Association Between Maternal Pertussis Vaccination During Pregnancy and Early Childhood Health Outcomes

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A thesis submitted in partial fulfillment of the requirements for the
Master's degree in Epidemiology

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ABSTRACT

Background: Little is known about whether there are any longer-term adverse health effects in children following Tdap (tetanus, diphtheria, and acellular pertussis) vaccination during pregnancy.

Objective: To assess the association between maternal Tdap vaccination during pregnancy and risk of the following early childhood adverse health outcomes: (1) infections (upper and lower respiratory tract infections, gastrointestinal infections, and otitis media), (2) pediatric asthma, (3) neoplasm, (4) vision or hearing loss, and (5) urgent and in-patient health services utilization.

Methods: This retrospective cohort study used multiple linked health administrative databases in the province of Ontario, Canada containing vaccine information in mothers and information on health outcomes in their children up to age 6 years. Infants exposed to prenatal Tdap were matched 1:5 with unexposed infants and outcomes were compared using hazard ratios and incidence rate ratios.

Results: No significant adverse associations between prenatal Tdap and our study outcomes were observed. Inverse associations were found with upper respiratory infections (adjusted incidence rate ratio [aIRR]: 0.96, 95% CI: 0.93-0.99), lower respiratory infections (aIRR: 0.93, 95% CI: 0.89-0.98), gastrointestinal infections (aIRR: 0.88, 95% CI: 0.82-0.94), and urgent and in-patient health service utilization (aIRR: 0.95, 95% CI: 0.94-0.97).

Conclusions: Our findings support the long-term safety of Tdap administration in pregnancy.

ACKNOWLEDGEMENTS

I would first like to thank my thesis supervisor, Dr. Deshayne Fell, for the invaluable support and advice she offered me during the research process and writing of this thesis. Because of her mentorship, I've been able to learn and grow so much more from this experience than I had ever imagined. I consider myself incredibly lucky to have been one of her students.

I would also like to thank my thesis advisory committee members, Dr. Kumanan Wilson and Dr. Steve Hawken, for the insight and feedback they have offered me throughout this process. My project would not have been the same without their expertise.

To the classmates I worked alongside these past two years – having peers to both celebrate and commiserate with made my degree so much more enjoyable. I can't wait to see what you go on to accomplish.

I also have to thank my employers at both HAI and MCYH for providing me with such wonderful opportunities to continue to learn outside of school and for being incredibly supportive as I pursued my degree. It was only because of their flexibility and understanding that I was able to achieve my goals both in my degree and outside of it. I would also like to acknowledge the financial support I received through the Ontario Graduate Scholarship and University of Ottawa Graduate Studies and Excellence Scholarships.

Finally, to my parents Tom and Diane and my partner Dan, I am so fortunate to have had your love, support, and encouragement. This would not have been possible without you.

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LIST OF ABBREVIATIONS

ASD	Autism Spectrum Disorder
CCC	Complex Chronic Disease
CI	Confidence interval
CIHI	Canadian Institute for Health Information
DAD	Discharge Abstract Database
DTaP	Diphtheria toxoid and acellular pertussis
ED	Emergency Department
HR	Hazard ratio
ICD	International Classification of Diseases and Related Health Problems
IKN	ICES Key Number
IRR	Incidence rate ratio
LMP	Last menstrual period
NACI	National Advisory Committee on Immunization
NACRS	National Ambulatory Care Reporting System
OHIP	Ontario Health Insurance Plan
OR	Odds ratio
RPDB	Registered Persons Database
RR	Rate ratio
SD	Standardized difference
Tdap	Tetanus, diphtheria and acellular pertussis
VE	Vaccine effectiveness

CHAPTER 1. INTRODUCTION

1.1 Background

Maternal immunization during pregnancy is a relatively new strategy with the potential to reduce infant morbidity and mortality from infectious diseases worldwide[1]. Routine pediatric immunization schedules start when infants are 2 months of age in most high- and middle-income countries and are not complete until infants are 6 months of age, leaving an immunity gap that results in a higher proportion of infection-related hospitalizations and deaths in young infants compared to older children[2]. Maternal immunization can provide infants with passive immunity during their first months of life by inducing the production of antibodies in the mother, which are then transferred across the placenta to the fetus before birth[1]. This strategy has gained considerable interest following the global reduction in neonatal tetanus as a result of maternal immunization with tetanus toxoid containing vaccines[3]. In Canada, recommendations for vaccination during pregnancy currently include inactivated influenza vaccine at any time during pregnancy, to prevent influenza-associated morbidity in pregnant women and their infants, and as of February 2018, the tetanus, diphtheria, and acellular pertussis (Tdap) vaccine between 27- and 32-weeks' gestation, to prevent pertussis infection in young infants[4,5]. Although nearly all women of childbearing age have pre-existing humoral immunity to pertussis, without a dose of vaccine, their antibody concentrations may be insufficient to provide passive protection to their offspring[1].

