.org/10.1007/S10654-020-00600-Z>

30. Dodds L et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *CMAJ*. 2007

[accessed 2024 Jun 1];176(4):463–468. <https://www.cmaj.ca/content/176/4/463>.
<https://doi.org/10.1503/CMAJ.061435>

31. Mertz D et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. *BMJ*. 2013 [accessed 2024 Oct 19];347(7923).

<https://www.bmj.com/content/347/bmj.f5061>. <https://doi.org/10.1136/BMJ.F5061>

32. Pierce M et al. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. *BMJ*. 2011 [accessed 2024 Jun 1];342(7811).

<https://www.bmj.com/content/342/bmj.d3214>. <https://doi.org/10.1136/BMJ.D3214>

33. Michaan N et al. Maternal and neonatal outcome of pregnant women infected with H1N1 influenza virus (Swine Flu). *The Journal of Maternal-Fetal & Neonatal Medicine*. 2012 [accessed 2024 Jun 1];25(2):130–132.

<https://www.tandfonline.com/doi/abs/10.3109/14767058.2011.562569>.

<https://doi.org/10.3109/14767058.2011.562569>

34. Memoli MJ, Harvey H, Morens DM, Taubenberger JK. Influenza in pregnancy. *Influenza and Other Respiratory Viruses*. 2013 [accessed 2024 Jun 1];7(6):1033–1039.

<https://onlinelibrary.wiley.com/doi/full/10.1111/irv.12055>.

<https://doi.org/10.1111/IRV.12055>

35. Abdullahi H, Elnahas A, Konje JC. Seasonal influenza during pregnancy. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2021 [accessed 2024 Oct 19];258:235–239. <https://doi.org/10.1016/J.EJOGRB.2021.01.005>

36. Fell DB et al. The Relationship Between 2009 Pandemic H1N1 Influenza During Pregnancy and Preterm Birth: A Population-based Cohort Study. *Epidemiology (Cambridge, Mass.)*. 2018 [accessed 2023 Sep 27];29(1):107–116.

<https://pubmed.ncbi.nlm.nih.gov/28930786/>.

<https://doi.org/10.1097/EDE.0000000000000753>

37. Regan AK et al. Seasonal Trivalent Influenza Vaccination During Pregnancy and the Incidence of Stillbirth: Population-Based Retrospective Cohort Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2016 [accessed 2023 Oct 30];62(10):1221–1227. <https://pubmed.ncbi.nlm.nih.gov/27033634/>.

<https://doi.org/10.1093/CID/CIW082>

38. Fell DB, Dodds L, McNeil S, MacDonald NE. H1N1 influenza vaccination during pregnancy. *BMJ (Clinical research ed.)*. 2014 [accessed 2023 Oct 27];348.

