Assessing Obstetrical and Perinatal Outcomes Associated with Maternal Tdap Immunization

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ABSTRACT

Background: In February 2018, Canada's National Advisory Committee on Immunization (NACI) began recommending maternal immunization with pertussis-containing vaccine (Tetanus-diphtheria-acellular pertussis [Tdap]) during every pregnancy as a strategy to prevent pertussis infection in young infants. As a baseline for future evaluation of the NACI policy, this thesis aimed to describe the characteristics of women who received Tdap immunization during pregnancy in the pre-policy time period and assess the relationship between maternal Tdap immunization with obstetrical and perinatal outcomes.

Methods: We performed a population-based retrospective cohort study of all live births in Ontario, from April 2012 to March 2017 using multiple linked provincial health administrative databases. Tdap immunization during pregnancy was ascertained using Tdap-specific immunization fee codes. We used an extended Cox regression model with a time-dependent exposure variable to estimate adjusted hazards ratios (aHR) for preterm and very preterm birth. All other outcomes (gestational hypertension, chorioamnionitis, small-for-gestational-age birth, neonatal intensive care unit admissions >24 hours, composite outcome for neonatal morbidity) were assessed using log-binomial regression to generate adjusted risk ratios (aRR). All estimates were adjusted using inverse probability of treatment weights derived from propensity scores.

Results: Of the 621,903 pregnancies ending in a live birth, 11,750 (1.9%) women received Tdap during pregnancy. The maternal Tdap vaccination rate increased by 8-fold across the study time period, from 4.6 per 1000 women in fiscal-year 2012 to 39.1 per 1000 women in fiscal-year 2016. Women who were nulliparous, residing in a higher-income neighbourhood, and receiving

adequate or intensive prenatal care had the highest vaccination rates. There were no significant increased risks (aHR/aRR [95% CI]) for preterm birth (0.99 [0.87-1.12]), very preterm birth (1.03 [0.71-1.50]), or small-for-gestational-age birth (0.95 [0.90-1.02]) in Tdap-exposed infants. A significant reduction in risk for neonatal hospitalization and morbidity (measured by a composite outcome) was found among exposed infants; however, these associations were attenuated following sensitivity analyses. Among Tdap-vaccinated women, compared to unvaccinated women, there was no association with chorioamnionitis (0.95 [0.79-1.15]), but a 19% lower risk of gestational hypertension was observed (0.81 [0.74-0.90]).

Conclusions: We did not detect any adverse obstetrical or perinatal outcomes following Tdap vaccination during pregnancy. These results complement existing evidence that maternal Tdap vaccination is not associated with adverse outcomes in either the mother or infant. On-going evaluation in Canada is needed as Tdap coverage among pregnant women increases in the coming years.

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LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
aHR	Adjusted hazard ratio
aRR	Adjusted risk ratio
BPA	Best Practice Advisory
CCI	Canadian Classification of Health Interventions
CHEO	Children's Hospital of Easter Ontario
CI	Confidence interval
CIHI	Canadian Institute for Health Information
DAD	Discharge Abstract Database
DTwP	Diphtheria tetanus toxoid and whole-cell pertussis vaccine
EMR	Electronic Medical Record
FY	Fiscal year
GAIA	Global Alignment of Immunization Safety Assessment in pregnancy
HR	Hazard ratio
ICD-10-CA	Canadian implementation of the International Classification of Diseases, 10th Revision
IKN	ICES key number
IPDB	ICES Physicians Database
IPTW	Inverse probability of treatment weights
IRCC	Immigration, Refugee and Citizenship Canada
LMP	Last menstrual period
MNTE	Maternal and Neonatal Tetanus Elimination program
NACI	National Advisory Committee on Immunization
NAOI	Neonatal adverse outcome indicator
NICU	Neonatal intensive care unit
NNV	Number needed to vaccinate
OHIP	Ontario Health Insurance Plan

OHSN	Ottawa Hospital Science Network
ON-Marg	Ontario Marginalization Index
OR	Odds ratio
PCR	Polymerase chain reaction
PROM	Premature rupture of membranes
RAE	Research analytical environment
REB	Research ethics board
R-GINDEX	Revised-Graduated Prenatal Care Utilization Index
RPDB	Registered Persons Database
RR	Rate ratio/risk ratio
SGA	Small-for-gestational age
SOGC	Society of Obstetricians and Gynaecologists of Canada
Tdap	Tetanus-diphtheria-acellular pertussis vaccine
TT	Tetanus toxoid vaccine
UK	United Kingdom
US	United States
UTI	Urinary tract infection
VSD	Vaccine Safety Datalink
WHO	World Health Organization

CHAPTER 1. INTRODUCTION

1.1 Background

Pertussis, a highly infectious and vaccine-preventable illness, has proven to be a public health challenge owing to reoccurring outbreaks across Canada and abroad.[1–5] Infants who have not initiated vaccination or completed their primary vaccine series (i.e., less than 1 year of age) are at the highest risk for pertussis-related morbidity and mortality.[6,7] Pertussis vaccination during pregnancy, using a reduced antigen acellular pertussis-containing vaccine (Tetanus-diphtheria-acellular pertussis [Tdap]), conveys passive immunity to newborns through transplacental transfer of maternal antibodies.[8,9] Hence, maternal Tdap immunization helps to initially protect these highly susceptible infants, until their pertussis vaccine series is initiated at 2 months of age.

In February 2018, Canada joined the many other jurisdictions, such as the United States (US) and United Kingdom (UK), that have incorporated pertussis vaccination during pregnancy into their routine recommendations and practices.[7] Several epidemiological studies have attempted to assess the impacts of maternal pertussis vaccine initiatives by reporting trends and evaluating safety.[10,11,20–22,12–19] Despite this growing collection of literature, however, population-based research on safety within the Canadian context is limited. To help gain support and adherence to the revised vaccine recommendation in Canada, additional research focussing on the Canadian population is required.

Although Canada's policy change is quite recent, some maternity care providers were already vaccinating their pregnant patients against pertussis during the years preceding the official recommendation release. This decision was likely based on Tdap recommendations already in place within the US and UK, temporary recommendations in several Canadian provinces,[23,24] and

persistent pertussis outbreaks occurring throughout the world. While vaccine uptake is anticipated to increase in Canada in the coming years as a result of the new policy in 2018, this thesis aimed to provide a baseline understanding of Tdap immunization practices and safety in the pre-policy era.

1.2 Research objectives

The objectives of this Master's thesis were to:

I. Describe the characteristics of women in Ontario who received or did not receive Tdap immunization during pregnancy in pre-policy era.

II. Assess the association between maternal Tdap immunization with obstetrical and perinatal outcomes in the pre-policy era.

CHAPTER 2. LITERATURE REVIEW

2.1 Pertussis infection

2.1.1 Transmission of pertussis

Pertussis, commonly known as whooping cough, is a highly communicable respiratory illness caused by the bacterial pathogen *Bordetella pertussis*.[25] Pertussis is exclusively transmitted by humans via airborne droplets, as neither animal nor environmental reservoirs have been identified.[26,27] Once transmitted, the bacteria damage the upper respiratory tract cilia by releasing toxins that cause inflammation.[26] The characteristic cough associated with the disease is violent and uncontrollable, often resulting in breathing difficulty.[28] As a result, severely affected individuals occasionally produce a high-pitched "whoop" sound when they attempt to inhale between coughs.[28] As pertussis infection is highly contagious, secondary attack rates can reach as high as 80% among susceptible individuals.[29]

2.1.2 Clinical features of pertussis

The clinical severity of pertussis varies depending on age, immunization status, and prior disease history.[30] Although pertussis can affect all age groups, the potential clinical severity is considerably greater in young infants.[31] The most common source of infant infection is household members, as pertussis infections among adults and older children are often mild or asymptomatic.[32] Even with the presence of a cough, symptoms of pertussis can be mistaken for a generic viral or bacterial infection.[33] In addition, healthcare providers are more likely to misdiagnose pertussis during the winter season, as they face an influx of other viruses (e.g., influenza, respiratory syncytial virus) with a higher observed incidence.[25] In these cases, clinicians occasionally bypass laboratory confirmation through culture or polymerase chain reaction (PCR) analysis.[33]

Globally, pertussis is one of the top 10 causes of childhood mortality (less than 5 years of age), resulting in a disproportionate number of deaths among infants less than 1 year of age.[34] Moreover, infant deaths attributable to pertussis are highly underestimated as pathologists and medical examiners are unfamiliar with clinical manifestations of fatal pertussis pneumonia.[35] Young infants with immature lungs are not able to produce the typical "whoop" sound while coughing, making these cases more challenging to diagnose.[36] These infants often exhibit abnormally long apneic pauses which leads to decreased arterial oxygen levels and severe hypoxia during breathing.[37] As such, approximately 70% of infant deaths from pertussis involve apnea or cyanosis.[38] Paddock et al. suggests that infant deaths, notably those occurring in the first 4 months of life, associated with increases in leukocyte count, bronchopneumonia, or refractory pulmonary hypertension should be suspected of pertussis infection.[35]

Vaccination status has also been associated with the clinical severity of pertussis. Individuals with a history of receiving a pertussis-containing vaccine have been reported to have less severe symptoms and a shorter duration of disease.[39] Barlow et al. found that ever-vaccinated cases of pertussis were significantly less likely to be hospitalized or develop severe pertussis illness, compared to unvaccinated cases.[39] Similarly, patients with up-to-date pertussis vaccinations ceased coughing significantly faster than unvaccinated patients.[39]

2.2 Immunity to pertussis

2.2.1 Vaccination against pertussis

From 1940 to 1990, the United States (US) provided immunization against pertussis using a whole-cell pertussis vaccine, combined with diphtheria and tetanus toxoids (DTwP).[40] Canada introduced a whole-cell pertussis vaccine in 1943, which contributed to a dramatic decrease in pertussis incidence over the subsequent 40 years.[32] Beginning in the 1970s and

1980s, however, the reactogenicity and associated adverse events associated with DTwP vaccination lead to widespread apprehensions towards DTwP safety.[41] Although none of the adverse events were associated with long term consequences,[42] the public perceptions regarding whole-cell vaccine safety ultimately led to the development of an acellular pertussis-containing vaccine.[43] By the 1980s, acellular vaccine development was initiated, and eventually several acellular vaccine variants, containing combinations of five pertussis antigens, underwent further testing in clinical trials.[41] Acellular vaccines demonstrated improved safety and reduced reactogenicity, so by 1998, vaccine recommendations across Canada replaced the whole-cell pertussis vaccine with an acellular pertussis vaccine.[44,45] Due to the high cost of acellular vaccines, however, low resource settings still rely on whole-cell vaccines.[46]

The National Advisory Committee on Immunization (NACI) develops recommendations for immunization use in Canada. Infants and young children are recommended to receive 5 doses of DTaP (Diphtheria, Tetanus and acellular Pertussis vaccine) prior to school entry.[47] Vaccination usually occurs at 2, 4, 6, 12 to 23 months of age, followed by a booster dose at 4 to 6 years of age.[48] Each province follows a slightly varied childhood immunization schedule, however, as provinces are responsible for their own programs. To increase protection after childhood, a booster dose of Tdap (Tetanus, Diphtheria, and acellular Pertussis vaccine containing reduced antigens) during both adolescence (14-16 years) and adulthood (18 years and older) was introduced across Canada between 1999 and 2005.[48,49] Based on a 2014 survey of Canadian adults, however, only 9.3% of adults report receiving the acellular pertussis vaccine after their 18th birthday.[7]

2.2.2 Waning immunity

Adolescents and adults continue to contract pertussis due to waning immunity, as neither pertussis vaccines nor infection provide life-long immunity. Initial US data from 1993 concluded that addressing waning immunity among adults is a critical component for controlling pertussis transmission.[50] In addition, clinical presentation upon reinfection is often asymptomatic or mildly symptomatic, which creates a source of transmission for un- or under-immunized infants.[51]

Canada, US and Australia have found acellular vaccines to be less effective and result in waning immunity more quickly.[52] A Canadian study using passive surveillance data from 1995 to 2005 found that the transition of using a whole-cell vaccine to an acellular was associated with an increase in pertussis incidence among infants and young children (0-4 years).[53]

A case-control study within Kaiser Permanente Northern California found that after the fifth dose of DTaP, the odds of pertussis infection increased by an average of 42% per year (OR 1.42; 95% CI: 1.21, 1.66). The authors translated this 42% annual waning into a DTaP effectiveness from 95% to 71% (i.e. 100-29%) five years after the fifth dose.[54]

In Australia, Quinn et al. studied the duration of protection following the first three doses of DTaP and found the effectiveness of DTaP after the first, second and third dose to be 53.7% (95% CI: 43.8, 61.9), 80.8% (95% CI: 73.5, 86.1) and 83.5% (95% CI: 79.1, 87.0), respectively.[55] The authors reported a sizeable decline in vaccine effectiveness at 3 years of age (59.2% [95% CI: 51.0, 66.0]).[55]

Similarly, Schwartz et al. reported high effectiveness of pertussis vaccines within 3 years of administration but observed evidence of waning immunity beyond 4 years, and almost no protection after 7 years of initial vaccination.[52] The authors reported that among those with up-

to-date vaccination for their age, a 27% increase in odds of pertussis infection was seen after each year that elapsed from acellular vaccine administration.[52] Although acellular pertussis vaccines are considered to be safer, adopting these vaccines may require earlier and more frequent booster vaccinations in order to maintain the community immunity required to achieve disease control.[30]

2.2.3 Cocoon strategy

Cocooning strategies to reduce serious pertussis outcomes in early infancy involve vaccinating close contacts of the newborn (including the mother) immediately postpartum.[56] Countries such as Canada, US, France and Australia initially adopted this strategy to address the short time period of severe pertussis risk during early infancy.[48,57,58] Although cocooning programs achieved moderate coverage among postpartum mothers, obtaining similar coverage among fathers and other family members has proven difficult with this approach.[59] Moreover, the main factor associated with countries, specifically countries with relatively high vaccine rates, experiencing reoccurring outbreaks of pertussis is that immunity wanes without boosting.[60] Thus, protecting infants completely against pertussis via cocooning strategies would require lifelong vaccination of the population—an unfeasible and unrealistic solution.

A Canadian study utilized epidemiologic data from Quebec and British Columbia to determine the number needed to vaccinate (NNV) for a parental cocoon program to be successful.[56] The NNV to prevent 1 infant death, ICU admission, and hospitalization was 1 million, 100,000 and >10,000, respectively.[56] These NNV estimates are based solely on parental immunization and would increase further if other household members were incorporated, as the proportion of infant pertussis attributed to this group is substantially lower.[56] The authors concluded that in regions with lower rates of pertussis (e.g., Canada), the parental cocoon

program is a resource intensive and inefficient method in reducing pertussis-related outcomes in infancy.[56]

2.3 Pertussis epidemiology

2.3.1 Global burden of pertussis

Currently, pertussis is endemic worldwide and despite the widespread use of vaccination, epidemics still occur every 2 to 5 years.[61] The ongoing cyclic nature of the disease depicts the complications involved with achieving complete infection control. In 2008, there were an estimated 16 million cases of pertussis reported worldwide, resulting in approximately 195,000 deaths.[62] Despite these estimates, there are several challenges with reporting the global disease burden of pertussis, particularly in low resource settings. Countries without adequate surveillance infrastructure cannot support routine reporting of clinically suspected pertussis cases.[27] In addition, access to laboratory equipment to perform molecular diagnostic testing, such as PCR, is often limited.[63] Lastly, the number of trained health professionals may be inadequate, which can interfere with accurate case reporting if clinical methods of identifying pertussis cases are not standardized.[27]

2.3.2 Burden of pertussis among infants

In 2012, a notable pertussis outbreak occurred in Canada and the national incidence was 13.9 cases per 100,000.[64] Although incidence rates increased among all age groups, the highest rate was among infants less than 1 year of age (120.8 per 100,000).[64] In addition, the age distribution of pertussis-related hospitalization admissions has remained fairly consistent over time, with the highest proportion continuously being among infants less than 1 year of age.[1]

Infants under 2 months represent the population group with the highest incidence of pertussis (160/100,000),[65] and over 80% of cases in this age group are hospitalized.[6] Despite the

implementation of immunization programs worldwide, newborns (<2 to 3 months of age) remain the most vulnerable for pertussis-related intensive care unit admissions, hospitalizations and deaths.[44,66–68] Studies from the US have shown that from 2001 to 2010, the case-fatality ratio for pertussis was 6.8 per 1,000 infant (<2 months) cases.[69] However, given the fact that pertussis mortality and hospitalization are highly under-reported among infants, the true case-fatality estimates are likely 2- to 3-fold higher than reported values.[70]

A recent Canadian study assessed the impact of changes to Canada's national immunization program, specifically the introduction of the acellular vaccine and addition of adolescent boosters, on infant pertussis hospitalizations between the pre-implementation period (1981 to 1995) and post-implementation period (2006 to 2016).[71] Although infant pertussis hospitalizations have greatly decreased between the two time periods, the burden remained disproportionately high among infants less than 2 months of age during the post-implementation period. The average hospitalization rate during the post-implementation period was highest among infants less than 1 month of age, at a rate of 126.6 per 100,000 infants (95% CI: 113.1, 140.1).[71]

Similarly, a study by Masseria et al. found that among infants less than 12 months of age, those less than 3 and 2 months of age had the highest pertussis incidence rates at 247.7 per 100,000 person-years (95% CI: 214.5, 284.5) and 235.3 per 100,000 person-years (95% CI: 203.7, 270.5), respectively.[72] These findings emphasize the vulnerability of young infants (<3 months) who are too young to complete their vaccination series and remain the most at-risk age group for pertussis infection and related complications.

2.3.3 Resurgence of pertussis

Despite long-standing routine immunization programs and high coverage, high-income countries such as Australia, Belgium France, Germany, the US and Canada, have been experiencing pertussis resurgence.[5,73–75] Between 1991 and 2011, the number of new pertussis cases reported in Australia increased one hundred-fold.[76] The United Kingdom (UK) reported 10 deaths among infants less than 1 year of age in 2012, which was their highest mortality from pertussis since 1982.[77]

In addition to a global resurgence, there has been a noticeable shift in the epidemiology of pertussis. Although pertussis incidence continues to be highest among the youngest infants, incidence among older children and adolescents began to increase during the late 1990s and early 2000s.[6] During a 2004/2005 outbreak in the US, over 30% of pertussis cases were adolescents.[6] Subsequently during the 2010 US outbreak, a substantial number of cases were observed in children aged 7 to 11 years.[6] Likewise, during the 2012 UK outbreak, the number of pertussis cases among children aged 10 to 14 years were much higher than previous years.[6] These trends suggest that despite children being vaccinated according to current recommendations, immunity induced by vaccination is waning earlier than expected.[6] This increased incidence among adolescents and older children is concerning as these age groups are likely reservoirs of infection, adding to the risk of transmission among un- or under-immunized infants.[78]

2.3.4 Epidemiology of pertussis in Canada

Since 1924, pertussis has been under national surveillance in Canada.[1] Vaccination programs targeting pertussis were introduced in 1943 and have had a significant impact in reducing the rates of pertussis.[1] Despite robust immunization programs and high vaccine

coverage, pertussis still remains one of the most common vaccine-preventable diseases in Canada.[1]

After the introduction of the whole-cell pertussis vaccine, the incidence of the disease dropped significantly in Canada. However, beginning in 1990, Canada experienced a notable pertussis resurgence.[2] Several factors have been attributed to this resurgence of pertussis, most importantly, poor effectiveness of the whole-cell vaccine used in Canada between 1980 and 1997[41,67], waning immunity among adolescents and adults, advances in surveillance and diagnostic procedures, and increased physician awareness.[64]

In 2010, Saskatchewan reported 6 pertussis-related deaths among infants under 1 year of age, with an incidence rate exceeding those recorded in California in that same year.[79] Low immunization rates among First Nation communities is believed to be partly responsible for this increase in pertussis incidence.[79] In Ontario, an under-immunized religious community contributed to a prolonged pertussis outbreak beginning in 2011, which subsequently spread to the general population.[80] New Brunswick had over 1400 cases of pertussis reported in 2012, corresponding to almost one-third of the cases reported in Canada.[1] The persistent peaks of pertussis occurring every few years suggests the inability to control the disease by immunization programs currently in place.

2.4 Maternal immunization

2.4.1 Immunity induced by maternal immunization

Immunization during pregnancy is progressively being incorporated into national vaccine recommendation policies as a mechanism to reduce the risk of infection in the pregnant mother, fetus and newborn. During the first few months of infancy, the adaptive immune system is underdeveloped making it difficult to have an effective response that will protect the infant from

various pathogens.[81] Thus, infants rely on the passive transfer of maternal antibodies across the placenta during fetal development for protection during the early months after birth. Yet, the concentration of maternal antibodies transferred is often suboptimal and may not provide the protection required to prevent infection in infancy.[9] Given that an estimated 23% of neonatal deaths and 10% to 50% of stillbirths are thought to be caused by infectious diseases, maternal immunization is a potential strategy to protect newborns from infection.[82–84]

2.4.2 Maternal immunization strategies to date

Maternal vaccination is a promising public health strategy that has been continuing to gain support from both health professionals and the public. Notably, the Maternal and Neonatal Tetanus Elimination (MNTE) program, which involves routine immunization of pregnant women with tetanus toxoid (TT) vaccine, has had a worldwide impact in reducing rates of neonatal tetanus while posing minimal risks to the mother or fetus.[85] For resource-limited areas that lack routine DTaP vaccination during childhood, The World Health Organization (WHO) recommends two doses of TT during the first pregnancy, with one dose in each subsequent pregnancy, to a maximum of five doses.[86] The MNTE program, together with hygienic improvements during delivery, has decreased neonatal tetanus mortality by 92%.[87]

Following the 2009 H1N1 pandemic, a large proportion of case reports were published regarding influenza infections and related complications among pregnant women, which demonstrated the vulnerability of this population.[88] Seasonal influenza also disproportionately affects pregnant women, due to changes in their immune system and overall physiological state.[89] Pregnant women have been shown to have increased rates of febrile, respiratory and cardiopulmonary morbidity during influenza season—complications which have been associated with adverse birth and neonatal outcomes.[90–93] Current recommendations in many countries,

including Canada and the US, recommend annual inactivated influenza vaccination for all women, who are pregnant or may become pregnant during influenza season. This strategy, intended to reduce maternal mortality and adverse birth outcomes associated with influenza infection during pregnancy, has gained support through scientific evidence of the safety and immunogenicity of maternal immunization against influenza.