The focus of this Master's thesis is on maternal Tdap immunization. Pertussis, also known as whooping cough, is an endemic, highly contagious respiratory tract infection from which un- and under-immunized young infants are at greatest risk of severe complications and death[5]. Although

pertussis incidence in Canada declined dramatically with the introduction of routine vaccination in 1943, there has been a resurgence of cases since 2011, and it remains a major public health concern[6]. One to four deaths, typically in very young infants, are reported in Canada every year[6]. With a disproportionate burden of illness on newborns, the aim of maternal Tdap immunization is to reduce morbidity and mortality from severe pertussis among the very young[5].

1.2 Rationale for the thesis project

Safety surveillance is a critical component of any successful vaccine program, to identify any associated risks and ensure public confidence in vaccination. Concerns about vaccine safety are one of the main reasons for pregnant women not becoming immunized and for health care providers choosing not to recommend vaccination to their pregnant patients[7–9]. Although there have been reassuring safety data for Tdap immunization during pregnancy in which maternal serious adverse events, obstetrical complications, and perinatal outcomes were evaluated, research on outcomes in children past the neonatal period is limited[10]. The aim of this thesis project, therefore, was to address evidence gaps about the longer-term safety of the Tdap vaccine in pregnancy on offspring health.

1.3 Research objective

The specific objective of this thesis was to assess the association between maternal Tdap (tetanus, diphtheria, and acellular pertussis) vaccination during pregnancy and the risk of early childhood adverse health outcomes, both immune-related and non-immune related. Immune-related outcomes included: infections (upper and lower respiratory tract infections, gastrointestinal infections, and otitis media) and pediatric asthma. Non-immune related outcomes

were both specific (neoplasm, vision or hearing loss) and non-specific (urgent and in-patient health services utilization).

1.4 Structure of the thesis

This thesis has four chapters. Chapter 1 provides an introduction to the topic, the rationale for the thesis, and the specific research objective. Chapter 2 presents a review of the literature on pertussis in Canada, maternal vaccination with Tdap in pregnancy, and vaccine safety research thus far. Chapters 3 and 4 present a description of the study methods and results, respectively. Lastly, Chapter 5 presents a discussion which interprets the main findings and discusses the strengths, limitations, and implications of the study.

CHAPTER 2. LITERATURE REVIEW

2.1 Pertussis

2.1.1 Pertussis epidemiology and clinical features

Pertussis, commonly known as whooping cough, is a highly contagious respiratory tract infection caused by the bacterium *Bordetella pertussis*[11]. In its early stage, its secondary attack rate is up to 90% among non-immune household contacts[12]. The bacteria spread from person to person through airborne droplets expelled by coughing or sneezing, or by direct contact with infected throat or nasal discharges[13]. Pertussis is the least controlled of all bacterial vaccine-preventable diseases, and despite a significant decline in incidence following the introduction of pertussis vaccines, the disease has remained endemic, causing an estimated 24.1 million cases and 160,700 deaths in children <5 years worldwide in 2014[11,14].

Since the 1980s, there has been a gradual resurgence of pertussis in Canada, the United States, and other countries with long-standing vaccination programs and high vaccine coverage[15]. In Canada, this was followed by a period of low incidence; however, there has been a trend toward increasing incidence rates since 2011[5]. Epidemic cycles of pertussis occur every 2-5 years and incidence peaks associated with numerous outbreaks across Canada occurred in 2012 and 2015[5]. In 2012, there was a 7-fold increase in incidence rates compared to the preceding 5 years, with 4,845 cases reported and an incidence rate of 13.9 per 100,000[6]. Factors associated with the rise in cases include waning immune protection after vaccination, due to a reduced duration of protection by acellular vaccines (introduced into routine use in 1997/1998) compared to previously-used whole cell vaccines, increased physician awareness and improved reporting, and possibly, genetic adaptation of circulating *Bordetella pertussis* strains[6,13,16,17]. A shift in the age

distribution of pertussis infections away from school-age children and toward adolescents and young adults has been reported in some high-income countries, due in part to high vaccination rates in children followed by waning vaccine-derived protection and a reduced boosting of immunity by circulating bacteria[12]. This pattern is problematic as adolescents and adults are significant sources of transmission to infants who are too young to be vaccinated[12].