<https://pubmed.ncbi.nlm.nih.gov/24874846/>. <https://doi.org/10.1136/BMJ.G3500>

39. Number of live and stillbirths among infants born in Ontario, by COVID-19 Vaccination Status - BORN Ontario. [accessed 2023 Oct 28].
<https://www.bornontario.ca/en/news/number-of-live-and-stillbirths-among-infants-born-in-ontario-by-covid-19-vaccination-status.aspx>
40. Stillbirths and stillbirth rates - UNICEF DATA. [accessed 2024 Oct 18].
<https://data.unicef.org/topic/child-survival/stillbirths/>
41. The Daily — Stillbirths, 2022. [accessed 2025 Jan 10].
<https://www150.statcan.gc.ca/n1/daily-quotidien/231127/dq231127d-eng.htm>
42. What are possible causes of stillbirth? | NICHD - Eunice Kennedy Shriver National Institute of Child Health and Human Development. [accessed 2023 Oct 28].
<https://www.nichd.nih.gov/health/topics/stillbirth/topicinfo/causes>
43. McClure EM et al. Maternal infection and stillbirth: a review. *Journal of Maternal-Fetal and Neonatal Medicine*. 2022 [accessed 2024 Oct 18];35(23):4442–4450.
<https://doi.org/10.1080/14767058.2020.1852206>
44. Veetil SK et al. The economic burden associated with stillbirth: A systematic review. *Birth (Berkeley, Calif.)*. 2023 [accessed 2024 Jun 1];50(2):300–309.
<https://pubmed.ncbi.nlm.nih.gov/36774590/>. <https://doi.org/10.1111/BIRT.12714>
45. Heazell AEP et al. Stillbirths: economic and psychosocial consequences. *The Lancet*. 2016 [accessed 2024 Oct 18];387(10018):604–616. [https://doi.org/10.1016/S0140-6736\(15\)00836-3](https://doi.org/10.1016/S0140-6736(15)00836-3)
46. Strand LB, Barnett AG, Tong S. Methodological challenges when estimating the effects of season and seasonal exposures on birth outcomes. *BMC medical research methodology*. 2011 [accessed 2025 Sep 14];11.
<https://pubmed.ncbi.nlm.nih.gov/21501523/>. <https://doi.org/10.1186/1471-2288-11-49>
47. ICES | About ICES Data. [accessed 2024 Jun 1]. <https://www.ices.on.ca/about-ices-data/>
48. Discharge Abstract Database (DAD) metadata | CIHI. [accessed 2025 Jul 20].
<https://www.cihi.ca/en/discharge-abstract-database-dad-metadata>
49. Codes and classifications for clinical health data. [accessed 2025 Jul 20].
<https://www.cihi.ca/en/submit-data-and-view-standards/codes-classifications-and-terminologies>
50. ICES Data Dictionary. [accessed 2025 Jul 20].
<https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx>

51. ICES Data Dictionary for MOMBABY. [accessed 2025 Jul 20].
<https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library=MOMBABY>
52. National Ambulatory Care Reporting System (NACRS) metadata | CIHI. [accessed 2025 Jul 20]. <https://www.cihi.ca/en/national-ambulatory-care-reporting-system-nacrs-metadata>
53. 2021 Ontario Marginalization Index User Guide. 2023.
54. Postal Code OM Conversion File. [accessed 2025 Jul 22].
<https://www150.statcan.gc.ca/n1/en/catalogue/92-154-X>
55. Registered Persons Database (RPDB) - Dataset - Ontario Data Catalogue. [accessed 2025 Jul 20]. <https://data.ontario.ca/dataset/registered-persons-database-rpdb>
56. ICES | Data Privacy and Security. [accessed 2025 Jun 13]. <https://www.ices.on.ca/data-privacy/>
57. ICD-10 Version:2019. [accessed 2024 Jan 9]. <https://icd.who.int/browse10/2019/en>
58. Online ICD9/ICD9CM codes. [accessed 2024 Jan 9].
<http://icd9cm.chrisendres.com/index.php?srctype=diseases&srchtext=influenza&Submit=Search&action=search>
59. Clark TG, Bradburn MJ, Love SB, Altman DG. Survival Analysis Part I: Basic concepts and first analyses. *British Journal of Cancer*. 2003 [accessed 2025 Jul 22];89(2):232.
<https://pmc.ncbi.nlm.nih.gov/articles/PMC2394262/>.
<https://doi.org/10.1038/SJ.BJC.6601118>
60. Regression Models and Life-Tables on JSTOR. [accessed 2025 Jul 22].
<https://www.jstor.org/stable/2985181>
61. VanderWeele TJ. Principles of confounder selection. *European Journal of Epidemiology*. 2019 [accessed 2025 Feb 20];34(3):211–219.
<https://link.springer.com/article/10.1007/s10654-019-00494-6>.
<https://doi.org/10.1007/S10654-019-00494-6/FIGURES/5>
62. Madhi SA et al. Influenza Vaccination of Pregnant Women and Protection of Their Infants. *New England Journal of Medicine*. 2014 [accessed 2024 Oct 21];371(10):918–931.
<https://www.nejm.org/doi/full/10.1056/NEJMoa1401480>.
https://doi.org/10.1056/NEJMoa1401480/SUPPL_FILE/NEJMoa1401480_DISCLOSURES.PDF