2.5 Tdap Immunization during pregnancy

2.5.1 Transplacental transfer of immunity

Almost all women have some level of humoral immunity to pertussis, resulting from childhood/adolescent vaccinations or natural infection, but by early adulthood, these serum antibody concentrations reach low and sometimes undetectable levels.[9] Studies have shown that antibody titer in cord blood is much higher for infants whose mother received Tdap before or during pregnancy, compared to unvaccinated mothers.[21,94–96] Further, pertussis vaccination during pregnancy has shown to be up to 93% effective in preventing pertussis infection in infants during the first 8 weeks of life.[8] Thus, receiving a single dose of Tdap during pregnancy will not only protect infants through maternally-derived antibodies, but also reduce the risk of pertussis infection in the mother.[9]

Acquiring high concentration of maternally-derived antibodies, however, has raised concerns of immunological blunting, whereby the presence of maternal antibodies might interfere with the strength of the immune response of young infants after active immunization.[21] Research findings have shown significantly higher levels of maternal antibodies among Tdap exposed infants during their early infancy (<4 months)[21,97,98], with immunological evidence of blunting during their primary series and potentially beyond 12 months.[97] Despite this observed immunological effect, studies evaluating the clinical effectiveness of maternal Tdap vaccination

during the infants' first year of life have shown evidence of protection against pertussis during this time.[99,100] Thus, the underlying mechanism of immune blunting by maternal Tdap vaccination needs to be further investigated to determine if pertussis protection among infants is impacted clinically.

2.5.2 Safety of maternal Tdap immunization

Aspects regarding the safety of maternal pertussis immunization are crucial in the decision-making process. The body of literature examining safety of Tdap vaccination during pregnancy has been increasing, with no findings to-date that suggest an increase in adverse events relating to vaccination. **Appendix I** provides a summary of studies focusing on safety of pertussis vaccines during pregnancy.

DeSilva et al. did not find any significant association between maternal Tdap administration (less than 14 weeks gestation) and microcephaly.[101] Sukumaran et al. determined that women who had previously received a tetanus-containing vaccine and were then administered Tdap during pregnancy were not at any increased risk for acute adverse events or adverse birth outcomes.[17] Donegan et al. found that the rate of stillbirths among women immunized with Tdap was similar to the national stillbirth rate.[12] A recent systematic review was conducted which assessed various adverse outcomes, in both the infant and mother, relating to antenatal Tdap vaccination.[102] The authors did not find any studies which reported an increased risk for preterm birth, small-for-gestational-age (SGA) birth, low birth weight, stillbirth or congenital anomalies after exposure to pertussis-containing vaccines either antenatally, or during the late second or early third trimester of pregnancy.[102] Included in this review were two studies conducted by Morgan et al.[20] and Berenson et al.[10], where there were no associations found between Tdap vaccination during pregnancy and adverse pregnancy (preterm birth, SGA,

premature rupture of membranes [PROM]) or neonatal (low birth weight, birth defects, neonatal intensive care unit [NICU] admissions) outcomes.

Griffin et al. recently conducted a national retrospective observational study using administrative datasets in New Zealand.[14] Adverse events prioritised by WHO and Brighton Collaboration were assessed.[14] Maternal Tdap vaccination was not associated with an increased risk for any primary outcomes, including: preterm labour, pre-eclampsia, pre-eclampsia with severe features, gestational hypertension, fetal growth restriction or post-partum haemorrhage.[14] An unexpected association between Tdap vaccination and an increased rate of lactation disorders was observed, which the authors attributed to residual confounding.[14] Lastly, Tdap vaccination during pregnancy had a protective effect on pre-eclampsia with severe features, preterm labour, preterm delivery and antenatal bleeding.[14] Again, these associations are most likely attributed to residual confounding.[14]

Several studies have examined the local and systemic reactions following Tdap vaccination during pregnancy, and overall the vaccine has been reported to be well tolerated in pregnant women. Fortner et al. found an increased frequency for moderate/severe injection-site pain and malaise in pregnant women following vaccination, however these post injection symptoms were consistent with clinically reported rates for the Tdap vaccine.[13] Petousis-Harris et al. intensively followed 793 pregnant women who had received Tdap during pregnancy for solicited and unsolicited adverse outcomes.[15] Although mild injection site reactions were common, none of the SAEs reported in the study were found to be vaccine-related.[15] Similarly, a study conducted by Regan et al. found location reactions more common among women who received Tdap vaccination compared to influenza vaccination.[103] Despite this slight difference, the results still support the safety of pertussis vaccination during pregnancy.[103]

A cohort study conducted by the Vaccine Safety Datalink (VSD) in the US found a small, but significantly increased, risk of chorioamnionitis following Tdap vaccination during pregnancy (RR 1.19; 95% CI: 1.13, 1.26).[16] However, the VSD study did not find an increased risk for preterm birth[16]— a pregnancy outcome often associated with chorioamnionitis.[104] A subsequent review of the Vaccine Adverse Event Reporting System (VAERS) system in the US found that 58% of women with chorioamnionitis had at least one pre-disposing factor related to the condition.[105] Given this information, the authors concluded that the link between maternal pertussis vaccination and chorioamnionitis was unlikely to be causal.[105] Since various adverse events are expected to occur in any pregnant population, authors must take precautions in order to avoid misinterpreting these occurrences as being vaccine-related.

2.5.3 Current recommendations for Tdap vaccination during pregnancy

In 2006, the Advisory Committee on Immunization Practices (ACIP) in the US initially attempted to reduce the rate of pertussis infection in infants by employing "cocooning" strategies.[57] However, due to the persistent increase in pertussis-related infant mortality, ACIP released a recommendation in June 2011 which advised unimmunized pregnant women to receive the Tdap vaccine during the late second or third trimester.[106] In October 2012, this recommendation was revised to include all pregnant women, regardless of their Tdap immunization history, preferably between 27 and 36 weeks' gestation in each pregnancy, or outside this time period in the case of outbreaks, wound management, and other special circumstances.[107] Following the updated ACIP recommendation, several countries including the UK, Australia, New Zealand, Argentina, Belgium and Israel released similar advisories.

Until very recently, Canada was one of the few high-income countries that lacked a formal recommendation for universal pertussis immunization during pregnancy.[7] As of February 2018,

Canada's vaccine advisory committee (NACI) recommends Tdap immunization during every pregnancy, ideally between 27 and 32 weeks' gestation.[7] Vaccination can be offered from 13 weeks up to the time of delivery in certain situations (i.e. high risk for preterm birth); however, evidence for safety and effectiveness when administered earlier in pregnancy is limited.[7] Although this formal recommendation is recent, some Canadian maternity care providers were already immunizing pregnant women against pertussis in several regions, likely on the basis of demonstrated successes of programs in the US and the UK,[108] pertussis outbreak reports in other countries, temporary provincial advisories prompted by NACI, and partial recommendations released by both the Society for Obstetricians and Gynaecologists of Canada (SOGC)[23] and NACI[24] in 2008 and 2014, respectively. In the 2018 statement, the NACI indicated that administering the Tdap vaccine exclusively for outbreak circumstances was not considered a sufficient method for protecting infants against pertussis.[7] Thus, routine maternal Tdap vaccination is the preferred approach.[7] Although NACI's Tdap recommendations reflect similar policies already adopted by other high-income countries worldwide, regularly conducting studies on vaccine evaluation aids in optimizing uptake and provides confidence to the population regarding safety.[109]

2.5.4 Vaccine uptake

Monitoring the uptake of pertussis vaccines among pregnant women is essential for assessing the success of these recent recommendations, and aids in identifying subgroups of women with low coverage. In a study conducted in Belgium, the maternal Tdap vaccination coverage rate was determined by interviewing pregnant women with subsequent verification using hospital medical data.[110] In their study sample, the documented maternal Tdap uptake was 39.2%; however, when all documented and undocumented vaccine information was taken into account, coverage

increased to 46.0%.[110] In the US, Kerr et al. documented Tdap vaccination coverage during pregnancy to be as low as 9% in 2012 when the recommendations were first implemented, with notable increases to 28% and 54% in 2013 and 2015, respectively.[111] Similarly, a study in Wisconsin reported a gradual increase in Tdap vaccination uptake after the ACIP recommendation release, from 13.8% during January 2013 to 51.0% during March 2014.[112]

During the initial rollout of the 2012 ACIP recommendation in the US, Chamberlain et al. conducted a survey of pregnant women to assess factors associated with intention to receive Tdap during pregnancy.[113] In their cohort, 81% and 92% believed that pertussis infection would have serious health implications for themselves and their infants, respectively.[113] Despite these perceptions, this assessment found that only 44% of pregnant women were willing to actually receive Tdap vaccination during their current pregnancy.[113] As such, the authors advocated for persistent discussion and promotion of the vaccine during routine prenatal visits, especially among vaccine-hesitant mothers, to encourage Tdap vaccination prior to delivery.[113]

A recent study by Greenfield et al. examined whether implementing an Electronic Medical Record (EMR) based intervention, called "Best Practice Advisory" (BPA), would improve adherence to Tdap vaccination during the optimally recommended time period (i.e. 27 to 32 weeks' gestation).[114] The BPA intervention, built within the EMR, alerts clinicians during the mother's visit to provide Tdap during this optimal window.[114] The authors report a significant increase in optimally-timed Tdap vaccination, from 91% before to 96% after BPA implementation ($P<.0001$).[114]

Studies on predictors of maternal vaccine uptake have demonstrated the importance of physician recommendations on vaccine acceptance.[113,115–118] Health care providers are not only highly trusted by their patients, but also the most common source for receiving general

information on maternal and childhood vaccines.[116,118–120] Danchin et al. found this especially true for first-time mothers, who reported greater levels of vaccine hesitancy and overall concerns.[121] However, providers can often feel unprepared to discuss immunization during pregnancy with mothers, as a result of inadequate knowledge and training.[122] In addition to encouragement by health care providers, other barriers to vaccine uptake during pregnancy include lack of awareness about the disease, as well as insufficient information regarding the safety of maternal vaccination.[118,123] Thus, in order for pregnant women to make an informed choice, that best meets their needs and values, they must be presented the information in an accurate manner, and encouraged to be engaged and involved in the overall decision-making process.[122]

2.6 Rationale for this thesis

Although several studies have been published regarding the safety of Tdap vaccination during pregnancy, evidence from large cohorts with high quality data is warranted for evaluating maternal and neonatal outcomes, particularly outcomes that are rare. Furthermore, studies currently available focus on recommendations within the US, UK and Australia, revealing a need for research within the Canadian context.

Understanding how maternal Tdap vaccination existed prior to the 2018 NACI recommendation will help to highlight trends and characteristics associated with vaccine participation, as well as identify any potential barriers. Also considering how recent the NACI recommendation was released, pregnant women require ongoing safety evidence to increase uptake during pregnancy. Providing national data on infant-pertussis epidemiology that is relatable to the public will aid in gaining support and reassurance from the pregnant population

in Canada. In addition, studying the implications of maternal Tdap vaccination within a local context will provide new data on Canadian women—a population who might have discrepancies in their immunological profiles, owing to Canada's specific formulations and schedule for pertussis vaccination.

CHAPTER 3. METHODOLOGY

3.1 Study design

This was a population-based retrospective cohort study utilizing multiple health administrative databases housed at ICES. We included all hospital live births in the Canadian province of Ontario, between April 1, 2012 and March 3, 2017. Our study time period encompassed 5 years of data prior to the 2018 NACI recommendation on Tdap immunization in pregnancy.

3.2 Study population

The birth cohort for Objectives 1 and 2 was assembled using linked maternal-newborn records within the MOMBABY database. We first excluded maternal and infant records for administrative reasons including invalid identifiers (i.e. invalid IKN for either mother or infant) and linkage warnings (e.g. duplicate records, invalid date of birth). To allow for complete exposure and outcome information we additionally excluded maternal records belonging to non-Ontario residents or women who did not have continuous enrolment in the Ontario Health Insurance Plan (OHIP) during the study period. Further, infant records with implausible birthweight and gestational age combinations were excluded. Following these administrative data exclusions, we applied our study exclusions for maternal records belonging to women younger than 12 years or older than 50 years of age and infant records indicating a stillbirth. Lastly, we excluded maternal and infant records with any missing covariate information.

3.3 Data sources

3.3.1 MOMBABY database

The MOMBABY database contains inpatient admission records of delivering mothers and their respective newborns (including stillbirths), which are linked by a unique matching identifier on each hospitalization record. This administrative dataset, maintained and annually updated at ICES, links approximately 98% of maternal-infant records for in-hospital deliveries in Ontario.[124] This database was used to assemble our study cohort, as well as collect maternal and newborn information such as gestational age at birth, maternal age, birth weight, baby's sex, parity and plurality.

3.3.2 ICES Registered Persons Database (RPDB)

The ICES **Registered Persons Database (RPDB)** is a demographic repository containing information on all Ontario residents eligible for publicly-funded health care in the province.[125,126] The RPDB was used to establish the duration for which each participant was eligible to receive health care services, as well as obtain demographic information regarding neighbourhood income quintiles and region of residence.[125,126]

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

The Canadian Institute for Health Information **Discharge Abstract Database (CIHI-DAD)** captures demographic and clinical information regarding hospital admissions from all acute care institutions throughout Canada.[127] Standard diagnostic ICD-10-CA codes (Canadian implementation of the International Classification of Diseases, 10th Revision) and procedural or interventional CCI codes (Canadian Classification of Health Interventions) are used to document clinical information pertaining to the admission.[128] We used this database to collect information from both the mothers and newborns regarding medical diagnoses (e.g., gestational diabetes),

interventions (e.g., neonatal ventilatory support), number of previous preterm deliveries, as well as admissions and discharges to any special care units (e.g., neonatal intensive care unit).

3.3.4 Ontario Health Insurance Plan (OHIP) claims database

The **Ontario Health Insurance Plan (OHIP) Database** contains health care billing information made by physicians, or other health care providers, for service reimbursement.[125] This database includes information on the diagnosis (i.e., reason for the visit), type of service received, and the associated billing code. Specific OHIP fee codes are used when a vaccine is administered, which provided the information to identify our exposure group.[125] In addition, we identified prenatal care visits (via OHIP fee codes) and health care provider specialties (via SPEC variable) through from this database.

3.3.5 Immigration, Refugee and Citizenship Canada (IRCC) Permanent Resident Database

The **Permanent Resident Database**, led by **Immigration, Refugee and Citizenship Canada (IRCC)**, contains records of permanent residents that immigrated to Canada.[129] The Ontario portion of the IRCC Permanent Resident database was used to collect information regarding maternal country of birth.

3.3.6 ICES Physician Database (IPDB)

The **ICES Physician Database (IPDB)** comprises information from OHIP Corporate Provider Database, the Ontario Physician Human Resource Data Centre database and the OHIP database of physician billings.[130] IPDB contains yearly collected demographic information pertaining to all physicians in Ontario, such as specialty training, year of graduation and whether medical training was completed in Canada.[130] This database was used specifically for Objective 1 of the thesis to describe the care provider characteristics for women who received the Tdap vaccine during pregnancy.

3.3.7 Ontario Marginalization Index (ON-Marg)

The **Ontario Marginalization Index (ON-Marg)**, adapted from the Canadian Marginalization Index (CAN-Marg), is a data tool that quantifies the level of marginalization occurring in Ontario. This multifaceted index uses data from Statistics Canada's Census and consists of four dimensions that indicate marginalization: residential instability, material deprivation, dependency and ethnic concentration.[131] The residential instability dimension indicates area-level concentrations of family or housing instability and relates to the overall neighborhood quality, support and cohesiveness.[131] Material deprivation measure indicates the inability for individuals and communities to acquire and access basic material needs by including measures of income, education, housing quality and family structure.[131] The dependency dimension refers to area-level concentrations of individuals who do not receive an income through employment (e.g., children, seniors and adults without paid employment).[131] Lastly, ethnic concentration identifies high area-level concentrations of recent immigrants (past 5 years) and visible minorities (self-identified). Scores corresponding to each of these four dimensions were previously divided into quintiles, where quintile 1 represents areas that are the least marginalized and quintile 5 represents the most marginalized areas.

ON-Marg has been extensively used in research and has demonstrated stability across varying time periods and geographic locations (i.e., urban and rural areas).[131] Further, greater marginalization identified through this index has been shown to be associated with many adverse health outcomes including hypertension, depression, smoking among youth, alcohol consumption, injuries, and low infant birth weight.[132–137]

3.4 Data linkage, data access, privacy and ethical considerations

Linking records across administrative databases is an important tool, as it allows information from individuals to be combined across multiple data sources. ICES implements numerous policies, procedures and practices to ensure privacy protection for individuals whose personal health information is stored at ICES under section 45 of Ontario's Personal Health Information Protection Act (PHIPA).[138] Each successfully linked patient record is assigned a unique encrypted ICES key number (IKN), which allows for confidential linkage of individual patient health information across all databases. The unique IKN used by ICES facilitates successful and confidential linkage across various datasets, as all patient identifiers are removed before researchers are granted data access.

To further decrease the risk of re-identification, no dates were provided on any of the study datasets. For each maternal-newborn record, 'day zero' corresponded to the LMP (derived by the ICES Analyst using infant's date of birth and gestational age at birth). All health care encounters during pregnancy (e.g., Tdap immunization) or at/after the birth (e.g., admission to the NICU) were given a number corresponding to the number of days that had passed in relation to day zero, with no reference to any calendar dates. To ensure privacy compliance, the de-identified, linked data were accessed and analysed only within the secure, online research analytical environment (RAE) at ICES. Prior to gaining access to ICES information, successful completion of privacy and ethical training took place.

Research ethics board (REB) approval was acquired from the Children's Hospital of Eastern Ontario (CHEO) Research Ethics Board, the Ottawa Hospital Science Network (OHSN) Research Ethics Board, and the ICES Privacy Office (see **Appendix II** and **III** for approval forms).

3.5 Data cleaning and preparation

3.5.1 Missing data

Infant records with missing information on gestational age and birth weight were excluded, since these variables were an integral part of defining our perinatal outcomes. Similarly, infant records that were not classified as either male or female were also excluded, as sex was required for determining if an infant was small-for-gestational age at birth—a perinatal outcome assessed in this study. Maternal records with missing covariate information regarding income, rural residence, parity, preterm birth history and dimensions of marginalization were additionally excluded. We did not use any imputation methods in our model analyses, as less than 1% of records had missing information for any characteristic, and the cumulative percentage of records missing information across all variables was close to 1%. Imputing these missing values were unlikely to impact our findings, thus we used a complete case analysis in all our statistical analyses.

3.5.2 Implausible birth weight and gestational age combination

Birth weight and gestational age were critical for defining our perinatal outcomes, therefore, as part of our data cleaning and pre-processing ,we used an algorithm described by Basso and Wilcox to identify records for which the infant's birth weight was incompatible with the documented gestational age.[139,140] This process identifies records with likely errors by computing z-scores based on estimates of gestational age and birth weight. Using data from the current study, we first calculated the median birth weight within each sex-and-gestational-age stratum, between 25-42 weeks' gestation. Next, we utilized the population-based Canadian reference standard, developed by Kramer et al.[141] to acquire standard deviation estimates for each sex-and-gestational age stratum. A birth weight z-score was then calculated by subtracting the stratum-specific medians (generated from the current dataset) from each infant's documented

birth weight and dividing by the population reference standard deviation (as documented by Kramer et al.).[141]

The criteria for which infant records were flagged as having an implausible birth weight-gestational age combination, differed depending on if the infant was born at term or preterm gestation.[139,140] For term infants (≥37 completed weeks), records with an absolute z-score of 5 or greater were flagged as implausible. For preterm infants (<37 weeks), records with a z-score outside the range of -4 and +3 standard deviations were excluded. This cut-off was used because heavier preterm infants are more likely to be flagged for errors in their gestational age and birth weight.[139,140] All records flagged for implausible birth weight-gestational age combinations were excluded from the study cohort.

3.6 Exposure measurement

The main exposure was receiving a pertussis-containing vaccine during pregnancy. Immunization against pertussis is given in combination with tetanus and diphtheria (tetanus-diphtheria-acellular pertussis: Tdap). In Ontario, this vaccine is primarily administered by physicians, and thus the OHIP billing code specific to Tdap administration in adults (code: G847) was used to identify exposure status. We categorized Tdap immunization as occurring during pregnancy if the vaccine was administered 14 days after the LMP (i.e., probable ovulation/fertilization) through to 1 day before delivery. These cut-offs were used to avoid misclassifying vaccines given prior to the onset of pregnancy or in the post-partum period.

3.7 Outcome measurement

Section 3.7.1 describes outcome measurements that apply to Objective 1, while the remaining sections apply to Objective 2.

3.7.1 Tdap vaccination during pregnancy

The outcome of interest for the Objective 1 of this thesis was Tdap vaccination during pregnancy. This was defined as the total number of women who received Tdap between the estimated date of conception (14 days after LMP) through to 1 day prior to delivery. We examined immunization rates across a variety of characteristics including maternal, temporal, and pregnancy characteristics. Further, as the study time period encompasses five years of pre-policy data, we additionally described care provider characteristics by Tdap immunization status to report any meaningful differences.