Bordetella pertussis bacteria cause illness by infecting the ciliated epithelial cells of the human upper respiratory tract and releasing toxins that damage the cilia and cause the airway to swell[13]. Following an incubation period of 9-10 days (range 6-20 days), patients develop symptoms that may initially be mild, including a runny nose, sneezing, low-grade fever, and occasional cough[13]. After 1-2 weeks, the cough becomes more severe, with bursts of rapid coughs followed by a long inspiration accompanied by a distinctive high-pitched "whooping" sound[13]. In typical cases, the cough is most severe at night and often followed by vomiting[12]. Clinical manifestations may be different in very young infants, presenting as apnea (cessation of breathing) and cyanosis (blue spells)[12]. Complications of pertussis infection in infants and children can include seizures, encephalopathy, pneumonia, and death[13].

2.1.2 Risk to infants

Although cases occur in all age groups, the highest incidence of pertussis is among infants less than 6 months of age who have not yet completed their primary vaccine series[5]. Almost three quarters of cases in Canada (60% to 74%) occur in infants less than two months of age, followed by infants three to four months (16% to 24%)[5]. During the outbreaks in 2012, there were 120.8 cases per 100,000 infants aged less than one year compared to 13.9 cases per 100,000 in the

Canadian population overall[6]. Infants are also the most vulnerable to experiencing serious or fatal complications from the disease[6]. In the United States, >40% of cases in infants <6 months require hospitalization and >90% of pertussis deaths occur in those <6 months[18]. In Canada, outbreaks in 2012 resulted in 3 pertussis deaths in previously healthy infants <2 months of age[19].

2.2. Maternal pertussis immunization during pregnancy

2.2.1 Tetanus, diphtheria, and acellular pertussis (Tdap) vaccine

In Canada, pertussis vaccine is only available as an acellular preparation in a combination vaccine[20]. Although acellular vaccine offers a shorter duration of protection compared to the inactivated whole-cell vaccine originally introduced in the mid-twentieth century, the acellular preparation is preferred as it is associated with fewer mild (e.g., redness, swelling) and severe (e.g., fever, seizures) adverse events[21,22]. In Canada, Tdap vaccines administered to adults are sold under the brand names Adacel® and Boostrix® and contain tetanus toxoid, diphtheria toxoid, and acellular pertussis in different antigen concentrations, with a reduced dose of diphtheria toxoid and acellular pertussis antigen compared to the DTaP vaccine given to infants[20]. In Canada and several other Western and European countries, the Tdap vaccine is given as a booster shot every 10 years[20]. These adult vaccine formulations have not been explicitly indicated for use in pregnancy; however, neither are they contraindicated for use in pregnancy, according to current product monographs[5].

2.2.2 Immunity induced by maternal immunization

The transplacental transfer of maternal antibodies across the placenta to the fetus begins as early as 8-10 weeks of gestation, with the majority of the transfer occurring in the last trimester[23].

Passively acquired maternal antibodies offer young infants immunity from disease in their first few months of life, however the amount and type of antibodies transferred depend on factors including the gestational age of the infant at birth and the immunity of the mother[1,23]. Immunization with Tdap vaccine during pregnancy increases the likelihood of passive infant protection from pertussis by boosting the level of maternal pertussis-specific antibodies, thereby increasing the transplacental transfer of pertussis-specific IgG[1]. Infants born to women immunized with Tdap during pregnancy have significantly higher antibody concentrations at birth and at 2 months of age compared to infants born to unimmunized women[10]. Several studies have also reported an increase in the avidity (binding strength) of Tdap vaccine-induced antibodies in umbilical cord samples, suggesting a potential increase in antibody effectiveness[24–26]. Maternal immunization also decreases the risk of disease in the mother, reducing any risk of post-partum transmission to their child[10]. However, unlike immunization during pregnancy, maternal postpartum immunization alone has not been found to be effective in reducing the burden of infant pertussis disease, highlighting the importance of antibody transfer in the protection of infants[27,28].