63. Pierce M et al. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. *BMJ*. 2011 [accessed 2025 Aug 7];342(7811).
<https://www.bmj.com/content/342/bmj.d3214>. <https://doi.org/10.1136/BMJ.D3214>
64. Håberg SE et al. Risk of Fetal Death after Pandemic Influenza Virus Infection or Vaccination Abstract. *N Engl J Med*. 2013 [accessed 2025 Aug 21];368:333–373.
<https://doi.org/10.1056/NEJMoa1207210>
65. Da Silva AA et al. Impact on pregnancies in south Brazil from the influenza A (H1N1) pandemic: Cohort study. *PLoS ONE*. 2014 [accessed 2025 Aug 7];9(2).
<https://pubmed.ncbi.nlm.nih.gov/24558404/>.
<https://doi.org/10.1371/JOURNAL.PONE.0088624>,
66. Nieto-Pascual L et al. Early prophylactic treatment in pregnant women during the 2009-2010 H1N1 pandemic: Obstetric and neonatal outcomes. *Journal of Obstetrics and Gynaecology*. 2013 [accessed 2025 Aug 16];33(2):128–134.
<https://doi.org/10.3109/01443615.2012.740526>
67. Magnus MC et al. Infection with SARS-CoV-2 during pregnancy and risk of stillbirth: a Scandinavian registry study. *BMJ Public Health*. 2023 [accessed 2023 Dec 3];1(1):e000314.
<https://bmjpublichealth.bmj.com/content/1/1/e000314>. <https://doi.org/10.1136/BMJPH-2023-000314>
68. Kwong JC et al. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. *New England Journal of Medicine*. 2018 [accessed 2025 Aug 19];378(4):345–353.
<https://www.nejm.org/doi/pdf/10.1056/NEJMoa1702090>.
https://doi.org/10.1056/NEJMoa1702090/SUPPL_FILE/NEJMoa1702090_DISCLOSURES.PDF
69. Dodds L et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *CMAJ. Canadian Medical Association Journal*. 2007 [accessed 2025 Aug 12];176(4):463–468.
<https://pubmed.ncbi.nlm.nih.gov/17296958/>. <https://doi.org/10.1503/CMAJ.061435>,
70. Hansen C et al. A large, population-based study of 2009 pandemic influenza a virus subtype H1N1 infection diagnosis during pregnancy and outcomes for mothers and neonates. *Journal of Infectious Diseases*. 2012 [accessed 2025 Aug 12];206(8):1260–1268.
<https://pubmed.ncbi.nlm.nih.gov/22859826/>. <https://doi.org/10.1093/INFDIS/JIS488>,

APPENDICES**Appendix A. Variables used associated with each data source.**

Variable	Source	Remark
Year of pregnancy	MOMBABY	
Calendar quarter of pregnancy	MOMBABY	
Year of baby delivery	MOMBABY	
Calendar quarter of baby delivery	MOMBABY	
Mother birth year	RPDB	
Maternal age at baby delivery	RPDB	
Sex on RPDB	RPDB	
Year of death	RPDB	
Mother had a stillbirth (T/F)	MOMBABY	
Number of previous livebirths derived from all mom's delivery records	MOMBABY	
Gestational age in weeks	MOMBABY	
Nearest Census Based Neighbourhood Income Quintile (within CMA/CA)	RPDB	
Rural residence	RPDB	
Public Health Unit	RPDB	
Local Health Integration Network	RPDB	

Households and Dwellings Quintile	ONMARG	
Material Resources Quintile	ONMARG	
Age and Labour Force Quintile	ONMARG	
Racialized and Newcomer Populations Quintile	ONMARG	
Pregnancy overlaps with influenza season	MOMBABY and 01 Nov to 31 MAR every year (provided by PI)	
Pregnancy overlaps with pandemic season	MOMBABY and pandemic period (May 17, 2009, to Feb 6, 2010 (provided by PI))	
Influenza diagnosis in trimester 1	DAD, NACRS, or OHIP	
Influenza diagnosis in trimester 2	DAD, NACRS, or OHIP	
Influenza diagnosis in trimester 3	DAD, NACRS, or OHIP	
Influenza diagnosis during pregnancy	DAD, NACRS, or OHIP	
Influenza diagnosis in trimester 1 at pandemic	DAD, NACRS, or OHIP and pandemic period (May 17, 2009, to Feb 6, 2010 (provided by PI))	