To describe care provider characteristics, we assessed the type of physician that provided the majority of prenatal care to vaccinated and unvaccinated women. Prenatal visits were defined by limiting to one record per person per type of doctor per day. Only visits with an associated OHIP fee code related to prenatal care (refer to **Table 3-1**) were included in this definition. Physician specialties were assigned using the specialty variable (SPEC) within the OHIP database, which specifies the physician specialty for payment purposes. Only visits to a family physician/general practitioner and obstetrician were included. Women were assigned the type of physician (family physician or obstetrician) providing the "majority" of prenatal care, which was defined as at least 75% of the total number of prenatal care visits. If neither type of physician provided three-quarters or more of the prenatal care (i.e. <75% of visits to both providers), then the category of "mix of providers" was assigned. The prenatal care visits were assessed for provider assignment over two time periods: (1) health care visits occurring from 20 weeks' gestation until the day

before delivery; (2) health care visits occurring from 27 to 32 weeks' gestation (i.e. optimal timing for Tdap vaccination). Lastly, amongst vaccinated women, the characteristics of the provider who administered the Tdap vaccine was reported using the IPDB database (refer to **Section 3.3.6** for database details).

Table 3-1. 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

3.7.2 Obstetrical outcomes

The two obstetrical outcomes assessed in the study, along with their definitions and diagnostic codes, are presented in **Appendix IV**. We identified cases of gestational hypertension and chorioamnionitis using ICD-10 codes that were present on any maternal antenatal hospitalization record from the LMP to the date of delivery, including the delivery hospitalization itself, available in the DAD (refer to **Appendix IV**).

Gestational hypertension, defined as hypertension in pregnant women (blood pressure >140/90mmHg) after 20 weeks of gestation without the presence of proteinuria or preeclampsia,[142] was the first obstetrical outcome assessed. The diagnostic codes identify cases of gestational, or pregnancy-induced, hypertension without the presence of proteinuria (ICD-10

code: O13), as well as general cases of unspecified maternal hypertension (ICD-10 code: O16). Preeclampsia and eclampsia were not included in this outcome definition.

Chorioamnionitis, the second obstetrical outcome assessed, is an acute inflammation of the chorion and membranes of the placenta due to a bacterial infection and can affect up to 1-2% of term and 5-10% of preterm pregnancies.[143] Chorioamnionitis is associated with several adverse maternal and fetal outcomes, including stillbirth, rupture of membranes, premature labour, developmental delays and childhood asthma.[144,145] Accessing uncontaminated amniotic fluid (through amniocentesis) or placental culture for diagnosis assessment requires invasive procedures and is therefore generally avoided.[143] Thus, diagnosis of chorioamnionitis is initially based on clinical symptoms, with later confirmation with laboratory testing.[143] Maternal fever is the key clinical symptom as it is present in approximately 95% to 100% of cases of chorioamnionitis. Along with the presence of fever, two additional symptoms are required for diagnosis of chorioamnionitis: uterine tenderness, maternal tachycardia (>100 beats/min), fetal tachycardia (>160/min) and purulent or foul-smelling amniotic fluid.[146–148] The diagnostic codes associated with this outcome are presented in **Appendix IV.**

3.7.3 Perinatal outcomes

The perinatal outcomes selected for this study were based on prior research on vaccine safety, for their overall importance to perinatal health, and to align with recommendations made by the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) network.[149] The guidelines established by GAIA are intended to create a global and common understanding of priority outcomes and approaches to monitor the safety of vaccines administered during pregnancy.[149] A list of the perinatal outcomes assessed in Objective 2, along with detailed

definitions, associated data sources, and diagnostic/intervention codes, is presented in **Appendix IV**.

Infants born prior to 37+0 completed weeks of gestation were defined as being a **preterm birth**. In addition, the subgroup of **very preterm birth**, birth before 32+0 weeks of completed gestation, was also assessed. The gestational age of the infant was identified using a specific variable within the MOMBABY database. Although the method of gestational age determination is not documented within the MOMBABY database, approximately 95% of women in Ontario undergo prenatal ultrasonography prior to 20 weeks' gestation, improving the accuracy of gestational age estimates at birth.[150]

Small-for-gestational-age (SGA), an indicator for fetal growth restriction, is often associated with an increased risk for fetal and infant mortality and morbidity.[151] Due to the difficulties of measuring growth in-utero, fetal growth is estimated at birth using a combination of the infant's sex, gestational age, and birth weight. Size for gestational age was determined using an algorithm (SAS macro code) developed by the University of Manitoba and based on a Canadian reference standard published by Kramer et al. (2001).[141] Using the Kramer et al. growth tables,[141] infants in this study were considered SGA if they were below the 10th percentile of the sex- and gestational age-specific birth weight distribution.

Neonatal intensive care unit (NICU) admissions lasting greater than 24 hours were identified by computing the length of stay for each infant encounter to the NICU, using special care unit (SCU) admission and discharge variables within the DAD. As reported by a Canadian study, infants delivered via cesarean are more likely to be admitted to the NICU for short term medical observation (less than 24 hours), compared to infants delivered vaginally.[152] These findings suggest that cesarean delivery can be a predominant reason for short-term NICU

admissions among low-risk infants;[152] therefore, we designated a threshold of 24 hours to exclude these cases.

An infant was considered to have a NICU admission if there were any documented admissions to an SCU during the neonatal period (i.e., admitted within the first 28 days after birth), with SCU values on the DAD record of 50, 51, 52, or 53. The infant record within the DAD also included information regarding any transfers to another hospital facility. For privacy reasons, exact admission and discharge dates were not provided; instead, the number of days from birth to the first, second, third etc. admission and corresponding discharge was given. For each NICU admission, the number of days from birth to NICU admission was subtracted from the number of days from birth to discharge to determine the length of stay. Infants with lengths of stay above 1 day (i.e., 24 hours) were classified as having this outcome.

Severe adverse outcomes in infants, such as seizures and intraventricular hemorrhage, are difficult to study due to their low incidence. These individual outcomes require a large sample size to detect subtle differences across groups. To overcome these challenges, Lain et al. developed and validated a composite **neonatal adverse outcome indicator (NAOI)**, which includes ICD-10 diagnosis and procedural codes (Australian-modified version) associated with occurrences and treatments of severe infant events.[153] The NAOI, which includes 15 neonatal diagnoses and 7 procedures (refer to **Appendix V** for the complete list), can be used with population health data to reliably identify infants with severe morbidity at birth. Infants having one or more of the neonatal conditions (e.g., cerebral infarction, seizures, sepsis etc.) and procedures (e.g., resuscitation, blood transfusion, ventilatory support etc.) included in composite outcome are identified with the NAOI.[153] We used a Canadian adaptation of the NAOI, reported by Ramage et al.,[154] which encompassed ICD-10-CA and CCI codes to replace the original

Australian diagnostic and procedural codes, respectively. The NAOI was measured using database variables within MOMBABY, supplemented with diagnostic and procedural codes for any other infant records, up to 28 days of life, within the DAD (refer to **Appendix V**).

3.8 Confounding variables

Potential confounding variables, identified *a priori*, were selected based on previous studies[10,11,14,16,18–20,101,155] as well as demographic and clinical variables readily available within the study databases. **Appendix VI** provides a complete list of the potential confounding variables included in our models for adjustment of our estimates, described below.

3.9 Propensity score adjustment

In 1983, Rosenbaum and Rubin introduced the concept of propensity scores, which represent the probability of treatment assignment conditional on the measured observed covariates in the propensity score model.[156] In observational studies, propensity score methods are frequently applied to estimate treatment effects when randomization of treatment is not possible.[157] In theory, the propensity score is a balancing score—exposed and unexposed participants with the same propensity score will be similar in terms of their distribution of baseline covariates and propensity to be exposed.[157] Methods of propensity score adjustment rely on two assumptions: conditional independence and common support.[156] Conditional independence assumes that treatment assignment is independent of potential outcomes conditional on the observed baseline covariates.[156] Common support assumes that every subject has a nonzero probability to receive either treatment.[156] When these conditions are satisfied, treatment assignment is assumed to be strongly ignorable.[156]

In studies using large administrative databases, propensity score methods have exhibited higher success in reducing confounding bias compared to conventional methods of multivariable adjustment.[158,159] However, complete consensus as to which variables to include in the propensity score model is generally lacking. Covariate selection often consists of choosing from the following possibilities of variable sets: all measured baseline covariates, baseline covariates associated with the exposure, covariates that affect the outcome (i.e., potential confounders), or covariates the affect both the exposure and outcome (i.e., true confounders). In practice, however, it is often difficult to distinguish which category the potential covariate belongs to. Thus, in most situations, it is generally safe to include all characteristics measured at baseline in the model.[160,161]

We used a logistic regression model to compute a propensity score for each participant, which represented the predicted probability of receiving the Tdap vaccine during pregnancy, conditional on the variables included in the model. All measured baseline covariates available in the selected databases were included in the model (refer to **Appendix VI**). We assessed our propensity score model by creating side-by-side histograms displaying the distribution of estimated probability scores by exposure status. The range of propensity scores within the two groups was evaluated to ensure appropriate balance and overlap. Additionally, the c-statistic, or area under the receiver operating characteristic curve, was used to assess model fit.

3.9.1 Stabilized inverse probability of treatment weighting

After establishing our propensity score model, we computed inverse probability of treatment weights (IPTW) based on our propensity scores to control for confounding. Theoretically, weighting individual study records with IPTWs forms a pseudo-population in

which the distribution of baseline covariates is independent of the treatment assignment (i.e., the exposure).[157] Each subject was assigned a weight which represented the inverse of the predicted probability of exposure. For example, subjects that received an "expected" treatment based on the propensity score (i.e., high propensity score and received the vaccine) had a smaller weight, whereas subjects that received an "unexpected" treatment (i.e., low propensity score and received vaccine) had a larger weight. To assist with extreme and influential weights, we calculated stabilized IPTWs. In this technique, the weights for exposed and unexposed subjects are separately multiplied by a constant, which is equal to the average predicted probability (i.e., average propensity score) in the entire study population. Stabilization does not influence the point estimate of the treatment effect; however, it does reduce the overall variance and helps to increase precision.[160] **Equations 1** and **2** shown below were used to calculate the stabilized IPTW for vaccinated and unvaccinated subjects, respectively. In these equations, *PS* signifies the propensity score, *i* is the vaccinated person, *j* is the unvaccinated person, *NT* is the total number of vaccinated subjects, and *NC* is the total number of unvaccinated subjects.

$$\frac{\sum_{i=1}^{N_T} PS_i}{N_T} * \frac{1}{PS_i}$$

Equation 1: IPTW calculation for vaccinated subjects

$$\frac{\sum_{j=1}^{N_C} (1 - PS_j)}{N_c} * \frac{1}{(1 - PS_j)}$$

Equation 2: IPTW calculation for unvaccinated subjects

3.10 Objective 1 statistical analyses

For Objective 1 of this thesis, Tdap immunization rates and their 95% confidence intervals (CI) were calculated across various demographic characteristics. Vaccination rates among the various groups were compared by calculating unadjusted rate ratios (RR) and 95% CI. The association between maternal Tdap vaccination and each demographic predictor was further assessed by calculating adjusted RR and 95% CI, using a log-binomial regression model while controlling for all other predictors. In this model, Tdap vaccination and all predictor characteristics were treated as the dependent variable and independent variables, respectively.

3.11 Objective 2 statistical analyses

3.11.1 Descriptive analyses

We used frequencies to describe the distribution of baseline categorical variables between mothers who did or did not receive the Tdap vaccine during pregnancy. Standardized differences were calculated before and after weighting using the stabilized IPTWs, to assess whether weighting improved comparability between the two exposure groups, as well as to additionally evaluate our propensity score model. The formula for calculating standardized differences to assess the balance of two groups is defined in **Equation 3**, where $\hat{P}$*treatment* and $\hat{P}$*control* signify the prevalence or mean of the binary variable in exposed and unexposed subjects, respectively.[162]

$$d = \frac{(\hat{p}_{\text{treatment}} - \hat{p}_{\text{control}})}{\sqrt{\frac{\hat{p}_{\text{treatment}}(1-\hat{p}_{\text{treatment}}) + \hat{p}_{\text{control}}(1-\hat{p}_{\text{control}})}{2}}}$$

Equation 3: Standardized difference calculation for dichotomous variables

Considering the size of our study population, *P* values were not appropriate as they are highly influenced by sample size. Unlike *P* values, standardized differences quantify the

magnitude of differences between the exposure groups regardless of the sample size. An absolute value above 10% was considered indicative of imbalance of baseline covariates across the two exposure groups.[160,163]

3.11.2 Cox regression model

Two different regression models were employed based on the type of outcome being assessed. We used a Cox regression model, with a time-dependent exposure variable, for the preterm and very preterm birth outcomes. The Cox model, a semiparametric model introduced in 1972,[164] is used for analysis of time-to-event outcomes. The follow-up for each infant started at the estimated LMP and ended either when the outcome occurred, or if the outcome was no longer possible in the pregnancy (i.e., no longer at risk). The at-risk gestations were censored upon completing 32+0 weeks and 37+0 weeks, for very preterm and preterm birth outcomes, respectively, since ongoing gestations after those thresholds are no longer at risk for the outcomes.

An advantage of the Cox model is the ability to encompass a time-varying exposure, which helps to reduce potential temporal bias arising from women with longer gestations having more 'opportunity' to receive Tdap vaccination during their pregnancy.[165] In this approach, any follow-up time after LMP and prior to vaccination among vaccinated women was treated as non-exposed. Their follow-up time was then reclassified as exposed time from the date of vaccination until the end of the at-risk time period or until the event. Similar to the approach used by Kharbanda et al.,[16] we also limited analyses to Tdap administration at 36+0 weeks' gestation or earlier and at 31+0 weeks' gestation or earlier, for preterm (<37 weeks' gestation) and very preterm (<32 weeks' gestation) birth, respectively. This additional precaution was taken to further reduce bias as a result of differences in potential exposure periods. Using an extension of

the Cox proportional hazards regression model, with gestational age in days as the time scale, we computed unadjusted and adjusted hazard ratios (HR) for these two outcomes, with corresponding 95% CI. Robust sandwich variance estimation was used to account for the lack of statistical independence across repeated observations. Estimates were adjusted to control for confounding using stabilized IPTW based on propensity scores (refer to **Section 3.9**).

3.11.3 Log-binomial regression model

We used a log-binomial model to compute risk ratios (RR) and 95% CI for the remaining outcomes: gestational hypertension, chorioamnionitis, SGA, NICU admission >24 hours, and the NAOI composite outcome. We computed adjusted estimates to control for confounding using stabilized IPTW as described in **Section 3.9**.

P values were two-sided at a 0.05 significance level for all outcomes, and statistical analyses were conducted using SAS version 9.4.

3.12 Sensitivity analyses

We conducted a series of sensitivity analyses to assess the potential impact of analytical strategies on our main findings from Objective 2.

3.12.1 Propensity score matching

Four different propensity score methods have been described to adjust for confounding: IPTW, propensity score matching, stratification on the propensity score and covariate adjustment using the propensity score.[156,160] Yet, no clear consensus has been reached on which of these four methods are the most appropriate depending on the type of observational study being conducted.[157,161,166] Thus, to assess the robustness of our IPTW-adjusted analyses, we additionally applied a second method of confounding adjustment through propensity scores—

propensity score matching. Matched sets of Tdap-exposed and unexposed subjects were established based on similar propensity score values. Propensity-score matching is frequently utilized within medical and social sciences literature, including in studies evaluating the safety of vaccines.[167–170]

As part of our first sensitivity analysis, adjusted estimates (HR and RR) calculated in the main analyses were reproduced but using propensity score matching to control for confounding. For each Tdap-exposed subject, we matched 5 unexposed subjects (1:5 ratio). Subjects were matched without replacement, using the greedy method and a caliper width score of ±0.2 standard deviations. Greedy matching is a linear matching algorithm which involves randomly selecting an exposed subject and then matching the unexposed subjects with the nearest propensity score.[167] Once the match is created, the matched sets are removed from any further possibility of matching—even if a better suited control is present in subsequent matches. The criteria for determining if exposed and unexposed subjects have similar propensity scores is established with a specified caliper width distance. Currently, a uniform definition for an acceptable caliper distance is lacking.[167] Rosenbaum and Rubin originally used a caliper of 0.25 standard deviations.[156] Based on more recent findings by Austin et al., however, a tighter caliper of 0.2 standard deviations is preferred, especially when the pool of unexposed subjects is large, as was the case with our study.[171]

3.12.2 Tdap probable vaccination

As reported by Schwartz et al., newer vaccine-specific codes in the OHIP database have lower sensitivity than general immunization codes.[172] As such, a sensitivity analysis was conducted using a more liberal exposure definition, in order to also include any instances of

probable Tdap vaccination during pregnancy. Unlike the definite cases included in our primary analyses, *probable* vaccination additionally incorporated general OHIP vaccine codes [OHIP fee codes: G538, G539] that were billed during pregnancy. The exception was general vaccine codes that were administered during influenza vaccination season (between October 1st to January 31st, annually), as immunization during this time was more likely to have been influenza vaccine. We repeated all of our main statistical analyses with this alternate definition of our exposure (i.e., Tdap *probable* vaccination), and compared the results to our main findings.

3.12.3 Health care utilization

The decision to seek medical care is correlated with individual subject characteristics. To account for potential differences between Tdap-vaccinated and unvaccinated women relating to maternal health care utilization and access, we separately introduced two additional covariates in our original propensity score adjusted models. The first variable identified women with ≥2 outpatient visits during the 6 months prior to pregnancy, while the second identified women with ≥1 non-obstetric hospitalization during the 2-year period prior to the index pregnancy. For these two sensitivity analyses, we separately restricted the study cohort to women with continuous OHIP eligibility for the 6 months and 2 years prior to pregnancy.

3.12.4 Prenatal care index

The importance of adequate prenatal care on maternal vaccine acceptance has been continuously shown in the literature. Kharbanda et al. reported higher Tdap coverage among women that received early prenatal care[173] and Morgan et al. found that women who refused Tdap vaccination during pregnancy were more likely to begin prenatal care later and require high-risk obstetrical care referrals.[20] Similarly, fewer prenatal care visits prior to 32 weeks'

gestation has been associated with lower uptake of influenza vaccination during pregnancy.[174] An increase in biased estimates, specifically toward poorer outcomes among unvaccinated mothers, has been reported when prenatal care is not considered in the analyses.[10]

Based on these findings, we additionally adjusted our main propensity score adjusted models for adequacy of prenatal care using the Revised-Graduated Prenatal Care Utilization Index (R-GINDEX). The R-GINDEX, proposed by Alexander and Kotelchuck,[175] has 6 categories of prenatal care based on the current ACOG recommendations: inadequate, intermediate, adequate, intensive, no care, and missing. This index is preferred over the commonly used Kessner index, which is limited to 9 visits and not reflective of current recommendations for prenatal care.[176] Additionally, the R-GINDEX is less susceptible to effect modification by gestational age when assessing relationships between inadequate prenatal care and adverse perinatal outcomes, such as SGA or low birth weight.[177]

The index calculation relies on three pieces of information: the gestational age of the infant, the trimester during which prenatal care was initiated, and the total number of prenatal care visits during pregnancy. At 40 weeks' gestation, for example, a woman who initiated prenatal care in the first 3 months of pregnancy and received between 13 to 16 visits would be classified has having adequate prenatal care, while a woman who began care between 1 to 6 months of pregnancy and had less than 8 visits would be classified as having inadequate care.[177] The intensive prenatal care category identifies women with an unexpectedly large number of visits, which might suggest the presence of maternal morbidity or complications.[175]

Prenatal visits were defined by limiting to one record per person per type of doctor per day. Only visits with an associated OHIP fee code related to prenatal care (refer to **Table 3-1**) were included in this definition. We calculated the R-GINDEX using a published coding

algorithm.[178] None of the women were categorized into the missing prenatal care category, as records with missing information regarding gestational age were excluded when initially assembling the study cohort. After assigning the appropriate prenatal care category to each pregnancy, this additional covariate was added to our adjusted models to determine the impact on our original adjusted estimates for study outcomes.

CHAPTER 4. RESULTS

4.1 Characteristics of study population (both objectives)

During the study period (April 1st, 2012 to March 3rd, 2017), 690,510 total births were identified within the MOMBABY database (**Figure 4-1)**. We excluded 39,554 (5.7%) infant and maternal records due to data linkage warnings or invalid IKNs and 19,403 (2.8%) maternal records due to interrupted OHIP eligibility during pregnancy. After applying administrative data exclusions (listed in **Figure 4-1**), 631,351 live births remained. Of these, an additional 9,448 (1.5%) records were excluded due to missing covariate information (n=8,186), having an implausible birth weight/gestational age combination (n=634) or the infant being a stillborn (n=628). Our final study cohort, therefore, consisted of 621,903 live births, of whom 11,750 (1.9%) were born to mothers who received Tdap vaccination during pregnancy (**Figure 4-1**).