Immunization may offer additional immunity to breastfed infants, possibly through IgA antibody transfer via the breastmilk[1]. Pertussis-specific IgA antibodies are detectable in the breastmilk of women immunized before, during, or shortly after pregnancy until 8-9 weeks post-partum[29]. However, as breastfeeding in general offers protection against infection, the mechanism by which breastmilk in immunized mothers might augment infant protection over that of unimmunized mothers needs further elucidation[1].

2.2.3 Effectiveness of maternal Tdap immunization against infant pertussis

Studies on the effectiveness of maternal Tdap immunization during pregnancy consistently show high protection against pertussis infection and death in infants less than 2 months of age[30–34]. For example, estimates of vaccine effectiveness (VE) for infants younger than 2 months range from 90-93% in the United Kingdom and 78-91% in the United States[30–34]. Infants less than 2 months of age whose mothers received the Tdap vaccine during pregnancy have also been shown to have a milder disease course, with a lower risk of hospitalization and intensive care unit admission compared with infants born to unimmunized mothers[35].

In immunological studies, maternal Tdap vaccination during pregnancy has been shown to interfere with the infant's immune response to their primary immunization series, a phenomenon called "immune blunting"[36]. Specifically, maternally-derived IgG antibodies can inhibit the infant's immune response to antigens in the DTaP vaccines[36]. In a recent Canadian randomized controlled trial, infants of Tdap-immunized women had significantly higher antibody levels at 2 and 4 months of age, but significantly lower levels at 6 and 7 months compared to infants born to unvaccinated women, and this continued into their second year of life[37]. However, as there is no established immunological correlate of protection for pertussis, the clinical impact of "immune blunting" is unclear[10]. To date, two observational studies have assessed vaccine effectiveness after infants received their first, second, and third DTaP vaccine doses and found that, depending on the study, the protection offered through maternal immunization was retained through the infant's first 4 months or their first year of life as they received their primary vaccines[32,33]. The first study, conducted in England, estimated maternal Tdap VE at 82% (95% CI: 65% to 91%) after the infant's first dose of DTaP, 69% (95% CI: 8% to 90%) after the second dose, and 29%

(95% CI: -112% to 76%) (i.e. no additional protection) after the third dose at 4 months[32]. A larger American study estimated maternal Tdap VE at 88% (95% CI: 41% to 98%) before infants had any DTaP vaccine doses, 81% (95% CI: 43% to 94%) between doses 1 and 2, 6% (95% CI: -165% to 67%) between doses 2 and 3, and 66% (95% CI: 5% to 88%) after 3 DTaP doses at 6 months[33].

2.2.4 Current vaccination recommendations

Since 2012, the United States (US) and United Kingdom (UK) have recommended women be immunized with a Tdap vaccine in each pregnancy[2]. In the UK, these recommendations began as temporary vaccination programs, implemented in response to large pertussis outbreaks causing high morbidity and deaths in young infants, which were then extended[2]. The vaccine may be administered in any trimester, but the preference is for later in gestation, specifically recommended at 27 to 36 weeks in the US and 16 to 32 weeks in the UK in order to optimize maternal antibody transfer[38,39]. Immunization is recommended in each pregnancy as data suggest that high pertussis antibody titres late in the gestational period might not be sustained through subsequent pregnancies[1]. In addition to the US and UK, other countries that recommend pertussis vaccination during pregnancy include Australia, New Zealand, Belgium, Argentina, and Brazil[2].

In Canada, until recently, immunization with the Tdap vaccine was recommended to pregnant women only if they had not yet received their recommended booster dose in adulthood and offered to pregnant women during pertussis outbreaks[5]. However, in February 2018, the Public Health Agency of Canada's National Advisory Committee on Immunization (NACI) released a

recommendation for routine immunization of women in each pregnancy[5]. The recommendation was based on an assessment of the high risk of pertussis infection to infants, a body of evidence from the US and UK indicating the safety of Tdap immunization in pregnancy and effectiveness at protecting infants in their first two months of life, as well as the logistical advantage of routine immunization over immunization as an outbreak control measure only[5]. According to the Canadian recommendations, the vaccine may be administered from 13 weeks up to the time of delivery; however, it is ideally provided between 27 and 32 weeks of gestation[5]. Even prior to 2018 some Canadian women were being immunized with Tdap during pregnancy, as some maternity care providers were already immunizing pregnant women based on international recommendations, temporary provincial advisories, and partial recommendations by NACI and the Society of Obstetricians and Gynaecologists of Canada (SOGC)[19,40]. However, with the updated NACI recommendations, the number of Canadian women vaccinated with Tdap during pregnancy is likely to increase in the coming years.