Influenza diagnosis in trimester 2 at pandemic	DAD, NACRS, or OHIP and pandemic period (May 17, 2009, to Feb 6, 2010 (provided by PI))	
Influenza diagnosis in trimester 3 at pandemic	DAD, NACRS, or OHIP and pandemic period (May 17, 2009, to Feb 6, 2010 (provided by PI))	
Influenza diagnosis during pregnancy at pandemic	DAD, NACRS, or OHIP and pandemic period (May 17, 2009, to Feb 6, 2010 (provided by PI))	
Number of prenatal care visits	OHIP	
Trimester prenatal care began	OHIP and MOMBABY	
Asthma prior to pregnancy	DAD, SDS, OHIP, RPDB	ICD-10-CA Codes: J45-46
Diabetes prior to pregnancy	DAD, SDS, OHIP, RPDB, DIN	ICD-10-CA Codes: O24.0, O24.1 O24.3, O24.5, O24.6, O24.7, E10, E11, E13, E14
Hypertension prior to pregnancy	DAD, SDS, OHIP, RPDB, NACRS	ICD-10-CA Codes: I10, I15, O10.0
Heart disease prior to pregnancy	DAD, SDS, OHIP, RPDB, OMHRS, NACRS, IPDB	ICD-10-CA Codes: O10.1, I05-I09, I34-I39, I150.0, I20, I25, Q20-26, O99.4

Type of pre-existing maternal medical conditions	DAD, SDS, OHIP, RPDB, OMHRS, NACRS, DIN, IPDB	
Pregnancy induced hypertension, preeclampsia, eclampsia	DAD	ICD-10-CA Codes: O13, O16, O14, O14.0, O14.1, O14.2, O14.9, O15.0, O15.1, O15.2 O15.9
Gestational diabetes	DAD	ICD-10-CA Codes: O24.4, O24.8, O24.9
Placental praevia	DAD	ICD-10-CA Codes: O44.0, O44.1
Placental abruption	DAD	ICD-10-CA Codes: O45.0, O45.8, O45.9
Mode of delivery	DAD	
H1N1 vaccination during pregnancy	OHIP	

Appendix B. Diagnostic and procedural codes.

Study variable	ICD-10-CA diagnostic code, OHIP fee code, and/or CCI procedure code
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Gestational hypertension, preeclampsia, eclampsia	O13, O16, O14, O14.0, O14.1, O14.2, O14.9, O15.0, O15.1, O15.2 O15.9
Gestational diabetes	O24.4, O24.8, O24.9
Placenta previa	O44.0, O44.1
Placenta abruption	O45.0, O45.8, O45.9
Pre-existing asthma	J45-46
Pre-existing chronic hypertension	I10, I15, O10.0
Pre-existing diabetes	O24.0, O24.1 O24.3, O24.5, O24.6, O24.7, E10, E11, E13, E14
Pre-existing heart disease	O10.1, I05-I09, I34-I39, I150.0, I20, I25, Q20-26, O99.4
Vaginal delivery	5.MD.50, 5.MD.53, 5.MD.54, 5.MD.55, 5.MD.56
Cesarean section	5.MD.60

Appendix C. OHIP fee codes associated with a prenatal visit.

OHIP fee code	Description
A920	Medical management of early pregnancy, initial visit
A921	Medical management of early pregnancy, subsequent visit

A005	Consultation
A006	Re-consultation
A665	Prenatal consult
Q606	Prenatal care - gen. Assess - major prenatal visit
Q607	Prenatal care - min. Assess - subsequent prenatal visit
P002	High risk prenatal assessment
P003	Obs.-prenatal care-general assess - major prenatal visit
P004	Obs.-prenatal care-minor prenatal assess - subsequent prenatal visit
P005	Antenatal health screen