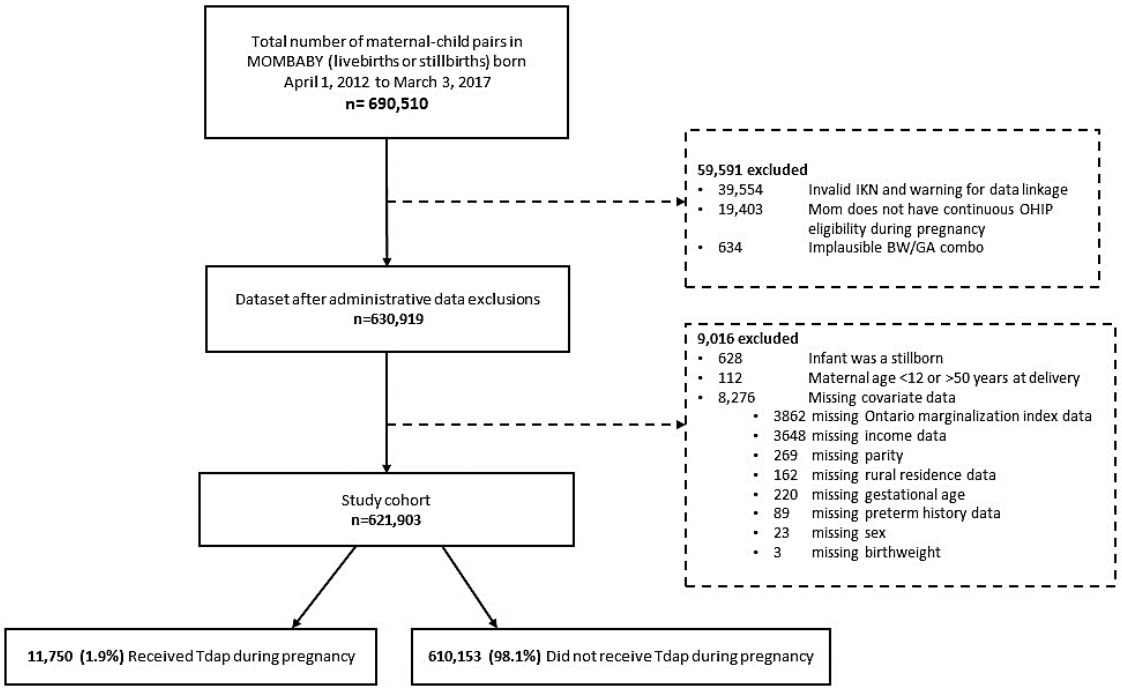


Figure 4-1 Study flow diagram

The demographic and pregnancy characteristics for the full study population are presented in **Table 4-1**. The number of births each year was similar across the study time period (2012 to 2016). Among the entire cohort of women, the highest proportion was 30 to 34 years of age at delivery (36.7%). Less than 10% of women resided in a rural location and over 30% resided in a public health unit region in Central Eastern Ontario. In addition, over 78% of women were born in North America and almost 34% of women were living in an area with the highest ethnic concentration (i.e., recent immigrants).

Overall, 29% of births were by cesarean and 44% were to nulliparous women. According to the R-GINDEX, almost half of pregnancies in our cohort were classified as receiving intermediate prenatal care (49.6%), and 27% as receiving adequate prenatal care. Less than 2% of pregnancies received intensive prenatal care, while approximately 8% of women received no prenatal care at all based on our definition.

Table 4-1. Characteristics of full study population

Characteristic	All births, N (%) *n*=621,903
Fiscal year of delivery	
2012	128,179 (20.6)
2013	126,372 (20.3)
2014	126,044 (20.3)
2015	125,670 (20.2)
2016	115,638 (18.6)
Maternal age (years)	
<20	14,259 (2.3)
20–24	66,402 (10.7)
25–29	167,247 (26.9)
30–34	228,366 (36.7)
≥35	145,629 (23.4)
Nulliparous	275,532 (44.3)
Multiple birth	21,374 (3.4)
Cesarean delivery	179,191 (28.8)
Neighbourhood median family income quintiles	
1 (Lowest)	128,08 (20.7)
2	124,675 (20.1)
3	126,716 (20.4)
4	136,626 (22.0)
5 (Highest)	105,078 (16.9)
Rural location of residence	60,841 (9.8)
Public health unit region of residence	
North West	8,937 (1.4)
North East	23,489 (3.8)
Eastern	77,963 (12.5)
Central East	189,752 (30.5)
Toronto	130,416 (21.0)
South West	69,358 (11.2)
Central West	121,988 (19.6)
Maternal world region of birth	
North America	486,957 (78.3)
Asia	85,108 (13.7)
Europe	12,223 (2.0)
Africa	11,669 (1.9)
Caribbean	8,297 (1.3)
Yugoslavia & USSR	7,773 (1.3)
South America	6,497 (1.0)
Central America	3,084 (0.5)
Oceania	295 (0.05)
Marginalization Indices [a]	
Residential instability quintile	
1	140,652 (22.6)
2	120,985 (19.5)
3	115,208 (18.5)

4	117,702 (19.0)
5	127,356 (20.5)
Material deprivation quintile	
1	96,889 (15.6)
2	118,303 (19.0)
3	123,066 (19.8)
4	128,539 (20.7)
5	155,106 (24.9)
Dependency quintile	
1	216,660 (34.8)
2	125,392 (20.2)
3	107,146 (17.2)
4	93,257 (15.0)
5	79,448 (12.8)
Ethnic concentration quintile	
1	87,321 (14.0)
2	92,160 (14.8)
3	104,470 (16.8)
4	128,827 (20.7)
5	209,125 (33.6)
Prenatal care [b]	
Intensive	9,180 (1.5)
Adequate	166,953 (26.8)
Intermediate	308,136 (49.6)
Inadequate	87,037 (14.0)
No care [c]	50,597 (8.1)

[a] 1= least marginalized; 5=most marginalized.

[b] Prenatal care assignment based on the Revised-Graduated Prenatal Care Utilization Index (R-GINDEX)

[c] Mother did not have any prenatal visits

4.2 Objective 1

4.2.1 Tdap vaccination rates

The vaccination rates (per 1,000 women) and rate ratios of Tdap vaccination by various demographic and clinical characteristics are presented in **Table 4-2**. The overall rate of Tdap vaccination during pregnancy across the study period was 18.9 per 1,000 women (95% CI: 18.6, 19.2), increasing by over 8-fold between 2012 and 2016 (from 4.6 per 1,000 women in 2012 to 39.1 per 1,000 women in 2016). The Tdap vaccination rate was highest among women aged 30-34 years of age (20.4 per 1,000 women) and lowest among women aged 20-24 years of age (11.9 per 1,000 women). There was no difference in the Tdap vaccination rate among women who had

a pre-existing medical condition (19.5 per 1,000 women, compared to 18.9 per 1,000 for women without any pre-existing conditions).

The vaccination rate was 23.0 per 1,000 among women living in a neighbourhood with a median household income in the highest quintile, compared to 15.8 per 1,000 among women within the lowest income quintile. Women residing in public health regions within Southwestern Ontario had the lowest observed vaccination rate (7.5 per 1,000 women). In contrast, women living within regions of Southern Ontario, most notably in Toronto, had the highest vaccination rate (26.4 per 1,000 women). Women born in Oceania had the highest vaccination rate (30.5 per 1,000 women), while women born in Central America had the lowest vaccination rate (8.1 per 1,000 women). Women living in areas with the highest residential instability had the highest observed vaccination rate (20.7 per 1,000 women). In relation to material deprivation, the lowest vaccination rate was observed among the most materially deprived women (17.2 per 1,000 women). Women living in areas with highest ethnic concentration (i.e., highest proportion of recent immigrants) had the highest vaccination rate (20.4 per 1,000 women). Compared to women living in areas with lower dependency, those who lived in areas with higher dependency had a higher vaccination rate (20.0 per 1,000 women).

The results from our analyses of demographic and clinical characteristics potentially associated with Tdap vaccine uptake are presented in **Table 4-2**. In the adjusted multivariable model, vaccine uptake was lowest among women: aged 20-24 years (aRR: 0.64; 95% CI: 0.59, 0.69); with a multiple birth (aRR: 0.70; 95% CI: 0.62, 0.79); residing in a neighbourhood with the lowest income quintile (aRR: 0.69; 95% CI: 0.63, 0.75); within the South Western public health region (aRR: 0.25; 95% CI: 0.23, 0.28); and who did not have any prenatal care visits by our definition (aRR: 0.27; 95% CI: 0.24, 0.30). Although the unadjusted rate ratio for Tdap

vaccination was highest among areas with the highest ethnic concentration (i.e., 5th quintile) compared to the lowest (i.e., 1st quintile), this estimate was reduced after adjusting for all the predictor variables (aRR: 0.86; 95% CI: 0.79, 0.94). Vaccine uptake was similar between mothers receiving either adequate or intensive prenatal care (**Table 4-2**).

Table 4-2. Vaccination rates and rate ratios for Tdap vaccination among pregnant women by various characteristics

Characteristic	No. vaccinated/ total in category	Vaccination rate per 1000 women (95% CI)	Unadjusted RR (95% CI)	Adjusted RR (95% CI) [a]
Overall	11,750	18.9 (18.6, 19.2)	-	-
Maternal age (years)				
<20	179/14,259	12.6 (10.7, 14.4)	0.62 (0.53, 0.71)	0.70 (0.60, 0.81)
20–24	787/66,402	11.9 (11.0, 12.7)	0.58 (0.54, 0.63)	0.64 (0.59, 0.69)
25–29	3,305/167,247	19.8 (19.1, 20.4)	0.97 (0.93, 1.01)	1.01 (0.96, 1.05)
30–34	4,659/228,366	20.4 (19.8, 21.0)	1.00 (ref)	1.00 (ref)
≥35	2,820/145,629	19.4 (18.7, 20.1)	0.95 (0.91, 0.99)	0.95 (0.91, 1.00)
Fiscal year of delivery				
2012	594/128,179	4.6 (4.3, 5.0)	1.00 (ref)	1.00 (ref)
2013	1,628/126,372	12.9 (12.3, 13.5)	2.78 (2.53, 3.05)	2.78 (2.53, 3.05)
2014	2,099/126,044	16.7 (15.9, 17.4)	3.59 (3.28, 3.93)	3.58 (3.27, 3.92)
2015	2,903/125,670	23.1 (22.3, 23.9)	4.98 (4.57, 5.44)	4.95 (4.54, 5.41)
2016	4,526/115,638	39.1 (38.0, 40.3)	8.45 (7.76, 9.20)	8.34 (7.66, 9.08)
Parity				
0 (nulliparous)	6,066/275,532	22.0 (21.5, 22.6)	1.34 (1.29, 1.39)	1.33 (1.29, 1.39)
≥1 (multiparous)	5,684/346,371	16.4 (16.0, 16.8)	1.00 (ref)	1.00 (ref)
Multiple birth				
No	11,474/600,529	19.1 (18.8, 19.5)	1.00 (ref)	1.00 (ref)
Yes	276/21,374	12.9 (11.4, 14.4)	0.68 (0.60, 0.76)	0.70 (0.62, 0.79)
Infant's sex				
Female	5,706/302,989	18.8 (18.3, 19.3)	0.99 (0.96, 1.03)	0.99 (0.96, 1.03)
Male	6,044/318,914	19.0 (18.5, 19.4)	1.00 (ref)	1.00 (ref)
Pre-existing maternal medical condition [b]				
No	11,399/603,895	18.9 (18.5,19.2)	1.00 (ref)	1.00 (ref)
Yes	351/18,008	19.5 (17.5,21.5)	1.03 (0.93, 1.15)	0.76 (0.64, 0.89)
Type of pre-existing maternal medical condition				
Asthma	25/1,533	16.3 (10.0, 22.6)	0.86 (0.58, 1.27)	0.89 (0.60, 1.31)
Chronic hypertension	41/2,368	17.3 (12.1, 22.6)	0.92 (0.68, 1.24)	0.97 (0.71, 1.31)
Diabetes	55/4,834	11.4 (8.4,14.4)	0.60 (0.46, 0.78)	0.62 (0.48, 0.81)
Heart disease	51/3,037	16.8 (12.2, 21.4)	0.89 (0.68, 1.17)	0.86 (0.66, 1.13)
Thyroid disease				
No	11,548/614,543	18.8 (18.5, 19.1)	1.00 (ref)	1.00 (ref)
Yes	202/7,360	27.4 (23.7, 31.2)	1.46 (1.27, 1,68)	1.44 (1.17, 1.78)
Obstetrical complication [c]				
No	9,096/491,618	18.5 (18.1, 18.9)	1.00 (ref)	1.00 (ref)
Yes	2,654/130,285	20.4 (19.6, 21.1)	1.19 (1.05, 1.15)	1.02 (0.98, 1.07)

Type of obstetrical complication				
Preeclampsia & Eclampsia	247/12,086	20.4 (17.9, 23.0)	1.08 (0.96, 1.23)	1.01 (0.89, 1.14)
Gestational diabetes	771/39,254	19.6 (18.3, 21.0)	1.04 (0.97, 1.12)	0.93 (0.87, 1.01)
Placenta previa	82/4,451	18.4 (14.5, 22.4)	0.97 (0.79, 1.21)	1.01 (0.81, 1.25)
Placental abruption	112/6,365	17.6 (14.4, 20.8)	0.93 (0.77, 1.12)	0.96 (0.80, 1.16)
PROM	1,599/76,540	20.9 (19.9, 21.9)	1.12 (1.07, 1.18)	1.06 (1.01, 1.12)
Mode of delivery				
Vaginal	8,558/442,712	19.3 (18.9, 19.7)	1.00 (ref)	1.00 (ref)
Cesarean	3,192/179,191	17.8 (17.2, 18.4)	0.92 (0.89, 0.96)	0.90 (0.87, 0.94)
Urinary tract infection during pregnancy				
No	11,740/620,825	18.9 (18.6, 19.2)	1.00 (ref)	1.00 (ref)
Yes	10/1,078	9.3 (3.6, 15.0)	0.49 (0.26, 0.91)	0.53 (0.29, 0.97)
Neighbourhood median family income quintiles				
1 (Lowest)	2,030/128,808	15.8 (15.1, 16.4)	0.68 (0.64, 0.72)	0.69 (0.63, 0.75)
2	2,377/124,675	19.1 (18.3, 19.8)	0.83 (0.78, 0.87)	0.82 (0.77, 0.88)
3	2,297/126,716	18.1 (17.4, 18.9)	0.79 (0.74, 0.83)	0.82 (0.77, 0.87)
4	2,624/136,626	19.2 (18.5, 19.9)	0.83 (0.79, 0.88)	0.88 (0.84, 0.94)
5 (Highest)	2,422/105,078	23.0 (22.1, 24.0)	1.00 (ref)	1.00 (ref)
Rural residence				
No	106,66/561,062	19.0 (18.7, 19.4)	1.00 (ref)	1.00 (ref)
Yes	1,084/60,841	17.8 (16.8, 18.9)	0.94 (0.88, 1.00)	0.99 (0.92, 1.07)
Public health unit region				
North West	114/8,937	12.8 (10.4, 15.1)	0.48 (0.40, 0.58)	0.40 (0.33, 0.48)
North East	286/23,489	12.2 (10.8, 13.6)	0.46 (0.41, 0.52)	0.40 (0.35, 0.45)
Eastern	1,905/77,963	24.4 (23.4, 25.5)	0.93 (0.88, 0.98)	0.84 (0.79, 0.89)
Central East	4,240/189,752	22.3 (21.7, 23.0)	0.85 (0.81, 0.89)	0.83 (0.79, 0.88)
Toronto	3,439/130,416	26.4 (25.5, 27.2)	1.00 (ref)	1.00 (ref)
South West	521/69,358	7.5 (6.9, 8.2)	0.28 (0.26, 0.31)	0.25 (0.23, 0.28)
Central West	1,245/121,988	10.2 (9.6, 10.8)	0.39 (0.36, 0.41)	0.36 (0.33, 0.38)
Maternal world region of birth				
North America	9,075/486,957	18.6 (18.3, 19.0)	1.00 (ref)	1.00 (ref)
Asia	2,090/85,108	24.6 (23.5, 25.6)	1.32 (1.26, 1.38)	1.15 (1.09, 1.21)
Europe	163/12,223	13.3 (11.3, 15.4)	0.72 (0.61, 0.83)	0.65 (0.56, 0.76)
Africa	157/11,669	13.5 (11.4, 15.5)	0.72 (0.62, 0.84)	0.69 (0.59, 0.81)
Caribbean	73/8,297	8.8 (6.8, 10.8)	0.47 (0.38, 0.59)	0.43 (0.35, 0.55)
Yugoslavia & USSR	89/7,773	11.4 (9.1, 13.8)	0.61 (0.50, 0.76)	0.52 (0.42, 0.63)
South America	69/6,497	10.6 (8.1, 13.1)	0.57 (0.45, 0.72)	0.52 (0.41, 0.66)
Central America	25/3,084	8.1 (4.9, 11.3)	0.44 (0.29, 0.64)	0.44 (0.30, 0.64)
Oceania	9/295	30.5 (10.9, 50.1)	1.64 (0.86, 3.12)	1.39 (0.73, 2.62)

Marginalization Indices [d]				
Residential instability quintile				
1	2,574/140,652	18.3 (17.6, 19.0)	1.00 (ref)	1.00 (ref)
2	2,205/120,985	18.2 (17.5, 19.0)	1.00 (0.94, 1.05)	1.01 (0.95, 1.07)
3	2,181/115,208	18.9 (18.1, 19.7)	1.03 (0.98, 1.09)	1.04 (0.98, 1.11)
4	2,153/117,702	18.3 (17.5, 19.1)	1.00 (0.94, 1.06)	1.04 (0.97, 1.10)
5	2,637/127,356	20.7 (19.9, 21.5)	1.13 (1.07, 1.19)	1.16 (1.09, 1.23)
Material deprivation quintile				
1	2,000/96,889	20.6 (19.7, 21.5)	1.00 (ref)	1.00 (ref)
2	2,267/118,303	19.2 (18.4, 19.9)	0.93 (0.87, 0.99)	0.96 (0.90, 1.02)
3	2,358/123,066	19.2 (18.4, 19.9)	0.93 (0.88, 0.98)	0.97 (0.91, 1.03)
4	2,456/128,539	19.1 (18.4, 19.9)	0.93 (0.87, 0.98)	0.94 (0.87, 1.01)
5	2,669/155,106	17.2 (16.6, 17.9)	0.83 (0.79, 0.88)	0.97 (0.89, 1.06)
Dependency quintile				
1	3,861/216,660	17.8 (17.3, 18.4)	1.00 (ref)	1.00 (ref)
2	2,426/125,392	19.3 (18.6, 20.1)	1.09 (1.03, 1.14)	1.14 (1.08, 1.20)
3	2,105/107,146	19.6 (18.8, 20.5)	1.10 (1.05, 1.16)	1.18 (1.12, 1.25)
4	1,772/93,257	19.0 (18.1, 19.9)	1.07 (1.01, 1.13)	1.19 (1.12, 1.27)
5	1,586/79,448	20.0 (19.0, 20.9)	1.12 (1.06, 1.19)	1.17 (1.10, 1.25)
Ethnic concentration quintile				
1	1,479/87,321	16.9 (16.1, 17.8)	1.00 (ref)	1.00 (ref)
2	1,702/92,160	18.5 (17.6, 19.3)	1.09 (1.02, 1.17)	1.06 (0.98, 1.14)
3	1,939/104,470	18.6 (17.7, 19.4)	1.10 (1.02, 1.17)	0.92 (0.85, 1.00)
4	2,361/128,827	18.3 (17.6, 19.1)	1.08 (1.01, 1.15)	0.81 (0.75, 0.87)
5	4,269/209,125	20.4 (19.8, 21.0)	1.21 (1.14, 1.28)	0.86 (0.79, 0.94)
Prenatal care				
Intensive	247/9,180	26.9 (23.6, 30.2)	1.00 (0.88, 1.13)	0.91 (0.80, 1.03)
Adequate	4,493/166,953	26.9 (26.1, 27.7)	1.00 (ref)	1.00 (ref)
Intermediate	5,780/308,136	18.8 (18.3, 19.2)	0.70 (0.67, 0.72)	0.75 (0.72, 0.78)
Inadequate	898/87,037	10.3 (9.6, 11.0)	0.38 (0.36, 0.42)	0.43 (0.40, 0.46)
No care [e]	332/50,597	6.6 (5.9, 7.3)	0.24 (0.22, 0.27)	0.27 (0.24, 0.30)

Abbreviations: No., number; RR, rate ratio; CI, confidence interval; PROM, premature rupture of membranes

[a] The main multivariable model included all the independent variables listed in this table, excluding the dichotomous variables for pre-existing medical conditions and obstetrical complications, which were added to a separate multivariable model than the model that contained the individual conditions/complications included in these variables.

[b] Conditions included: Asthma, chronic hypertension, diabetes, heart disease.

[c] Complications included: Preeclampsia & eclampsia, gestational diabetes, placenta previa, placental abruption, PROM.

[d] 1= least marginalized; 5=most marginalized.

[e] Mother did not have any prenatal visits within our definition.

4.2.2 Physician characteristics

Table 4-3 reports the type of physician who provided the majority of prenatal care (≥75% of prenatal visits) from 20 weeks' gestation to the day before delivery by Tdap vaccination status. We excluded 1,265 records that did not have any prenatal care visits during this time period. In addition, prenatal visits that were not be attributed to either provider of interest (i.e., family physician or obstetrician) were also excluded (n=157,927). These 157,927 records contained either OHIP fee codes that reflected specimen collection (i.e., urine collection during a prenatal visit), or a physician specialty variable (SPEC) indicating laboratory/microbiology. Among women who were vaccinated, 34.0% received the majority of their prenatal care (≥75% of their visits) from a family physician, compared to 12.9% among unvaccinated women (**Table 4-3**). The proportion of women who received the majority of their prenatal care from an obstetrician was higher among the unvaccinated group (86.8%), compared to the vaccinated group (65.7%). The category of "mix of both providers", which refers to prenatal care shared (<75% of visits) between obstetricians and family physicians, had a similar distribution between unvaccinated and vaccinated women (0.4%).

Table 4-3. Physician specialty most responsible for the majority of prenatal care from 20 weeks' gestation to one day prior to delivery, by Tdap vaccination status (n=462,711) [*]

Physician Specialty	Tdap vaccinated women (n=9,385)	Tdap unvaccinated women (n=453,326)	SD
	N (%)	N (%)	
Family physician/general practitioner	3,189 (34.0)	58,318 (12.9)	0.51
Obstetrician	6,163 (65.7)	393,421 (86.8)	0.51
Mix of both providers	33 (0.40)	1,587 (0.40)	0.0

[*] Excluded 159,192 records (n=1,265 records without any prenatal care visits within this time period; n=157,927 records with visits not by a family physician or obstetrician)
Abbreviations: SD=standardized difference

Similarly, **Table 4-4** reports the type of physician, by vaccination status, who provided the majority of prenatal care (≥75% of their visits) from 27 weeks' gestation to 32 weeks' gestation. We excluded 25,502 records that did not have any prenatal care visits during this time

period. In addition, prenatal visits that were not be attributed to either provider of interest during this time period were also excluded (n=230, 671). Again, these visits contained OHIP billing codes or physician specialties that could not be assigned to either type of physician (i.e., family physician or obstetrician). Compared to the previous time period (**Table 4-3**), the proportion of women receiving the majority of prenatal care from a family physician increased among both the vaccinated (37.2%) and unvaccinated (15.6%) groups. The distribution of shared prenatal care (<75% of prenatal visits) was equal between the two exposure groups (0.7%).