2.2.5 Vaccine uptake

Uptake of Tdap vaccine during pregnancy varies, even in settings where it is recommended and funded. Coverage was estimated to be 49% in 2016 and 50% in 2017 in the US and between 50% and 62% from 2012 and 2015 in the UK[32,41]. Tdap vaccine has only recently been recommended for all pregnant women in Canada, but seasonal influenza vaccine coverage (recommended for all pregnant women since 2007) is low, estimated at <20%[42]. The most commonly cited barriers to vaccination during pregnancy include a lack of knowledge about the burden of disease, no recommendation from a healthcare provider, and concerns (among both pregnant women and their healthcare providers) about the safety of the vaccine in pregnancy[7–9].

Additional research on the safety of the Tdap vaccine in pregnancy, particularly where there are evidence gaps, and the dissemination of this evidence to women and their healthcare providers may, therefore, be important in improving uptake.

2.3 Safety of maternal pertussis immunization during pregnancy

2.3.1 Serious adverse events, obstetric complications, and perinatal outcomes

Research published since 2012 has provided reassuring evidence that Tdap immunization is not associated with serious adverse events in the mother or clinically significant harms in the fetus or neonate during the perinatal period[10,43,44]. Obstetric complications and perinatal outcomes that have been evaluated include hypertensive disorder, preterm birth, small-for-gestational-age birth, stillbirth and neonatal death, with results indicating that there is no increased risk of any of these outcomes in women who received the Tdap vaccine during pregnancy compared to women who did not[10,43,44]. An exception is chorioamnionitis, for which a small increase in risk for Tdap-immunized women has been reported by three studies[45–47]. However, the clinical significance of these findings is unclear and requires further exploration; an increase in risk of adverse perinatal outcomes associated with chorioamnionitis such as preterm birth, NICU stays, respiratory distress, and neonatal sepsis has not been observed[45–47]. One study also found an increased risk of post-partum hemorrhage among women who received prenatal Tdap, although this association has not been found in several other studies that have evaluated this outcome[45,48,49].

2.3.2 Pediatric adverse health outcomes

Evidence on any long-term implications of Tdap vaccination during pregnancy on infant and children's health is much more limited than evidence on short-term outcomes. We identified six

studies published to date on the association between Tdap vaccination during pregnancy and adverse pediatric health outcomes, with only one study following up infants past 18 months of age (see **Table 2-1** for an overview of each publication)[24,37,50–53]. The outcomes that have been assessed vary widely and include infant growth and development, hospitalization, death, complex chronic conditions, and autism spectrum disorder (ASD)[24,37,50–53]. None of these studies found an increased risk for any of these adverse outcomes in children prenatally exposed to Tdap vaccination[24,37,50–53].

Two of the six studies followed a large number of children to evaluate longer-term outcomes: Sukumaran et al. (2018) assessed the association between Tdap during pregnancy and infant all-cause-hospitalization or mortality in the first 6 months and Becerra-Culqui (2018) assessed the association with a diagnosis of ASD in early childhood[52,53]. Sukumaran et al. (2018) conducted a case-control study using the US Vaccine Safety Datalink, which contains vaccination and healthcare data on 10 million people per year[52]. They included all singleton, live births from 5 participating sites between 2004 and 2014 (n=413,034) and compared the maternal vaccination histories of infants who were hospitalized or died in their first 6 months of life[52]. No association was found between infant hospitalization and maternal Tdap vaccination (OR: 0.94, 95% CI: 0.88-1.01) or between infant mortality and maternal Tdap vaccination (OR: 0.44, 95% CI: 0.17-1.13)[52]. Becerra-Culqui (2018) conducted a retrospective cohort study on mother-child pairs born from 2011 to 2014 in California (n=81,993), using electronic medical records to compare the incidence of ASD between children exposed and unexposed to prenatal Tdap[53]. Follow-up time ranged from 1.2 to 6.5 years, with the minimum diagnosis age set to 12 months[53]. Using inverse probability of treatment weighted analysis to adjust for confounding, they found that maternal

Tdap vaccination was not associated with an increased ASD risk (HR: 0.85, 95% CI: 0.77-0.95)[53].

Additional studies on long-term outcomes include three small studies that looked at the growth and development of infants exposed to maternal Tdap immunization: two randomized controlled trials (RCT) by Munoz et al. (2014) and Halperin et al. (2018) and a prospective cohort study by Walls et al. (2016)[24,37,51]. In a study conducted in the US, Munoz et al. (2014) randomly allocated 33 women to receive a Tdap vaccine and 15 women to receive a placebo injection at 30 to 32 weeks' gestation, followed by crossover vaccine administration postpartum[24]. Among the outcomes measured were infant growth (weight, length, and head circumference) at 2, 7, and 13 months of age and infant development at 13 months of age using the Bayley-III Scales of Infant and Toddler Development, which measures cognitive, communication, and motor skill development[24]. No statistically significant differences were found between the two groups in any of these measurements[24]. Halperin et al. (2018) randomly allocated 273 pregnant women in Canada to receive either Tdap or tetanus-diptheria (Td) vaccine and compared safety and immunological outcomes in their offspring at birth[37]. One longer-term outcome, infant development at 18 months, was assessed using the Bayley-III scales and no developmental differences were detected[37]. In New Zealand, Walls et al. (2016) compared the growth of infants born to 403 women who received Tdap during their pregnancy to baseline population data[51]. Infant weight was measured during routine infant checkups at 6 weeks and 5-7 months of age, and was found to be normally distributed at both time points, with no indication it differed significantly from the reference population[51].

Finally, one small retrospective cohort study by Shakib et al. (2013) compared the incidence of complex chronic conditions (CCC) within the first year between infants exposed and unexposed to prenatal Tdap[50]. 138 Utah women who were vaccinated with Tdap during their pregnancy were compared with 552 randomly selected controls, and the development of a CCC was ascertained using health administrative data[50]. Infants exposed to prenatal Tdap were found to be no more likely to have a CCC than infants who were not exposed (3.6% vs. 10.4%, p=0.054)[50].

Table 2-1. Studies assessing infant and child health outcomes following prenatal exposure to Tdap vaccination

Reference	Location	Study design	Study population and size	Infant outcomes	Results
Shakib, J. H., et al. (2013)	Utah (USA)	Retrospective cohort study	138 women vaccinated with Tdap, 552 randomly selected controls (n=690)	Complex chronic conditions (CCC)	No significant association between Tdap during pregnancy and pediatric complex chronic conditions within 12 months of age
Munoz et al. (2014)	Houston, Durham, Seattle (USA)	Randomized controlled trial	33 women allocated to receive Tdap and 15 to placebo (n=48)	Infant growth (weight, length and fronto-occipital circumference) and development (Bayley III screening test)	No difference in growth at 2, 7, or 13 months or development at 13 months
Walls et al. (2016)	Canterbury region (New Zealand)	Prospective observational study (no comparison group)	403 women/408 infants	Infant growth (weight, length, and head circumference)	Normally distributed measurements at 6 weeks and 5-7 months
Sukumaran et al. (2018)	5 Vaccine Safety Datalink sites in	Case-control study	All singleton, live births between	All-cause hospitalization, hospitalizations from	No significant association between Tdap during pregnancy

	California, Colorado, Wisconsin, and Oregon (USA)		2004 and 2014 (n=413,034)	respiratory causes and all-cause mortality	and all-cause hospitalization or mortality within 6 months, but significantly lower odds of hospitalizations from respiratory causes.
Becerra-Culqui et al. (2018)	Kaiser Permanente hospitals in Southern California (USA)	Retrospective cohort study	All singleton live births between 2011 and 2014 (n=109,536)	Autism spectrum disorder (ASD)	No increased risk of ASD following Tdap vaccination during pregnancy
Halperin et al. (2018)	Nova Scotia (Canada)	Randomized controlled trial	135 women allocated to receive Tdap and 138 to Td (n=273)	Infant development (Bayley III screening test)	No different in development at 18 months