Table 4-4. Physician specialty most responsible for the majority of prenatal care from 27-32 weeks' gestation, by Tdap vaccination status (n=365,730) [*]

Physician Specialty	Tdap vaccinated women (n=7,945)	Tdap unvaccinated women (n=357,785)	SD
	N (%)	N (%)	
Family physician/general practitioner	2,959 (37.2)	55,755 (15.6)	0.51
Obstetrician	4,933 (62.1)	299,625 (83.7)	0.50
Mix of both providers	53 (0.70)	2,405 (0.70)	0.0

[*] Excluded 256,173 records (n=25,502 records without any prenatal care visits within this time period; n=230,671 records with visits not by a family physician or obstetrician)
Abbreviations: SD=standardized difference

Table 4-5 presents the characteristics of the physician who administered the Tdap vaccine during pregnancy. Information was collected from the IPDB which contained various proportions of missing data for the variables examined. Among Tdap vaccinated women in our cohort (n=11,750), 75.6% received vaccine administration from a physician specializing in family or community medicine. Only 17.8% received the vaccine from an obstetrician. Physician specialty was missing for 5.0% of the vaccinated records. The remaining women were vaccinated by a physician whose specialization fell under the following categories: community medicine, internal medicine, emergency medicine, general pathology, anatomical pathology or medical microbiology. The average age of the physician administering the vaccine was 48.0

years (standard deviation=10.9). Over half of the physicians providing the vaccine had above 20 years of experience (55.9%) and graduated from a Canadian medical school (72.9%).

Table 4-5. Characteristics of physicians who administered the Tdap vaccine (N=11,750)

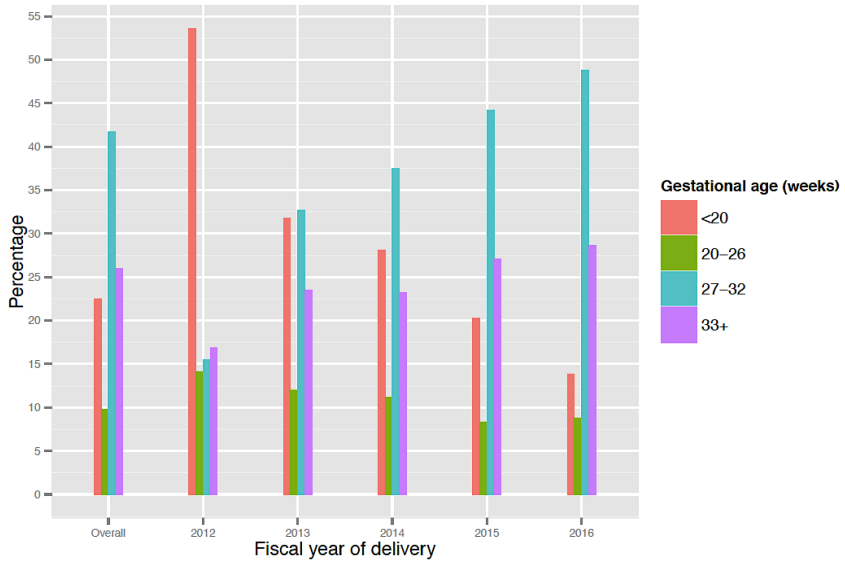
Physician Characteristic	Tdap vaccinated women (n=11,750)
	N (%)
Specialty	
Family physician/general practitioner	8,884 (75.6)
Obstetrician	2,094 (17.8)
Community medicine	7 (0.06)
Other	177 (1.51)
Missing	588 (5.0)
Age of physician (years)[a]	
Mean ± standard deviation	48.0 ± 10.9
Years of experience	
<5	150 (1.3)
5-10	2,278 (19.4)
11-20	2,851 (24.3)
>20	6,402 (54.5)
Missing	69 (0.60)
Attended a Canadian medical school	8,571(72.9)
Missing	817(7.0)

[a] Age of the physician was missing for 535(4.6%) maternal records.

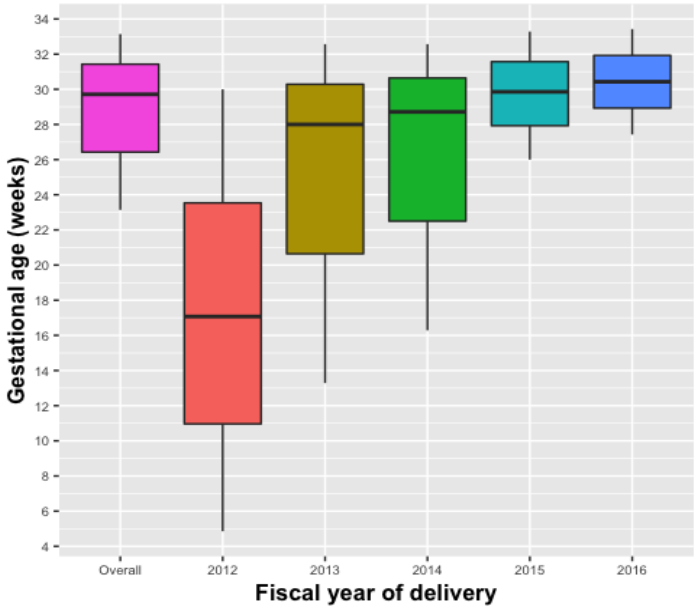
4.2.3 Timing of Tdap vaccination

Figure 4-2 presents the gestational timing of Tdap vaccination in the overall cohort and by fiscal year (FY) of delivery with a bar graph (panel **A)** and box-plot (panel **B**). Across the entire study period, 41.7% of the women (4,903/11,750) who received Tdap vaccination during their pregnancy were vaccinated within the recommended time period of 27-32-weeks' gestation. The percentage of vaccinated women who received Tdap during the recommended time period (27-32 weeks' gestation) increased from 15.5% among women who delivered in FY2012 to 48.8% among women who delivered in FY2016 (**Figure 4-2A**). Over half of the women who delivered during FY2012 received Tdap vaccination prior to 20 weeks' gestation (53.5%). Among the women who delivered in FY2012, the median gestational week of Tdap vaccination was 17 weeks (**Figure 4-2B**). The median gestational age of Tdap vaccination increased across

the study time period reaching a median gestational age of 30 weeks among women who delivered in FY2016 (**Figure 4-2B**).



A.



B.

Figure 4-2. Gestational timing of Tdap vaccination in the overall cohort and by fiscal year of delivery. Bar graph (panel **A** shows the percentage of the cohort (overall and within each year) that received Tdap vaccination by various gestational age categories. The horizontal line within each boxplot (panel **B**) denotes the median gestational age, while the vertical lines extending above and below each box represent the interquartile range (i.e., 25th and 75th percentiles).

4.3 Objective 2

4.3.1 Descriptive characteristics

In the unweighted population, several baseline characteristics differed between Tdap vaccinated and unvaccinated mothers, as indicated by a standardized difference >0.10 in **Table 4-6**. Compared to vaccinated women, unvaccinated women were more likely to have delivered at the beginning of the study period (2012 and 2013 fiscal years), be between 20 to 24 years of age, and live in the South or Central West public health regions of the province (**Table 4-6**). In contrast, vaccinated women were more likely to be nulliparous, to live in a higher-income neighbourhood and to have been born in Asia. None of the four indices of marginalization differed between the vaccinated and unvaccinated group. History of preterm delivery and cesarean delivery had standardized differences above 0.10; however, this difference was most likely influenced by parity. Lastly, the presence of maternal pre-existing medical comorbidities did not differ by Tdap vaccination status.

Table 4-6. Unweighted and weighted baseline characteristics of the study population (n=621,903)

Characteristic	Unweighted Cohort			IPTW-weighted Cohort		
	Tdap vaccinated women (n=11,750)	Tdap unvaccinated women (n=610,153)	Stand Diff [b]	Tdap vaccinated women	Tdap unvaccinated women	Stand Diff [b]
	N (%) [a]	N (%) [a]		%[a]	%[a]	
Gestational age at vaccination (week)						
<20	2,641 (22.5)	-	-	-	-	-
20-26	1,153 (9.8)	-	-	-	-	-
27-32	4,903 (41.7)	-	-	-	-	-
33+	3,053 (26.0)	-	-	-	-	-
Maternal age (years)						
<20	179 (1.5)	14,080 (2.3)	0.06	2.9	2.3	0.03
20–24	787 (6.7)	65,615 (10.8)	0.14	9.7	10.8	0.04
25–29	3,305 (28.1)	163,942 (26.9)	0.03	28.2	26.8	0.03
30–34	4,659 (39.7)	223,707 (36.7)	0.06	35.5	36.6	0.02
≥35	2,820 (24.0)	142,809 (23.4)	0.01	23.7	23.4	0.01
Fiscal year of delivery						
2012	594 (5.1)	127,585 (20.9)	0.49	23.9	21.2	0.07
2013	1,628 (13.9)	124,744 (20.4)	0.18	18.8	20.6	0.04
2014	2,099 (17.9)	123,945 (20.3)	0.06	19.3	20.4	0.03
2015	2,903 (24.7)	122,767 (20.1)	0.11	19.6	20.0	0.01
2016	4,526 (38.5)	111,112 (18.2)	0.46	18.3	17.8	0.01
Parity						
0 (nulliparous)	6,066 (51.6)	269,466 (44.2)	0.15	43.2	44.0	0.02
≥1 (multiparous)	5,684 (48.4)	340,687 (55.8)	0.15	56.8	56.0	0.02
Multiple birth						
No	11,474 (97.7)	589,055 (96.5)	0.07	96.8	96.5	0.02
Yes	276 (2.3)	21,098 (3.5)	0.07	3.2	3.5	0.02
Infant's sex						
Female	5,706 (48.6)	297,283 (48.7)	0.00	48.2	48.7	0.01
Male	6,044 (51.4)	312,870 (51.3)	0.00	51.8	51.3	0.01
History of preterm birth						
Nulliparous	6,066 (51.6)	269,466 (44.2)	0.15	43.2	44.0	0.02
Parous – no history of preterm birth	5,352 (45.5)	316,038 (51.8)	0.13	53.1	51.9	0.02
Parous – history of preterm birth	332 (2.8)	24,649 (4.0)	0.07	3.6	4.1	0.02
Pre-existing maternal medical condition [c]						
No	11,399 (97.0)	592,496 (97.1)	0.01	96.9	97.1	0.01
Yes	351 (3.0)	17,657 (2.9)	0.01	3.1	2.9	0.01
Type of pre-existing maternal medical condition						
Asthma	25 (0.2)	1,508 (0.2)	0.01	0.3	0.2	0.00

Chronic hypertension	41 (0.3)	2,327 (0.4)	0.01	0.4	0.4	0.01
Diabetes	55 (0.5)	4,779 (0.8)	0.01	0.9	0.8	0.01
Heart disease	51 (0.4)	2,986 (0.5)	0.01	0.5	0.5	0.01
Thyroid disease						
No	11,548 (98.3)	602,995 (98.8)	0.05	98.7	98.8	0.01
Yes	202 (1.7)	7,158 (1.2)	0.05	1.3	1.2	0.01
Obstetrical complication [d]						
No	9,096 (77.4)	482,522 (79.1)	0.04	78.9	79.1	0.00
Yes	2,654 (22.6)	127,631 (20.9)	0.04	21.1	20.9	0.00
Type of obstetrical complication [e]						
Preeclampsia and eclampsia	247 (2.1)	11,839 (1.9)	0.01	1.9	1.9	0.00
Gestational diabetes	771 (6.6)	38,483 (6.3)	0.01	6.6	6.3	0.01
Placenta previa	82 (0.7)	4,369 (0.7)	0.01	0.7	0.7	0.00
Placental abruption	112 (1.0)	6,253 (1.0)	0.01	1.0	1.0	0.00
PROM	1,599 (13.6)	74,941 (12.3)	0.04	12.0	12.3	0.01
Mode of delivery						
Vaginal	8,558 (72.8)	434,154 (71.2)	0.04	73.2	71.2	0.04
Cesarean	3,192 (27.2)	175,999 (28.8)	0.04	26.8	28.8	0.04
Previous cesarean delivery						
Nulliparous	6,066 (51.6)	269,466 (44.2)	0.15	43.2	44.0	0.02
Parous – no previous c-section	4,615 (39.3)	271,605 (44.5)	0.11	46.2	44.6	0.03
Parous – previous c-section	1,069 (9.1)	69,082 (11.3)	0.07	10.5	11.3	0.03
UTI during pregnancy						
No	11,740 (99.9)	609,085 (99.8)	0.02	99.8	99.8	0.01
Yes	10 (0.1)	1,068 (0.2)	0.02	0.2	0.2	0.01
Neighborhood median family income quintiles						
1 (Lowest)	2,030 (17.3)	126,778 (20.8)	0.09	22.3	20.8	0.04
2	2,377 (20.2)	122,298 (20.0)	0.00	19.2	20.0	0.02
3	2,297 (19.5)	124,419 (20.4)	0.02	19.6	20.4	0.02
4	2,624 (22.3)	134,002 (22.0)	0.01	22.5	22.0	0.01
5 (Highest)	2,422 (20.6)	102,656 (16.8)	0.11	16.4	16.8	0.01
Rural residence						
No	10,666 (90.8)	550,396 (90.2)	0.02	90.3	90.2	0.00
Yes	1,084 (9.2)	59,757 (9.8)	0.02	9.7	9.8	0.00
Public health unit region						
North West	114 (1.0)	8,823 (1.4)	0.04	1.0	1.5	0.04
North East	286 (2.4)	23,203 (3.8)	0.08	3.0	3.8	0.05
Eastern	1,905 (16.2)	76,058 (12.5)	0.11	10.7	12.4	0.05
Central East	4,240 (36.1)	185,512 (30.4)	0.12	31.0	30.3	0.01

Toronto	3,439 (29.3)	126,977 (20.8)	0.20	20.2	20.7	0.01
South West	521 (4.4)	68,837 (11.3)	0.26	12.7	11.4	0.04
Central West	1,245 (10.6)	120,743 (19.8)	0.26	21.4	20.0	0.03
Birth weight						
<1500 g	48 (0.4)	6,081 (1.0)	0.07	0.5	1.0	0.06
1500-2500 g	533 (4.5)	33,998 (5.6)	0.05	4.9	5.6	0.03
2500-3500 g	6,575 (56.0)	330,647 (54.2)	0.04	54.7	54.2	0.01
≥3500 g	4,594 (39.1)	239,427 (39.2)	0	39.8	39.3	0.01
Gestational weeks at delivery						
<28	9 (0.1)	2,717 (0.4)	0.07	0.1	0.4	0.06
28-31	50 (0.4)	4,145 (0.7)	0.03	0.5	0.7	0.02
32-33	62 (0.5)	5,725 (0.9)	0.05	0.5	0.9	0.05
34	82 (0.7)	6,006 (1.0)	0.03	0.7	1.0	0.03
35	154 (1.3)	9,919 (1.6)	0.03	1.7	1.6	0.01
36	352 (3.0)	19,902 (3.3)	0.02	3.0	3.3	0.02
≥37	11,041 (94.0)	561,739 (92.1)	0.07	93.4	92.1	0.05
Maternal world region of birth						
North America	9,075 (77.2)	477,882 (78.3)	0.03	78.5	78.3	0.00
Asia	2,090 (17.8)	83,018 (13.6)	0.12	12.8	13.5	0.02
Europe	163 (1.4)	12,060 (2.0)	0.05	2.0	2.0	0.00
Africa	157 (1.3)	11,512 (1.9)	0.04	2.3	1.9	0.03
Caribbean	73 (0.6)	8,224 (1.3)	0.07	1.4	1.4	0.00
Yugoslavia & USSR	89 (0.8)	7,684 (1.3)	0.05	1.6	1.3	0.02
South America	69 (0.6)	6,428 (1.1)	0.05	0.9	1.1	0.01
Central America	25 (0.2)	3,059 (0.5)	0.05	0.5	0.5	0.00
Oceania	9 (0.1)	286 (0.0)	0.01	0.0	0.0	0.00
Marginalization Indices [e]						
Residential instability quintile						
1	2,574 (21.9)	138,078 (22.6)	0.02	20.9	22.6	0.04
2	2,205 (18.8)	118,780 (19.5)	0.02	19.2	19.5	0.01
3	2,181 (18.6)	113,027 (18.5)	0	18.5	18.5	0.00
4	2,153 (18.3)	115,549 (18.9)	0.02	19.7	18.9	0.02
5	2,637 (22.4)	124,719 (20.4)	0.05	21.7	20.4	0.03
Material deprivation quintile						
1	2,000 (17.0)	94,889 (15.6)	0.04	15.5	15.5	0.00
2	2,267 (19.3)	116,036 (19.0)	0.01	18.7	19.0	0.01
3	2,358 (20.1)	120,708 (19.8)	0.01	19.3	19.8	0.01
4	2,456 (20.9)	126,083 (20.7)	0.01	19.7	20.6	0.02
5	2,669 (22.7)	152,437 (25.0)	0.05	26.8	25.1	0.04
Dependency quintile						
1	3,861 (32.9)	212,799 (34.9)	0.04	33.4	34.9	0.03
2	2,426 (20.6)	122,966 (20.2)	0.01	21.0	20.2	0.02
3	2,105 (17.9)	105,041 (17.2)	0.02	18.0	17.2	0.02

4	1,772 (15.1)	91,485 (15.0)	0	15.1	15.0	0.00
5	1,586 (13.5)	77,862 (12.8)	0.02	12.5	12.7	0.01
Ethnic concentration quintile						
1	1,479 (12.6)	85,842 (14.1)	0.04	15.2	14.1	0.03
2	1,702 (14.5)	90,458 (14.8)	0.01	15.8	14.9	0.02
3	1,939 (16.5)	102,531 (16.8)	0.01	17.8	16.8	0.03
4	2,361 (20.1)	126,466 (20.7)	0.02	19.4	20.7	0.03
5	4,269 (36.3)	204,856 (33.6)	0.06	31.8	33.5	0.04

Abbreviations: IPTW, inverse probability of treatment weighting; Stand diff, standardized difference; PROM, premature rupture of membranes.
[a] Column Percentages.
[b] Absolute standardized differences. Shaded cells indicate an imbalance (>0.10) between Tdap-vaccinated and unvaccinated women.
[c] Conditions included: Asthma, chronic hypertension, diabetes, heart disease.
[d] Complications included: Preeclampsia and eclampsia, gestational diabetes, placenta previa, placental abruption, PROM.
[e] Obstetrical complication categories are not mutually exclusive.
[f] 1= least marginalized; 5=most marginalized

4.3.2 Propensity score model assessment

The propensity score model produced a c-statistic of 0.724. After weighting the study population using the propensity score-derived IPTWs, the standardized differences among all measured baseline covariates were below 0.1, demonstrating improved balance and comparability between the exposure groups (**Table 4-6** and **Figure 4-3**). Side-by-side histograms shown in **Figure 4-4** display the distribution of the propensity scores by exposure status. Overall the propensity score distribution demonstrated good overlap across the exposure groups.

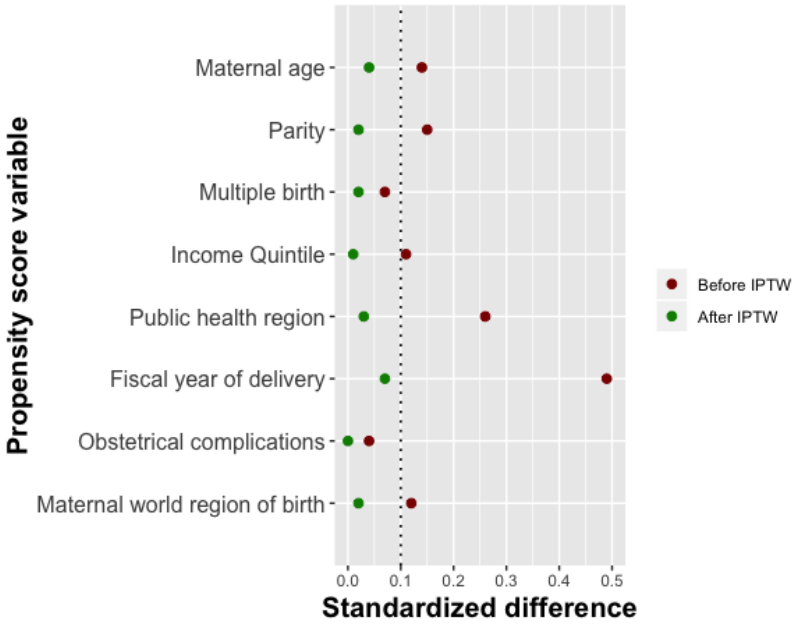


Figure 4-3 Comparison of standardized difference scores before and after IPTW

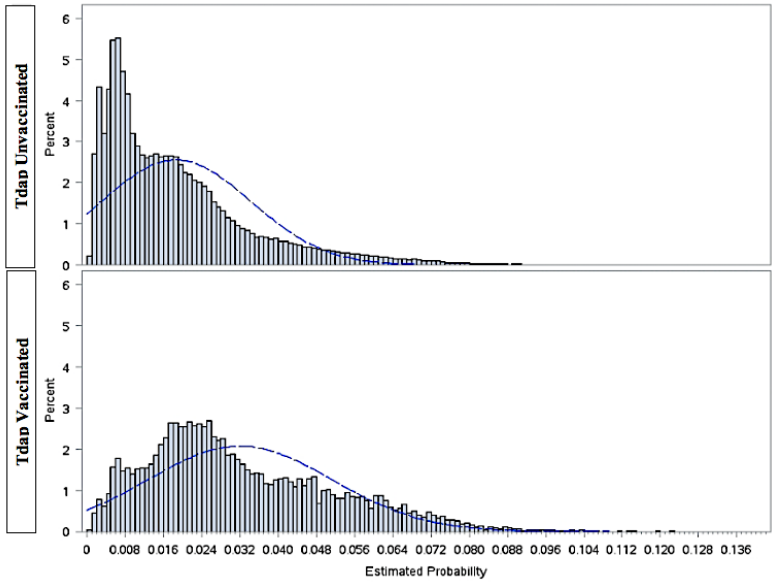


Figure 4-4 Distribution of the propensity score model by vaccination status.

4.3.3 Obstetrical outcomes

Table 4-7 presents the relationship between Tdap exposure and obstetrical outcomes using IPTW to adjust for confounding. Chorioamnionitis was recorded among 1.23% of Tdap-

vaccinated women and 0.99% of unvaccinated women. Following IPTW adjustment, Tdap vaccination was not associated with an increased risk of chorioamnionitis (aRR: 0.95; 95% CI: 0.79, 1.15). We found a significant inverse association between Tdap vaccination and gestational hypertension in the crude analysis that was slightly stronger in magnitude in the adjusted weighted model (aRR: 0.81; 95% CI: 0.74, 0.90).

Table 4-7. Association between Tdap vaccination during pregnancy and obstetrical outcome using propensity-score weighting (n=621,903)

Outcome	Tdap vaccinated (n=11,750)	Tdap unvaccinated (n=610,153)	RR (95% CI)	
	N (%)	N (%)	Unadjusted	IPTW-adjusted [a]
Chorioamnionitis	145 (1.23)	6,069 (0.99)	1.24 (1.05,1.46)	0.95 (0.79,1.15)
Gestational hypertension	399 (3.40)	23,698 (3.88)	0.87 (0.79,0.96)	0.81 (0.74,0.90)

Abbreviations: CI, confidence interval; RR, risk ratio.
[a] Adjusted using stabilized inverse probability of treatment weights (IPTW) based on propensity score.

4.3.4 Perinatal outcomes

Table 4-8 presents the relationship between Tdap exposure and perinatal outcomes using IPTW to adjust for confounding. The risk of preterm birth did not differ significantly between exposed and unexposed infants in the crude analyses (HR: 0.94; 95% CI: 0.87, 1.01) or after adjustment using IPTW (aHR: 0.99; 95% CI: 0.87, 1.12). Similarly, Tdap vaccination was not associated with very preterm delivery in either the crude or adjusted models (**Table 4-8**). The proportion of infants admitted to the NICU for longer than 24 hours was significantly lower among Tdap exposed infants (6.46%), compared to Tdap unexposed infants (8.31%). This association remained significant after adjustment using IPTW (aRR: 0.92; 95% CI: 0.87, 0.98). The proportion of SGA infants among unexposed infants was 9.78%, compared to 9.27% among exposed infants. After IPTW adjustment, Tdap vaccination was not associated with SGA delivery (aRR: 0.95; 95% CI: 0.90, 1.01).

The proportion of infants flagged as having one or more of the conditions within the NAOI decreased sharply from 73.8% at 32 weeks of gestation to 4.4% at 39 weeks of gestation (**Figure 4-5**). Morbidity after 39 weeks' gestation increased again, reaching 5.9% at 42 weeks' gestation. This pattern of infant morbidity by gestational age helped to verify the expected distribution and also aligned with similar descriptions by previous authors employing the NAOI. Within 28 days following delivery, 670 (5.70%) infants in the vaccinated group and 50,676 (8.31%) infants in the unvaccinated group were identified as having a condition included in the neonatal composite outcome (NAOI). This inverse association remained significant after propensity score adjustment using IPTW (**Table 4-8**).

Table 4-8. Association between Tdap vaccination during pregnancy and perinatal outcomes using propensity-score weighting (n=621,903)

Outcome	Tdap vaccinated (n=11,750)	Tdap unvaccinated (n=610,153)	Estimate (RR/HR [95% CI])	
	N (%)	N (%)	Unadjusted	IPTW-adjusted [a]
Small for gestational age [b]	1,089 (9.27)	59,697 (9.78)	0.95 (0.89,1.00)	0.95 (0.90,1.01)
NICU admission >24 hours [b]	759 (6.46)	50,676 (8.31)	0.78 (0.73,0.83)	0.92 (0.87,0.98)
NAOI Composite Outcome [b]	670 (5.70)	44,717 (7.33)	0.78 (0.72,0.84)	0.85 (0.79,0.91)
Preterm birth, <37 weeks [c,d]	709 (6.03)	48,414 (7.93)	0.94 (0.87,1.01)	0.99 (0.87,1.12)
Very preterm birth, <32 weeks [c,d]	59 (0.50)	6,862 (1.12)	1.06 (0.82,1.37)	1.03 (0.71,1.50)

Abbreviations: CI, confidence interval; RR, risk ratio; HR, hazard ratio; NICU, neonatal intensive care unit; NAOI, neonatal adverse outcome indicator.

[a] Adjusted using stabilized inverse probability of treatment weights (IPTW) based on propensity score.

[b] Estimate values represent the relative risk ratios (RRs) that were estimated using a log-binomial regression model.

[c] Estimate values represent the hazard ratios (HR) that were estimated using a time-dependent Cox model, where Tdap vaccination was modelled as a time-varying exposure.

[d] We limited analyses to Tdap administration at 36 weeks' gestation or earlier and 31 weeks' or earlier for preterm birth outcome (N=620,915) and very preterm outcome (N=616,762), respectively.

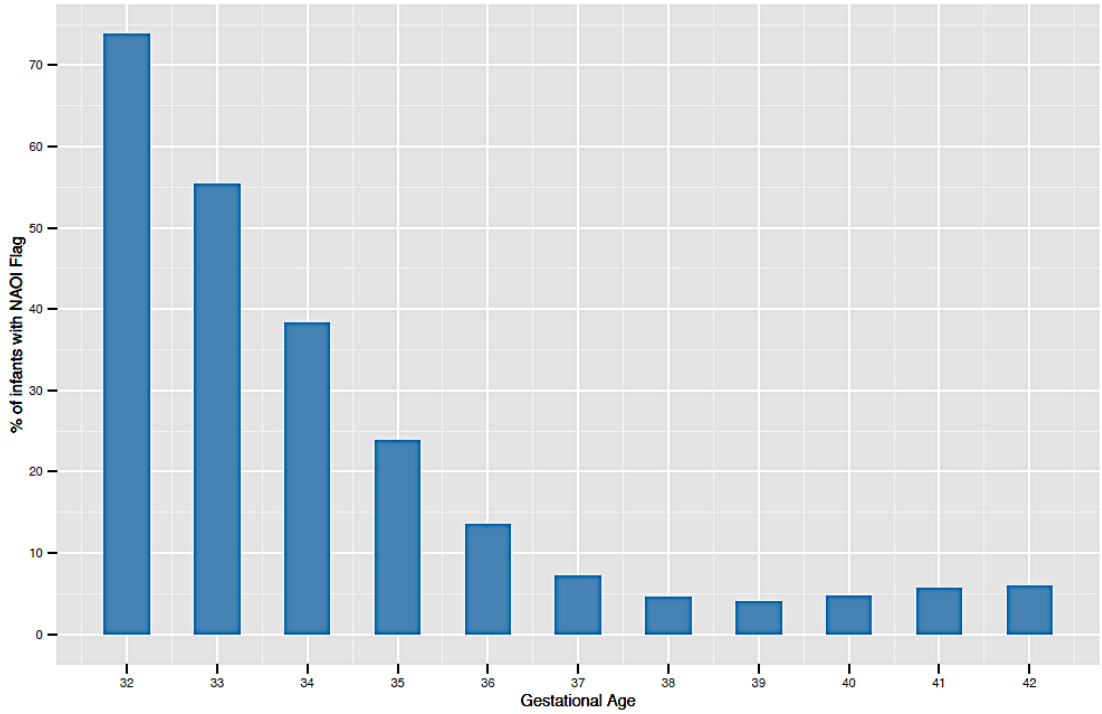


Figure 4-5 Rate of neonatal morbidity by gestational age at birth identified by the composite NAOI

4.4 Sensitivity analyses

4.4.1 Propensity score matching

To assess the robustness of our IPTW-adjusted analyses, we additionally ran models using a propensity score matched sample in our sensitivity analyses. After propensity score matching, there 11,750 pregnancies that were exposed to Tdap vaccination during pregnancy remaining in our sample, matched with 58,750 unexposed pregnancies. The distribution of baseline characteristics of the original unmatched cohort and propensity score matched cohort is presented in **Appendix VII**. Compared to the original cohort, baseline covariate differences in the propensity score matched cohort were minimal, as all standardized differences clustered around zero (**Appendix VIII)**. **Table 4-9** presents the relationship between Tdap exposure and obstetrical outcomes using propensity score matching, as opposed to IPTW, to adjust for confounding. Similar to our main findings, after propensity score matching, the RR between

Tdap exposure and chorioamnionitis was attenuated towards the null (aRR: 0.99; 95% CI: 0.83, 1.18). In contrast to our main findings, propensity score matching slightly attenuated the risk between Tdap vaccination and gestational hypertension (aRR: 0.88; 95% CI: 0.80, 0.98); however, the association remained significant. This alternate method of confounding adjustment had minimal impact on the magnitude of our IPTW adjusted estimates for preterm birth and very preterm birth (**Table 4-10**). Similarly, the associations between Tdap exposure during pregnancy and risk of neonatal hospitalization (NICU admissions >24 hours) and morbidity (as measured by the NAOI) remained significant after adjustment using propensity score matching. Unlike our main analyses, the 95% CI for the association between Tdap vaccination and SGA excluded 1 in the propensity score matched analyses (aRR: 0.91; 95% CI: 0.86, 0.97), providing evidence of a significant inverse association.

Table 4-9. Association between Tdap vaccination during pregnancy and obstetrical outcomes using propensity-score matching

Outcome	Unmatched Cohort Analysis (n=621,903)			Propensity Score-Matched Analysis (n=70,500)		
	Tdap Vaccinated (n=11,750) N (%)	Tdap Unvaccinated (n=610,153) N (%)	Unadjusted RR (95% CI)	Tdap Vaccinated (n=11,750) N (%)	Tdap Unvaccinated (n=58,750) N (%)	Adjusted RR (95% CI)
Chorioamnionitis	145 (1.23)	6,069 (0.99)	1.24 (1.05,1.46)	145 (1.23)	732 (1.25)	0.99 (0.83,1.18)
Gestational Hypertension	399 (3.40)	23,698 (3.88)	0.87 (0.79,0.96)	399 (3.40)	2260 (3.85)	0.88 (0.80,0.98)

Abbreviations: CI, confidence interval; RR, risk ratio.

Table 4-10. Association between Tdap vaccination during pregnancy and perinatal outcomes using propensity-score matching

Outcome	Unmatched Cohort Analysis (n=621,903)			Propensity Score-Matched Analysis (n=70,500)		
	Tdap Vaccinated (n=11,750) N (%)	Tdap Unvaccinated (n=610,153) N (%)	Crude Estimate (95% CI) [a]	Tdap Vaccinated (n=11,750) N (%)	Tdap Unvaccinated (n=58,750) N (%)	Adjusted Estimate (RR/HR [95% CI])
Small for gestational age [a]	1,089 (9.27)	59,697 (9.78)	0.95 (0.89,1.00)	1,089 (9.27)	5,985 (10.19)	0.91 (0.86,0.97)
NICU admission >24 hours [a]	759 (6.46)	50,676 (8.31)	0.78 (0.73,0.83)	759 (6.46)	4,513 (7.68)	0.84 (0.78,0.91)
NAOI Composite Outcome [a]	670 (5.70)	44,717 (7.33)	0.78 (0.72,0.84)	670 (5.70)	4,289 (7.30)	0.79 (0.72,0.85)
Preterm birth, <37 weeks [b,c]	709 (6.03)	48,414 (7.93)	0.94 (0.87,1.01)	709 (6.03)	4,213 (7.17)	0.98 (0.91,1.06)
Very preterm birth, <32 weeks [b,c]	59 (0.50)	6,862 (1.12)	1.06 (0.82,1.37)	59 (0.50)	606 (1.03)	1.13 (0.88,1.45)

Abbreviations: CI, confidence interval; RR, risk ratio; HR, hazard ratio; NICU, neonatal intensive care unit; NAOI, neonatal adverse outcome indicator.

[a] Estimate values represent the relative risk ratios (RRs) that were estimated using a log-binomial regression model.

[b] Estimate values represent the hazard ratios (HR) that were estimated using a time-dependent Cox model, where Tdap vaccination was modelled as a time-varying exposure.

[c] We limited analyses to Tdap administration at 36 weeks' gestation or earlier (N=69,627) and 31 weeks' or earlier (N=65,825) for preterm birth outcome and very preterm outcome respectively.

4.4.2 Tdap probable vaccination

From our final study cohort, consisting of 621,903 pregnancies, 14,595 (2.3%) were identified as receiving a *probable* Tdap vaccination during pregnancy, based on our broadened definition. **Table 4-11** presents the relationship between *probable* Tdap exposure and obstetrical

outcomes using IPTW to adjust for confounding. Inclusion of *probable* vaccination had minimal impact on the association between maternal vaccination and chorioamnionitis (refer to **Tables 4-11**). Unlike our main analyses, the association between Tdap *probable* vaccination and gestational hypertension was no longer significant (aRR: 0.92; 95% CI: 0.85, 1.00).

Table 4-12 reports the relationship between *probable* Tdap vaccination and perinatal outcomes using IPTW to adjust for confounding. Inclusion of *probable* Tdap vaccination did not impact our findings for the outcomes of preterm and very preterm birth. Similarly, the association between Tdap vaccination and neonatal hospitalizations and morbidity (measured by the NAOI) remained significant. A slightly significant association between Tdap *probable* vaccination and SGA delivery was observed, despite adjustment with IPTW (aRR: 0.94; 95% CI: 0.89, 0.99).

Table 4-11. Association between *probable* Tdap vaccination during pregnancy and obstetrical outcome using propensity-score weighting (n=621,903)

Outcome	Tdap Vaccinated (n=14,595)	Tdap Unvaccinated (n=607,308)	RR (95% CI)	
	N (%)	N (%)	Unadjusted	IPTW-Adjusted [a]
Chorioamnionitis	184 (1.26)	6,030 (0.99)	1.27 (1.10,1.47)	1.00 (0.85,1.18)
Gestational hypertension	506 (3.47)	23,591 (3.88)	0.89 (0.82,0.97)	0.92 (0.85,1.00)

Abbreviations: CI, confidence interval; RR, risk ratio; IPTW, inverse probability of treatment weights
[a] Adjusted using stabilized inverse probability of treatment weights (IPTW) based on propensity score

Table 4-12 Association between *probable* Tdap vaccination during pregnancy and perinatal outcomes using propensity-score weighting (n=621,903)

Outcome	Tdap Vaccinated (n=14,595)	Tdap Unvaccinated (n=607,308)	Estimate (RR/HR [95% CI])	
	N (%)	N (%)	Unadjusted	IPTW-Adjusted [a]
Small for gestational age [b]	1,381 (9.46)	59,405 (9.78)	0.97 (0.92,1.02)	0.94 (0.89,0.99)
NICU admission >24 hours [b]	962 (6.59)	50,473 (8.31)	0.79 (0.75,0.84)	0.90 (0.85,0.96)
NAOI Composite Outcome [b]	858 (5.88)	44,529 (7.33)	0.80 (0.75,0.86)	0.85 (0.79,0.90)

Preterm birth, <37 wk [c,d]	901 (6.17)	48,222 (7.94)	0.94 (0.88,1.00)	0.99 (0.90,1.08)
Very preterm birth, <32 wk [c,d]	83 (0.57)	6,838 (1.13)	1.09 (0.88,1.34)	1.12 (0.85,1.48)

Abbreviations: CI, confidence interval; RR, risk ratio; HR, hazard ratio; IPTW, inverse probability of treatment weights; wk, week; NICU, neonatal intensive care unit; NAOI, neonatal adverse outcome indicator

[a] Adjusted using stabilized inverse probability of treatment weights (IPTW) based on propensity score.

[b] Estimate values represent the relative risk ratios (RRs) that were estimated using a log-binomial regression model.

[c] Estimate values represent the hazard ratios (HR) that were estimated using a time-dependent Cox model, where Tdap vaccination was modelled as a time-varying exposure.

[d] We limited analyses to Tdap administration at 36 weeks' gestation or earlier and 31 weeks' or earlier for preterm birth outcome (N=620,915) and very preterm outcome (N=616,762), respectively.

4.4.3 Health care utilization

In order to assess the impact of health care utilization on our main findings, we additionally adjusted for maternal propensity to seek health care in the 6 months and 2 years prior to pregnancy. The analysis was separately restricted to women with continuous OHIP eligibility for the 6 months (n=609,916) and 2 years (n=579,768) prior to the index pregnancy. **Table 4-13** includes our original IPTW results, as well as results from our sensitivity analyses accounting for health care utilization and prenatal care (**Section 4.4.3** and **4.4.4**). The association between Tdap vaccination and risk for NICU admission exceeding 24 hours was attenuated following these additional health care utilization adjustments (aRR: 0.94; 95% CI: 0.88, 1.00). The remaining outcomes were impacted minimally (**Table 4-13)**.

4.4.4 Prenatal care index

Our final sensitivity analysis accounted for adequacy of prenatal care using the Revised-Graduated Prenatal Care Utilization Index (R-GINDEX). Women who received Tdap during pregnancy were significantly more likely to have had adequate prenatal care (38.2%), when compared to unvaccinated women (26.6%) (standardized difference=0.25). Overall, 8.2% and 2.8% of women did not receive any prenatal care in the unvaccinated and vaccinated groups, respectively (standardized difference=0.24). The proportion of mothers that received

intermediate prenatal care was very similar between the exposed (49.2%) and unexposed (49.6%) groups.

After additionally adjusting the IPTW-adjusted models for the R-GINDEX, the significant associations between Tdap vaccination and neonatal hospitalizations (NICU admissions >24 hours) and morbidity (measured by the NAOI) observed in our main analyses were attenuated in magnitude and no longer statistically significant (**Table 4-13**). All other outcomes were impacted minimally by this additional adjustment (**Table 4-13**).

Table 4-13. Additional sensitivity analyses for association between Tdap vaccination during pregnancy and obstetrical and perinatal outcomes

	Original adjusted results	Additional adjustment variable		
		Maternal outpatient visits (6 months)	Maternal non-obstetric hospitalization (2 years)	Prenatal care index
	IPTW-adjusted estimate (95% CI) [a] (n=621,903)	IPTW-adjusted estimate (95% CI) [a,b] (n=609,916)	IPTW-adjusted estimate (95% CI) [a,c] (n=579,768)	IPTW-adjusted estimate (95% CI) [a,d] (n=621,903)
Obstetrical Outcomes				
Chorioamnionitis [e]	0.95 (0.79,1.15)	0.95 (0.79,1.15)	0.98 (0.81,1.19)	0.95 (0.79,1.14)
Gestational hypertension [e]	0.81 (0.74,0.90)	0.82 (0.74,0.91)	0.82 (0.74,0.91)	0.81 (0.73,0.89)
Perinatal Outcomes				
Small for gestational age [e]	0.95 (0.90,1.01)	0.96 (0.91,1.02)	0.96 (0.90,1.01)	0.96 (0.91,1.01)
NICU admission >24 hours [e]	0.92 (0.87,0.98)	0.94 (0.88,1.00)	0.94 (0.88,1.00)	0.98 (0.92,1.04)
NAOI Composite Outcome [e]	0.85 (0.79,0.91)	0.84 (0.78,0.90)	0.84 (0.78,0.90)	0.94 (0.87,1.03)
Preterm birth, <37 wk [f]	0.99 (0.87,1.12)	0.94 (0.87,1.02)	0.94 (0.87,1.02)	0.94 (0.87,1.02)
Very preterm birth, <32 wk [f]	1.03 (0.71,1.50)	1.07 (0.83,1.39)	1.04 (0.79,1.35)	1.06 (0.82,1.37)

Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weights; NICU, neonatal intensive care unit; NAOI, neonatal adverse outcome indicator

[a] Adjusted using stabilized inverse probability of treatment weights (IPTW) based on propensity score.

[b] Additionally, adjusted for maternal propensity to use health care (≥2 outpatient visits during the 6-month period prior to the index pregnancy)

[c] Additionally, adjusted for maternal propensity to use health care (≥1 non-obstetric hospitalization during the 2-year period prior to the index pregnancy)

[d] Additionally, adjusted for adequacy of prenatal care (Revised-Graduated Prenatal Care Utilization Index (R-GINDEX))

[e] Estimate values represent the relative risk ratios (RRs) that were estimated using a log-binomial regression model.

[f] Estimate values represent the hazard ratios (HR) that were estimated using a time-dependent Cox model, where Tdap vaccination was modelled as a time-varying exposure.

CHAPTER 5. DISCUSSION

In February 2018, NACI published their revised Canadian recommendations on the use of Tdap vaccination during pregnancy.[7] This decision was based on similar policies implemented in jurisdictions such as the US, the UK and Australia, combined with the increasing collection of studies evaluating maternal Tdap vaccine safety and effectiveness. The goal of introducing universal maternal pertussis immunization programs in Canada and these other countries is to reduce pertussis-related morbidity and mortality among infants less than one year of age.

Although numerous epidemiological studies have already assessed the impacts of maternal pertussis vaccination initiatives by reporting trends and evaluating safety,[10,11,20–22,12–19] research within the Canadian context is limited. Prior to the routine recommendation release in Canada, temporary provincial advisories were introduced by NACI[24] in 2008 and partial recommendations by SOGC[23] in 2014. These initial Canadian recommendations, combined with the demonstrated success of maternal pertussis vaccine programs within other jurisdictions, and the persistent occurrence of pertussis outbreaks internationally, prompted some Canadian maternity care providers to begin immunizing pregnant women against pertussis even prior to 2018. Consequently, this has provided a unique opportunity to assess Tdap vaccination during pregnancy in Ontario prior to the policy change.

The aim of this Master's thesis, using data from the pre-policy time period, was to describe the characteristics of women in Ontario who received Tdap immunization during pregnancy and to assess the associations between maternal Tdap immunization with obstetrical and perinatal outcomes.

5.1 Objective 1

5.1.1 Statement of principal findings

This study provides novel and important data on Tdap coverage during pregnancy prior to Canada's routine recommendation for Tdap vaccination during pregnancy. Between FY2012 and FY2016, we identified 11,750 (1.9%) infants born in Ontario who were exposed to Tdap in utero. The maternal Tdap vaccination rate increased by over 8-fold across the study time period, reaching a value of 39.1 per 1000 women in FY2016. Given the recently revised NACI recommendation, the increase in Tdap coverage observed across our study time period is likely an indication that uptake will continue to increase. Our analysis found several maternal characteristics associated with higher Tdap vaccination rates in the pre-policy period, including nulliparity, residing in the Toronto region, receiving adequate or intensive prenatal care, and living in a high-income neighbourhood. Compared to unvaccinated women, vaccinated women in our cohort received a higher proportion of their prenatal care from a family physician or general practitioner during both gestational time periods assessed (20 weeks' gestation to delivery and 27-32 weeks' gestation). In addition, approximately 76% of our vaccinated cohort received Tdap vaccination from a family physician. Lastly, vaccination receipt during the optimal time period, according to current Canadian guidelines (27-32 weeks' gestation), increased from 15.5% among Tdap-vaccinated women who delivered in FY2012 to 48.8% among vaccinated women who delivered in FY2016.

5.1.2 Interpretation of study findings

Our finding that Tdap vaccination was lower among women of younger age (i.e., <24 years), from a neighbourhood of lower income, receiving inadequate or no prenatal care and having higher material deprivation, is consistent with previous studies on vaccine uptake during pregnancy.[112,179–183] Higher Tdap uptake among women receiving intensive and adequate

prenatal care could be attributed to increased contact with health care providers and therefore more opportunities to receive vaccination. Interestingly, in our multivariable model, we observed lower vaccine uptake among women residing in a neighbourhood with a higher concentration of recent immigrants—despite crude rates being highest among this group. Several previous studies report lower vaccination rates in geographic areas with a higher proportion of immigrants or ethnic minorities.[180,184,185] This has been attributed to lower socioeconomic status, low education, language barriers, inability to communicate effectively with health care providers and limited access to health care services.[115,180,186–188] Despite universal access to health care services in Ontario, it is possible that similar barriers exist.

Consistent with other evidence, our study found that most women who received Tdap during their pregnancy received the vaccine from a family physician (75.6%), compared to all other physician specialties.[109] This is likely attributed to vaccination being a standard part of practice for general practitioners. In contrast, less than 20% of vaccinated women in our study received Tdap administration from an obstetrician. A study conducted by Chamberlain et al. in Georgia, US found that despite 60% of pregnant mothers in their study assigning obstetricians as their primary care provider, only one-third reported ever receiving a vaccine from their obstetrician.[113] The authors stressed the importance of incorporating routine vaccination into prenatal care visits, which can help increase vaccine access within an obstetrical setting, and overall acceptance within the pregnancy. Further, the literature has repeatedly reported the impact of vaccine recommendations from health care providers on increasing vaccine uptake during pregnancy.[113,115–118] A recent study by Mehrota et al. consisted of 24 interviews with obstetricians to determine barriers of maternal Tdap vaccine recommendation.[189] Their findings indicate that although obstetricians recognize the benefits of Tdap, implementation challenges

such as insurance reimbursement, on-site storage and transportation issues, and financial concerns for practice all prevent routine recommendation and administration of Tdap during pregnancy. The ability to properly store the Tdap vaccine is of particular concern in the present study, as Tdap vaccination was not yet routinely recommended which likely reduced on-site vaccine availability for women who received prenatal care from an obstetrician. Moreover, compared to family physicians, obstetricians in our study might not have been aware of the OHIP billing code associated with Tdap vaccine administration, removing the financial incentive to immunize.

In our cohort, over half of the women who delivered in FY2012 and received Tdap were vaccinated prior to 20 weeks' gestation. Considering the gestational timing of immunization and policy revisions within other countries only beginning during this time, we hypothesize that the purpose of those vaccinations may have been unrelated to infant protection against pertussis. It is possible that the women were unaware of their pregnancy during their immunization encounter, or that the vaccine was administered as a prophylactic tetanus booster. Nevertheless, the percentage of vaccinated women who received Tdap during the recommended time period (27-32 weeks' gestation) increased considerably across our study time period, reaching almost 50% of Tdap-vaccinated women in FY2016. This increase is likely attributed to the advancement of knowledge on the safety and importance of maternal Tdap vaccination, particularly in the optimal time window, as well as the existence of routine recommendations in many other countries by this time period. This finding indicates early adherence to Canada's current recommendations, as Tdap was typically received within the optimal timing suggested to confer the greatest level of infant protection.

5.1.3 Strengths and limitations

This study provides a baseline description of maternal Tdap vaccination in Ontario and has several strengths. Utilization of multiple linked health administrative datasets allowed us to assemble a large sample of Tdap-vaccinated pregnant women, despite the pre-policy study time period. These datasets provided information on several maternal, pregnancy and care provider characteristics, all of which helped to understand Tdap vaccination practices in pregnant women in Ontario prior to the national policy recommending routine Tdap vaccination in pregnancy. Having access to the exact date of Tdap vaccination enabled assessment of timing of vaccination during the pregnancy, relative to recommended timing, and this will be important for ongoing policy assessment in the future.

Despite these strengths, our study has several limitations mainly due to the dependence on variables and data available within the selected databases. Our assessment of Tdap vaccination was reliant on accurate fee coding within the databases; if Tdap administration failed to generate a medical billing claim, we might have underestimated the true coverage. Among the unvaccinated women, we did not have information on whether the vaccine was offered, but not received, during prenatal care. Further, details regarding the reasons for not receiving vaccination were not available within the databases, precluding our ability to identify barriers to receiving maternal Tdap vaccination within Ontario. Assessment of physician characteristics was limited to family physicians and obstetricians, which excludes prenatal care conducted by midwives or other health care professionals. Finally, we restricted our cohort to women with uninterrupted OHIP insurance throughout pregnancy to ensure our ability to measure Tdap vaccination in the health administrative databases. It is possible that women with discontinuous

or no provincial health care insurance might have different characteristics than those reported here.

5.2 Objective 2

5.2.1 Statement of principal findings

For our second objective employing the same cohort of pregnant women in the pre-policy time period, we found no increased risk of any adverse obstetrical or perinatal outcomes following Tdap vaccination during pregnancy. Interestingly, we found a significant inverse association between maternal Tdap vaccination and gestational hypertension, which persisted throughout the majority of our sensitivity analyses. The exception to this was when cases of *probable* Tdap vaccination were incorporated within the definition of our exposure, which attenuated the estimate. With respect to the perinatal outcomes assessed, our main findings indicate a statistically significant inverse association between Tdap vaccination and NICU admissions exceeding 24 hours and neonatal morbidity (measured by the NAOI composite outcome); however, these associations were attenuated following sensitivity analyses accounting for health care utilization and access.

5.2.2 Interpretation of study findings

The unexpected significant inverse association between Tdap vaccination and gestational hypertension observed in our main analyses has not been reported in previous research assessing this outcome.[14,16] It is important to note that we did not have information regarding the timing of disease onset, which limited our ability to account for the temporality of the association in our analyses. In contrast, Griffin et al. was able to account for the timing of diagnosis in their statistical analyses and found no association between Tdap vaccination and gestational hypertension (aHR: 1.02; 95% CI: 0.88, 1.19).[14] Interestingly, however, the authors found a

significant reduction in risk of pre-eclampsia with severe features (aHR: 0.61; 95% CI: 0.39, 0.94), which they attributed to residual confounding.[14] Another study by Kharbanda et al. examined hypertensive disorders of pregnancy, which included gestational hypertension, preeclampsia, eclampsia, and hypertension not otherwise specified.[16] For this outcome, they limited their analyses to compare women exposed to Tdap prior to 20 weeks' gestation versus women unexposed throughout their pregnancy, to help ensure the exposure preceded the outcome. Receipt of Tdap before 20 weeks' gestation was not associated with hypertensive disorders of pregnancy (aRR: 1.09; 95% CI: 0.99, 1.20).[16] Unlike our study, these authors had data regarding maternal race/ethnicity, an important factor associated with the risk of developing gestational hypertension. Our findings on gestational hypertension should, therefore, be interpreted with caution as there have not yet been any biological mechanisms proposed to explain this association, and our analyses were limited to the information within the databases. It is very likely that the association was due to residual confounding and/or temporal issues with timing of diagnosis that we could not account for.

After adjusting our estimates for chorioamnionitis, we did not find a significant association with Tdap vaccination. Moreover, the association was non-significant throughout all our sensitivity analyses. The current evidence regarding Tdap vaccination and chorioamnionitis remains inconsistent with several studies finding contradictory findings. Initially, Kharbanda and colleagues conducted a large observational study of over 26,000 vaccinated women and detected a small increased risk of chorioamnionitis following maternal Tdap vaccination (aRR: 1.19; 95% CI: 1.13, 1.26).[16] The authors suggested interpreting their results with caution, as they did not find an increased risk for preterm birth, which is a major sequela of chorioamnionitis. Subsequent studies conducted by Morgan et al.[20] and Berenson et al.[10], however, were not able to

reproduce these findings. Potential explanations for Kharbanda et al.'s findings include heterogeneity in chorioamnionitis diagnosis and the inability to control for important risk factors (e.g., prolonged labour, genital tract infections). More recently, two additional studies by DeSilva et al.[11] and Layton et al.[19] also found a small increased risk for chorioamnionitis. Yet, the authors still did not find any increased risk for infant outcomes associated with maternal chorioamnionitis—indicating no clear consensus or biological plausibility for this association.

Throughout all our analyses, we did not observe any relationship between maternal Tdap vaccination and risk of preterm or very preterm birth. Our results are consistent with previous studies of Tdap exposure and preterm birth, which have reported point estimates either below or close to the null value.[10,14,16,20,155] In contrast, we observed an 8% reduction in the risk of a NICU admission exceeding 24 hours among infants exposed to Tdap in utero, compared to unexposed infants. Adjusting for maternal pre-pregnancy health care utilization and adequacy of prenatal care in our sensitivity analyses attenuated the magnitude of our estimate, making the relationship no longer statistically significant. This may be due to the demonstrated association between inadequate prenatal care and adverse neonatal outcomes.[177,190] For this reason , Berenson et al.'s study only included women with adequate prenatal care (>4 prenatal care visits).[10] As part of their sensitivity analyses, however, the authors included women with <4 prenatal care visits to evaluate the impact of their decision on their findings.[10] Including mothers with inadequate prenatal care generated a significant inverse association between maternal Tdap vaccination and risk of having an infant admitted to the NICU or having a low birth weight infant.[10] Thus, the authors reported an increased bias towards poorer outcomes for unvaccinated mothers when mothers with inadequate prenatal care were included in their analyses.[10]

Our study did not find an increased risk of SGA birth among infants exposed to Tdap vaccination in utero. Although the inverse association between Tdap vaccination and SGA birth was significant in two of our sensitivity analyses (adjustment through propensity score matching and using an expanded exposure definition), the magnitude of these changes were minimal and the direction of the association still resembled our main findings. Consistent with our findings, previous studies assessing adverse perinatal outcomes such as preterm birth, SGA birth and NICU admissions have not demonstrated any increased risk after exposure to Tdap during pregnancy.[10,11,14,16,20]

Most of this evidence, however, is drawn from retrospective studies, with varying levels of methodologic quality. Morgan et al. conducted a small low-quality retrospective study, which consisted of 7,152 vaccinated mothers and almost 97% Tdap coverage. Compared to vaccinated women, unvaccinated women in their cohort had significantly higher preterm birth rates (6% vs 12%, $p<0.001$), incidence of SGA birth (10% vs 15%, $p=0.03$) and length of neonatal hospitalization (3.9 vs 4.7 days, $p<0.001$).[20] The authors not only failed to employ analytical techniques to address potential confounding bias (e.g., propensity scores), but also did not account for the timing of Tdap in their analyses.[20] Another small retrospective study consisting of 1,759 women who delivered in Texas, found no association between maternal Tdap vaccination and preterm delivery (aOR: 1.09; 95% CI: 0.81, 1.48), NICU admission (aOR: 0.78; 95% CI: 0.56, 1.08), or SGA birth (aOR: 0.89; 95% CI: 0.55, 1.46).[10] In addition to the small sample size, the authors also did not use comprehensive statistical methods to minimize bias.[10] A national retrospective cohort study using linked administrative datasets within New Zealand, observed a 15% reduction in risk of preterm birth among Tdap vaccinated women, compared to unvaccinated women.[14] Despite the study's larger sample size (n=68,550), the Immunization

Subsidies Collection (IMMS) database used to capture exposure information was found to have very poor sensitivity when compared to a New Zealand referent standard (Primary Healthcare Organizations).[14] Due to these issues of vaccine exposure misclassification encountered within the IMMS database, the authors advised cautious interpretations of their study findings.[14]

To our knowledge, this is the first safety study of Tdap during pregnancy that utilized the NAOI composite outcome. The observed pattern of adverse events by gestational age at birth in our study was comparable to reports by the Australian creators[153] and UK adaptors[191] of the NAOI (refer to **Figure 4-5** within our results). We found a small and statistically significant inverse association between Tdap exposure and risk of having at least one of the outcomes included in the composite. This observed association persisted through most of our sensitivity analyses but was attenuated following adjustment for adequacy of prenatal care. A large-scale US cohort study examining the safety of maternal Tdap administration assessed several of the individual adverse outcomes that are components of the NAOI composite, such as respiratory distress, encephalopathy, seizures and neonatal sepsis.[19] After adjustment through IPTW, Tdap vaccination was not associated with increased risk of any newborn outcomes assessed, and a slight reduction in risk of neonatal sepsis (aHR: 0.89; 95% CI: 0.84, 0.94) following optimal Tdap vaccination (≥27 weeks' gestation) was observed.[19] Similarly, DeSilva et al. examined five neonatal outcomes individually (transient tachypnea, neonatal sepsis, neonatal pneumonia, respiratory distress syndrome, newborn convulsions) and as a composite outcome.[11] The authors found no increased risk of any of these five individual outcomes, or the composite outcome (aRR: 1.04; 95% CI: 0.98, 1.11), following Tdap vaccination.[11]

5.2.3 Strengths and limitations

Although numerous epidemiological studies have evaluated the safety of maternal pertussis vaccination on numerous obstetrical and perinatal outcomes,[10,11,20–22,12–19] this is the first study to assess these outcomes within the Canadian population. Using multiple linked province-wide health administrative datasets within Ontario was an important strength of our safety study. Even after study exclusions, we were able to evaluate a large number of pregnant women and linked newborns in our study, which included almost 12,000 women immunized with Tdap during pregnancy, despite reflecting the pre-policy time period. Additionally, having access to detailed information regarding pregnancy and birth allowed efficient assessment of multiple obstetrical and neonatal outcomes for a single exposure. Moreover, data regarding timing of Tdap vaccination (i.e., date of vaccination) were available, which allowed us to incorporate a time-varying exposure in our analyses. Considering the gestational timing of vaccination is critical for assessing time-dependent outcomes, such as preterm and very preterm birth.

There have been some concerns regarding the ability of hospital administrative data to accurately capture neonatal morbidity, partially as a result of underreporting.[192] By utilizing the composite NAOI, which includes a combination of procedures and diagnoses, our study was less susceptible to this issue as severely ill infants usually have multiple diagnoses and procedures recorded, reporting of procedures are most often more reliable than diagnoses, and the occurrence of highly severe conditions have a higher probability of being reported.[153,191]

Using a logistic regression model, we computed propensity scores for each participant, which represented the predicted probability of receiving Tdap vaccination, conditional on the baseline covariates included in our model. This technique attempts to improve the comparability

of exposure groups when randomization is not possible.[157] Methods of propensity score adjustment have exhibited greater success in reducing potential confounding, compared to conventional methods of multivariable adjustment.[158,159] Our main analyses employed stabilized IPTW, derived from propensity scores, to control for confounding. Weighting through IPTW allows for the formation of a pseudo-population, where the distribution of baseline covariates is effectively independent of the treatment assignment.[157] Further, stabilization of these weights helps to increase precision of the estimated treatment effect.[160]

As there are multiple ways to use propensity scores in an analysis, and no clear indication when to select one method over another, we used a second method of confounding adjustment through propensity scores—propensity score matching—in a sensitivity analysis. The two propensity score methods yielded similar results, with two exceptions. Compared to our IPTW-adjusted results, the magnitude of the association between maternal Tdap vaccination and gestational hypertension was slightly attenuated following adjustment through propensity score matching (18% reduction in risk [IPTW] versus 12% reduction in risk [propensity score matching]). Nonetheless, a significant inverse association was observed in both methods of propensity score adjustment. Second, the propensity score matched analyses provided evidence of a significant inverse association between maternal Tdap vaccination and SGA, which was not originally found in the IPTW results. Even with these differences, our conclusions regarding vaccine safety did not change, as the direction of association remained consistent with our main IPTW results.

Despite the achievement of balance with respect to baseline covariates in our sample, propensity scores are limited to accounting for measured variables included in the model. As we were restricted to the variables within the databases, we cannot rule out the possibility of residual

confounding owing to unmeasured confounders. In particular, information regarding smoking, alcohol and drug use, and body mass index were potentially important factors that were not available.[12] Vaccinated and unvaccinated women might have inherent differences based on these unmeasured confounders, all of which are also risk factors for poor birth outcomes. Typically, healthier women are more likely to receive vaccination and less likely to have adverse birth outcomes, introducing the possibility of confounding via "healthy vaccine" bias.[193,194]

Although timing of vaccination was available in the database, we did not have information regarding timing of disease diagnosis which limited our ability to account for the temporality of the association between Tdap exposure and gestational hypertension. This was of less concern for chorioamnionitis, as diagnosis most often occurs at the time of labour.[143] Owing to the difficulties of reliably diagnosing chorioamnionitis clinically, it is likely that there was some misclassification of the outcome. Since we would expect any such misclassification to be non-differential by exposure, this means that our estimated association is likely biased toward the null value, implying we could have underestimated the association between Tdap vaccination during pregnancy and chorioamnionitis. A future validation study to assess the sensitivity and specificity of diagnostic codes for chorioamnionitis in the administrative databases against medical chart review would be a useful contribution of future research given the important of ongoing monitoring of this outcome.

Misclassification of Tdap exposure was another potential limitation. Since 2011, only one adult dose of Tdap has been publicly funded in Ontario.[195] Although our study time period is prior to the NACI recommendation for routine Tdap vaccination of all pregnant women, some health care providers in Ontario were already administering Tdap to pregnant women. However, as public funding for multiple adult Tdap boosters is lacking in Ontario, there is a possibility that

providers refrained from billing for the Tdap vaccine to bypass additional costs for the mother. Since we relied on a pertussis vaccine billing code to identify our exposure (OHIP code: G847), mothers who had an undocumented Tdap vaccination for this reason would have been misclassified as unexposed in our study. Further, vaccine-specific codes, including G847 for Tdap, were introduced in September 2011[172]—only 7 months prior to the start of our study. Nonetheless, our sensitivity analysis which included cases of Tdap *probable* vaccination helped to mitigate this effect, by including potential cases of Tdap vaccination billed under a generic immunization code. Although the sensitivity of the Tdap vaccine code is uncertain in this study, specificity can be assumed to be relatively high, as OHIP billing claims have previously demonstrated high specificity for immunization among children (several childhood vaccines: 81% to 92%) [172] and adults (influenza vaccine: 97%) [196] in Ontario. In addition, any misclassification of exposure can be expected to be irrespective to disease status and therefore non-differential, resulting in a bias towards the null.

Low exposure prevalence is generally associated with a higher degree of bias when the specificity is low, regardless of sensitivity.[197]As Tdap during pregnancy was uncommon in our study, and specificity is likely to have been high, we conclude that any non-differential misclassification of the exposure likely have a small impact on the magnitude of our point estimates.[197]

5.3 Implications for future research and public health

Despite the low vaccine coverage relative to our large study population size, this study provides preliminary descriptive and safety information on maternal Tdap vaccination within Ontario, which is important for establishing baseline Canadian evidence to inform the NACI Tdap immunization policy recommendations.

Results from our first objective indicate differences in vaccination rates with respect to several maternal and pregnancy characteristics, which highlights the importance of using local data to identify specific populations requiring attention through public health initiatives. Further research is required to identify, and address barriers faced by Canadian health care providers in recommending and administering Tdap vaccination during pregnancy. More specifically, attempts to incorporate vaccination as part of routine prenatal care by obstetricians should be a priority to help increase adherence to the revised NACI recommendation. This includes increasing education for clinicians on the importance of vaccine administration and documentation for research purposes. Future studies should re-evaluate vaccine coverage in Ontario, to determine if improvements occur following the implementation of the NACI maternal Tdap vaccination policy in 2018.

Our findings from the second objective provide additional safety evidence of maternal Tdap vaccination in the Canadian context. Continued safety monitoring is required to retain support from the pregnant population and assist ongoing public health initiatives aimed at reducing pertussis related morbidity and mortality among infants. The outcomes assessed in our study are not representative of all relevant outcomes for the safety assessment of maternal Tdap vaccination. As such, our findings should be reviewed in conjunction with other large safety studies for a comprehensive interpretation. Considering a large proportion of safety data available consists of assessing the period during pregnancy and up to delivery, future research should extend the follow up period to provide further reassurance. Lastly, the association between maternal Tdap vaccination and chorioamnionitis requires additional investigation, to help understand the inconsistencies observed by studies thus far.

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APPENDICES

Appendix I. Summary of studies focusing on safety of pertussis containing vaccines during pregnancy

Reference	Study Design	Outcomes	Main Findings
Becerra-Culqui et al., 2018[198]	Retrospective cohort	Autism spectrum disorder	Maternal Tdap vaccination was not associated with an increased autism spectrum disorder risk.
Berenson et al., 2016 [10]	Retrospective analysis of electronic medical records	Numerous obstetric and neonatal outcomes	No difference in obstetric (chorioamnionitis, preterm birth, PROM, induced labour) or neonatal (SGA, low birth weight, birth defects, NICU admission) outcomes
DeSilva et al., 2016 [101]	Retrospective cohort	Structural defects in the offspring, including microcephaly	Maternal Tdap not associated with risk for microcephaly or other structural defects
DeSilva et al., 2017 [11]	Retrospective cohort	Chorioamnionitis, and individual and composite outcomes of the following: TTN, neonatal sepsis, neonatal pneumonia, respiratory distress syndrome, newborn convulsions	Small but positive association between chorioamnionitis and maternal Tdap, but absence of increased risk for clinically significant outcomes associated with chorioamnionitis
Donegan et al., 2014 [12]	Retrospective cohort	Stillbirth	No increased incidence of stillbirth.
Fortner et al., 2016 [13]	Prospective cohort	Local and systemic events	Tdap vaccine was well tolerated in both pregnant and nonpregnant women. Pregnant women reported more moderate/severe injection-site pain and malaise. but frequency was consistent with clinically reported rates for Tdap vaccine.

Griffin et al., 2018 [14]	Retrospective cohort using New Zealand national database	Numerous primary and secondary obstetrical and neonatal outcomes	No increased risk for any of their primary outcomes (preterm labour, pre-eclampsia, eclampsia, gestational hypertension, fetal growth restriction, post-partum haemorrhage). Lactation disorder was the only outcome with significantly increased hazard ratio (residual confounding). Tdap vaccination had protective effect on pre-eclampsia with severe features, preterm labour, preterm delivery, and antenatal bleeding.
Petousis-Harris et al., 2016[15]	Prospective observational study in New Zealand	Injection site reactions, systemic symptoms and SAEs	Vaccination with Tdap in pregnant women was well tolerated with no SAE likely to be caused by the vaccine.
Hoang et al., 2015 [199]	Randomized controlled trial	AEs and SAEs	All premature contractions occurred more than 1 month after vaccination. Preterm delivery occurred 5 weeks after vaccination. No significant differences between groups.
Kharbanda et al., 2014 [16]	Retrospective observational	SGA, chorioamnionitis, preterm birth and hypertensive disorders of pregnancy	No increased risk in preterm birth, SGA or hypertensive disorders in pregnancy. Small but statistically significant increase in chorioamnionitis.
Kharbanda et al., 2016[18]	Retrospective matched cohort	Composite outcome of medically attended acute adverse events, neurological events, thrombotic events, proteinuria, gestational diabetes, thrombocytopenia, cardiac events, venous thromboembolism	No acute maternal safety signals were detected.

Layton et al., 2017 [19]	Retrospective analysis of electronic medical records	Maternal adverse immunization reactions, maternal birth outcomes, and newborn outcomes	Prenatal Tdap immunization was not associated with newborn adverse event. Potential associations with chorioamnionitis and postpartum hemorrhage were found in original analysis, but a sensitivity analysis found no associations.
Morgan et al., 2015 [20]	Retrospective cohort	Numerous obstetric and neonatal outcomes	No adverse pregnancy outcomes associated with Tdap vaccination at 32 weeks gestation. Preterm birth rates, incidence of SGA and length of neonatal hospitalization were significantly increased in the unvaccinated group.
Moro et al., 2016 [200]	Retrospective analysis of electronic medical records	Adverse infant and pregnancy outcomes in women who received Tdap during pregnancy	No new or unexpected vaccine AEs were noted among women who received Tdap during pregnancy.
Munoz et al., 2014 [21]	Randomized controlled trial	Maternal and infant adverse events, pertussis illness, and infant growth and development until age 13 months	No increased risk of adverse events in pregnant women and infants.
Regan et al., 2016 [103]	Prospective cohort	Systemic and local reactions	Women who received pertussis vaccine during pregnancy more commonly reported a local reaction, compared to women who received an influenza vaccine during pregnancy. Results still support the safety of maternal pertussis vaccination.
Shakib et al., 2013 [22]	Retrospective cohort	Numerous obstetric and neonatal outcomes	No difference in adverse obstetric or neonatal outcomes.
Sukumaran et al., 2015 [17]	Retrospective cohort	Acute adverse events (fever, allergy, local reactions) and adverse birth outcomes (SGA, preterm birth, low birth weight)	No differences in maternal AEs or adverse birth outcomes relating to the timing of prior tetanus-containing vaccination.

Talbot et al., 2010 [201]	Prospective	Antenatal AEs	No new or unexpected vaccine AEs were noted among women who received Tdap during pregnancy.
Villarreal Pérez et al., 2017 [202]	Randomized controlled trial	Immunogenicity, interference of maternal antibodies and various safety outcomes	No statistically significant difference between experimental groups were found in terms of AEs for both mother and baby
Walls et al., 2016 [203]	Prospective observational	GA at birth, growth parameters, congenital anomalies, pertussis infection	No adverse events attributable to vaccine exposure. No cases of pertussis in cohort, despite high rates of disease in community.
Zheteyeva et al., 2012 [204]	Retrospective analysis of electronic medical records	Adverse maternal, infant or fetal events	No concerning patterns in maternal, infant or fetal outcomes

Abbreviations: PROM (premature rupture of membranes), SGA (small for gestational age), NICU (neonatal intensive care unit), AE (adverse event), SAE (serious adverse event), TTN (transient tachypnea of newborn); VSD (Vaccine Safety Datalink)

Appendix II. OHSN Research Ethics Board Approval

From: Garde, Avanti [mailto:agarde@ohri.ca]
Sent: June-22-18 8:22 AM
To: Fell, Deshayne
Cc: Wilson, Lindsay
Subject: OHSN-REB Protocol #20180432-01H: Ethics and Institutional Approval Granted

Good Morning Dr. Fell,

RE: Protocol #20180432-01H: Impact of maternal pertussis immunization on pregnancy outcome and child health

Ethics Approval has been granted for the above-listed protocol. The Approval Letter is uploaded in Ethics Tab 11: Response, Section 117.

Additionally, Institutional Approval has also been granted and is uploaded in the Approval Tab; you may begin your study.

Please do not hesitate to contact me should you have any questions or concerns.

Thank you,
Avanti Garde
Research Ethics Coordinator
Ottawa Health Science Network – Research Ethics Board (OHSN-REB)
Ottawa Hospital Research Institute

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The Ottawa Hospital | L'Hôpital d'Ottawa
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Appendix III. CHEO Research Ethics Board Approval

RESEARCH INSTITUTE
INSTITUT DE RECHERCHE

CHEO Research Ethics Board
Approval - Delegated Review

Principal Investigator: Dr. Deshayne Fell
REB Protocol No: 18/10PE
Romeo File No: 20180263
Project Title: CHEOREB# 18/10PE - Impact of maternal pertussis immunization on pregnancy outcome and child health

https://outlook.office.com/owa/?viewmodel=ReadMessageItem&ItemID=AAMkADUxZDAxMDlkLTJkNmMtNDIzYi04ODRmLTczNmY5NjA1MDZmYwBGAAAAAADSc

5/29/2018 FW: REB Protocol No 18/10PE - Final Approval - Delegated... - Fakhraei, Romina

Primary Affiliation: Clinical Research\Epidemiology
Protocol Status: Active
Approval Date*: May 28, 2018
Valid Until:** May 15, 2019
Annual Renewal Submission Deadline: April 15, 2019

Documents Reviewed & Approved:

Document Name	Comments	Version Date
Protocol	Study Protocol v. 1 May 16, 2018	2018/05/16
Other Document	List of Databases/Data fields	2018/05/16

Appendix IV. Study outcome definitions and diagnostic codes

Study Outcome	Definition	Data source and/or ICD10 Diagnostic Code
Obstetrical Outcomes		
Gestational hypertension	Hypertension in pregnant women (blood pressure >140/90mmHg) after 20 weeks of gestation without presence of proteinuria or preeclampsia.	O13, O16
Chorioamnionitis	Acute inflammation of the chorion and membranes of the placenta due to bacterial infection.	O41.12, O41.13, O41.19
Perinatal Outcomes		
Small for gestational age	Birth weight <10th percentile for gestational age and sex.	Measured using infant sex, gestational age, and birth weight variables in MOMBABY.
NICU Admission >24 hours	Intensive care unit admission lasting >24 hours	Measured using DAD variables (special care unit admission and discharge dates) from infant records.
NAOI composite outcome	The NAOI is a validated composite outcome that will be utilized to identify neonatal morbidity. It combined ICD-based codes relating to treatments of severe events.	Refer to **Appendix III** for a complete list of the diagnostic and procedural codes included.
Preterm birth	Live birth prior to 37 weeks of gestation.	Measured using gestational age variable in MOMBABY.
Very preterm birth	Live birth prior to 32 weeks of gestation.	Measured using gestational age variable in MOMBABY.

Appendix V. Components of the Neonatal Adverse Outcome Indicator (NAOI) composite outcome

Components of Variable	MOMBABY Variable	DAD Variable	Diagnosis Code (ICD-10)
Gestational age <32 weeks	B_GESTWKS_DEL (or M_GESTWKS_DEL)		
Birth weight <1500grams	B_WEIGHT		
Respiratory distress syndrome			P22.0

Seizures			P90, R56
Intraventricular hemorrhage (grades 2,3, or 4)			P52.1, P52.2
Cerebral infarction			I63
Periventricular leukomalacia			P91.2
Birth trauma (intracranial hemorrhage paralysis due to brachial plexus injury, skull or long bone fracture)			P10.0 to P10.3, P13.0, P13.2, P13.3, P14.0, P14.1
Hypoxic ischemic encephalopathy			P91.5, P91.81, P91.6
Necrotizing enterocolitis			P77
Bronchopulmonary dysplasia			P27.1
Sepsis/septicemia			P36, A40, A41.5, A41.9, B95.1, B96.2
Pneumonia			P23, J12 to J18
Primary atelectasis			P28.0
Respiratory failure			P28.5
	MOMBABY Variable	**DAD Variable**	**Procedure code (CCI)**
Resuscitation			1.GZ.30

Ventilatory support (mechanical ventilation and/or CPAP)			1.GZ.31
Central venous or arterial catheter			1.IS.53, 1.KV.53
Transfusion of blood or blood products		BTANY, BTOTHER	
Pneumothorax requiring an intercostal catheter			1.GT.33

Appendix VI. Baseline characteristics included in propensity score model

Variables included
Maternal age
Parity
Multiple birth
Baby's sex
Pre-existing maternal medical conditions (chronic hypertension, diabetes, asthma, heart disease, thyroid disease)
Obstetrical complications (placenta previa, placental abruption, preeclampsia, eclampsia, gestational diabetes, PROM)
UTI during pregnancy
Fiscal year of delivery
Maternal world region of birth
Marginalization indices from ONMARG database (residential instability, material deprivation, dependency, ethnic concentration)
Rural residency
Neighborhood income quintile
Public health unit region of residence

Appendix VII. Baseline characteristics of the cohort before and after propensity score matching

Characteristic	Unmatched cohort			Propensity score-matched cohort		
	Tdap vaccinated women, N (%) [a] (n=11,750)	Tdap unvaccinated women, N (%) [a] (n=610,153)	Stand Diff [b]	Tdap vaccinated women, % [a] (n=11,750)	Tdap unvaccinated women, % [a] (n=58,750)	Stand Diff [b]
Gestational age at vaccination (week)						
<20	2,641 (22.5)	-	-	-	-	-
20-26	1,153 (9.8)	-	-	-	-	-
27-32	4,903 (41.7)	-	-	-	-	-
33+	3,053 (26.0)	-	-	-	-	-
Maternal age (years)						
<20	179 (1.5)	14,080 (2.3)	0.06	1.5	1.4	0.01
20–24	787 (6.7)	65,615 (10.8)	0.14	6.7	6.6	0
25–29	3,305 (28.1)	163,942 (26.9)	0.03	28.1	28.0	0
30–34	4,659 (39.7)	223,707 (36.7)	0.06	39.7	39.6	0
≥35	2,820 (24.0)	142,809 (23.4)	0.01	24.0	24.3	0.01
Birth year (in fiscal year)						
2012-13	594 (5.1)	127,585 (20.9)	0.49	5.1	5.3	0.01
2013-14	1,628 (13.9)	124,744 (20.4)	0.18	13.9	13.6	0.01
2014-15	2,099 (17.9)	123,945 (20.3)	0.06	17.9	18.1	0.01
2015-16	2,903 (24.7)	122,767 (20.1)	0.11	24.7	24.9	0
2016-17	4,526 (38.5)	111,112 (18.2)	0.46	38.5	38.2	0.01
Parity						
0 (nulliparous)	6,066 (51.6)	269,466 (44.2)	0.15	51.6	51.4	0
≥1 (multiparous)	5,684 (48.4)	340,687 (55.8)	0.15	48.4	48.6	0
Multiple birth						
No	11,474 (97.7)	589,055 (96.5)	0.07	97.7	98.0	0.02
Yes	276 (2.3)	21,098 (3.5)	0.07	2.3	2.0	0.02
Baby's sex						
Female	5,706 (48.6)	297,283 (48.7)	0	48.6	48.4	0

Male	6,044 (51.4)	312,870 (51.3)	0	51.4	51.6	0
History of preterm birth						
Nulliparous	6,066 (51.6)	269,466 (44.2)	0.15	51.6	51.4	0
Parous – no history of preterm birth	5,352 (45.5)	316,038 (51.8)	0.13	45.5	45.2	0.01
Parous – history of preterm birth	332 (2.8)	24,649 (4.0)	0.07	2.8	3.4	0.03
Pre-existing maternal medical condition [c]						
No	11,399 (97.0)	592,496 (97.1)	0.01	97.0	97.0	0
Yes	351 (3.0)	17,657 (2.9)	0.01	3.0	3.0	0
Type of pre-existing maternal medical condition						
Asthma	25 (0.2)	1,508 (0.2)	0.01	0.2	0.2	0.01
Chronic hypertension	41 (0.3)	2,327 (0.4)	0.01	0.3	0.4	0.01
Diabetes	55(0.5)	4,779(0.8)	0.01	0.5	0.5	0
Heart disease	51 (0.4)	2,986 (0.5)	0.01	0.4	0.5	0.01
Thyroid disease						
No	11,548 (98.3)	602,995 (98.8)	0.05	98.3	98.4	0.01
Yes	202 (1.7)	7,158 (1.2)	0.05	1.7	1.6	0.01
Obstetrical complication [d]						
No	9,096 (77.4)	482,522 (79.1)	0.04	77.4	78.5	0.03
Yes	2,654 (22.6)	127,631 (20.9)	0.04	22.6	21.5	0.03
Type of obstetrical complication [e]						
Preeclampsia and eclampsia	247 (2.1)	11,839 (1.9)	0.01	2.1	2.0	0.01
Gestational diabetes	771 (6.6)	38,483 (6.3)	0.01	6.6	6.3	0.01
Placenta previa	82 (0.7)	4,369 (0.7)	0.01	0.7	0.6	0.01
Placental abruption	112 (1.0)	6,253 (1.0)	0.01	1.0	1.0	0
PROM	1,599 (13.6)	74,941 (12.3)	0.04	13.6	12.9	0.02
Type of delivery						
Vaginal	8,558 (72.8)	434,154 (71.2)	0.04	72.8	71.4	0.03

Cesarean	3,192 (27.2)	175,999 (28.8)	0.04	27.2	28.6	0.03
Previous cesarean delivery						
Nulliparous	6,066 (51.6)	269,466 (44.2)	0.15	51.6	51.4	0.01
Parous – no previous c-section	4,615 (39.3)	271,605 (44.5)	0.11	39.3	38.8	0.03
Parous – previous c-section	1,069 (9.1)	69,082 (11.3)	0.07	9.1	9.8	0
UTI during pregnancy						
No	11,740 (99.9)	609,085 (99.8)	0.02	99.9	99.9	0
Yes	10 (0.1)	1,068 (0.2)	0.02	0.1	0.1	0
Neighborhood median family income quintiles						
1 (Lowest)	2,030 (17.3)	126,778 (20.8)	0.09	17.3	17.2	0
2	2,377 (20.2)	122,298 (20.0)	0	20.2	20.3	0
3	2,297 (19.5)	124,419 (20.4)	0.02	19.5	19.3	0.01
4	2,624 (22.3)	134,002 (22.0)	0.01	22.3	22.8	0.01
5 (Highest)	2,422 (20.6)	102,656 (16.8)	0.11	20.6	20.4	0.01
Rural residence						
No	10,666 (90.8)	550,396 (90.2)	0.02	90.8	91.0	0.01
Yes	1,084 (9.2)	59,757 (9.8)	0.02	9.2	9.0	0
Public health unit region						
North West	114 (1.0)	8,823 (1.4)	0.04	1.0	1.0	0
North East	286 (2.4)	23,203 (3.8)	0.08	2.4	2.3	0.01
Eastern	1,905 (16.2)	76,058 (12.5)	0.11	16.2	16.1	0
Central East	4,240 (36.1)	185,512 (30.4)	0.12	36.1	36.3	0
Toronto	3,439 (29.3)	126,977 (20.8)	0.20	29.3	29.5	0
South West	521 (4.4)	68,837 (11.3)	0.26	4.4	4.3	0.01
Central West	1,245 (10.6)	120,743 (19.8)	0.26	10.6	10.4	0.01
Birth weight						
<1500 g	48 (0.4)	6,081 (1.0)	0.07	0.4	0.9	0.06
1500-2500 g	533 (4.5)	33,998 (5.6)	0.05	4.5	5.2	0.03
2500-3500 g	6,575 (56.0)	330,647 (54.2)	0.04	56.0	55.4	0.01
≥3500 g	4,594 (39.1)	239,427 (39.2)	0	39.1	38.4	0.01

Gestational weeks at delivery						
<28	9 (0.1)	2,717 (0.4)	0.07	0.1	0.4	0.06
28-31	50 (0.4)	4,145 (0.7)	0.03	0.4	0.6	0.03
32-33	62 (0.5)	5,725 (0.9)	0.05	0.5	0.8	0.03
34	82 (0.7)	6,006 (1.0)	0.03	0.7	0.8	0.02
35	154 (1.3)	9,919 (1.6)	0.03	1.3	1.5	0.02
36	352 (3.0)	19,902 (3.3)	0.02	3.0	3.0	0
≥37	11,041 (94.0)	561,739 (92.1)	0.07	94.0	92.8	0.05
Maternal world region of birth						
North America	9,075 (77.2)	477,882 (78.3)	0.03	77.2	77.5	0.01
Asia	2,090 (17.8)	83,018 (13.6)	0.12	17.8	17.8	0
Europe	163 (1.4)	12,060 (2.0)	0.05	1.4	1.4	0
Africa	157 (1.3)	11,512 (1.9)	0.04	1.3	1.3	0.01
Caribbean	73 (0.6)	8,224 (1.3)	0.07	0.6	0.6	0.01
Yugoslavia & USSR	89 (0.8)	7,684 (1.3)	0.05	0.8	0.8	0
South America	69 (0.6)	6,428 (1.1)	0.05	0.6	0.6	0
Central America	25 (0.2)	3,059 (0.5)	0.05	0.2	0.2	0
Oceania	9 (0.1)	286 (0.0)	0.01	0.1	0.1	0
Marginalization Indices [e]						
Residential instability quintile						
1	2,574 (21.9)	138,078 (22.6)	0.02	21.9	22.2	0.01
2	2,205 (18.8)	118,780 (19.5)	0.02	18.8	19.0	0.01
3	2,181 (18.6)	113,027 (18.5)	0	18.6	18.3	0.01
4	2,153 (18.3)	115,549 (18.9)	0.02	18.3	18.5	0.01
5	2,637 (22.4)	124,719 (20.4)	0.05	22.4	21.9	0.01
Material deprivation quintile						
1	2,000 (17.0)	94,889 (15.6)	0.04	17.0	16.8	0.01
2	2,267 (19.3)	116,036 (19.0)	0.01	19.3	19.7	0.01
3	2,358 (20.1)	120,708 (19.8)	0.01	20.1	20.8	0
4	2,456 (20.9)	126,083 (20.7)	0.01	20.9	21.0	0.02

5	2,669 (22.7)	152,437 (25.0)	0.05	22.7	21.7	0.02
Dependency quintile						
1	3,861 (32.9)	212,799 (34.9)	0.04	32.9	35.4	0.03
2	2,426 (20.6)	122,966 (20.2)	0.01	20.6	19.3	0.02
3	2,105 (17.9)	105,041 (17.2)	0.02	17.9	17.1	0.02
4	1,772 (15.1)	91,485 (15.0)	0	15.1	14.4	0.01
5	1,586 (13.5)	77,862 (12.8)	0.02	13.5	13.7	0.01
Ethnic concentration quintile						
1	1,479 (12.6)	85,842 (14.1)	0.04	12.6	11.9	0.02
2	1,702 (14.5)	90,458 (14.8)	0.01	14.5	12.8	0.03
3	1,939 (16.5)	102,531 (16.8)	0.01	16.5	16.2	0.01
4	2,361 (20.1)	126,466 (20.7)	0.02	20.1	22.4	0.02
5	4,269 (36.3)	204,856 (33.6)	0.06	36.3	36.7	0.01

Abbreviations: IPTW, inverse probability of treatment weighting; Stand diff, standardized difference; PROM, premature rupture of membranes.
[a] Column Percentages.
[b] Absolute standardized differences. Shaded cells indicate an imbalance (>0.10) between Tdap-vaccinated and unvaccinated women.
[c] Conditions included: Asthma, chronic hypertension, diabetes, heart disease.
[d] Complications included: Preeclampsia and eclampsia, gestational diabetes, placenta previa, placental abruption, PROM.
[e] Obstetrical complication categories are not mutually exclusive.
[f] 1= least marginalized; 5=most marginalized

Appendix VIII. Comparison of standardized difference scores in the original and propensity score matched cohort