This Master's study aimed to add to existing vaccine safety research and address evidence gaps about the longer-term safety of the Tdap vaccine in pregnancy. It has been well established that the prenatal period represents a critical window of development during which environmental exposures can have significant consequences on an individual's short- and long-term health (the Developmental Origins of Health and Disease Hypothesis)[54]. Maternal infection and immune activation have implications for neonatal immune programming, but whether activation of the maternal immune system by vaccination could be associated with later poor outcomes requires further investigation[55–58]. The primary focus of this study was on immune-related outcomes following prenatal exposure to Tdap vaccination; however, additional non immune-related childhood health outcomes that have been linked to other prenatal risk factors were also assessed[59–61].

2.4 Summary

Immunization with the Tdap vaccine is recommended to pregnant women in Canada as a strategy to prevent pertussis infection in their young infants[5]. Un- and under-immunized infants <6 months of age experience the highest incidence of pertussis and are at the greatest risk of severe complications and death[5]. Maternal Tdap immunization during pregnancy confers short-term passive immunity to infants in the first months of life through the transfer of vaccine-derived maternal antibodies across the placenta, decreasing the likelihood of infection[5]. While no long-term safety concerns about the administration of Tdap vaccine during pregnancy have been identified, research on outcomes in children past the perinatal period is limited[24,37,50–53]. The objective of this thesis was to assess the association between maternal Tdap vaccination and early childhood adverse health outcomes, both immune related and non-immune related, in order to address evidence gaps about the longer-term safety of the vaccine in pregnancy.

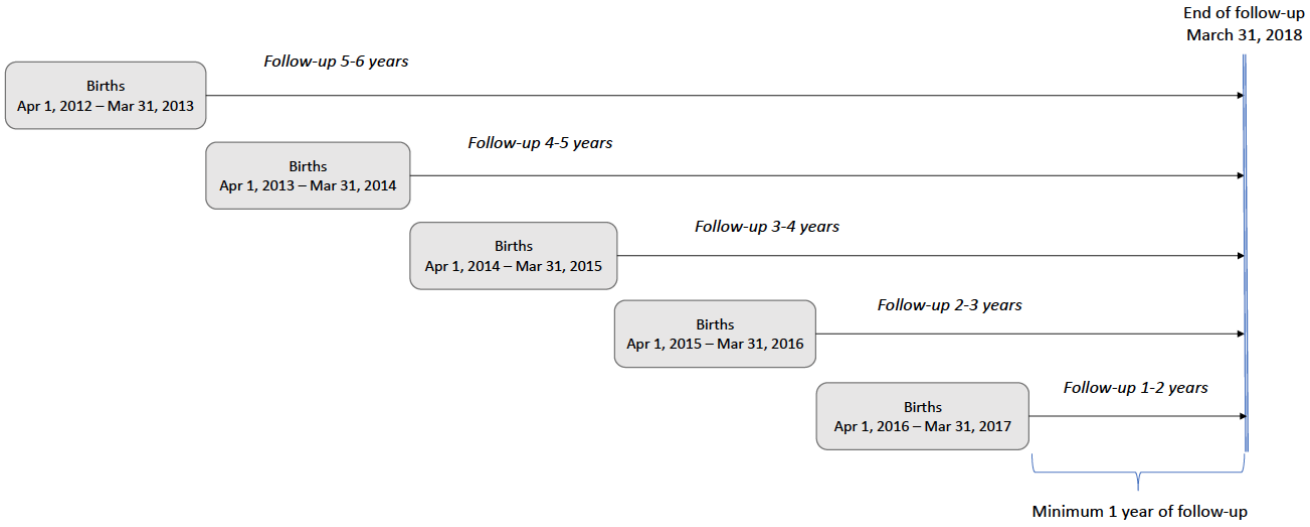
CHAPTER 3. METHODS

3.1 Study design

This was a population-based based retrospective cohort study of all live born infants born in Ontario hospitals between April 1, 2012 and March 31, 2017 to Ontario residents eligible for provincial health coverage. The study was conducted at ICES – a provincial research entity that houses a large network of health administrative databases (https://www.ices.on.ca). Maternal-infant pairs were identified using the ICES MOMBABY database which links the inpatient admission records of delivering mothers and their newborns in the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD). Using hospital births to define the cohort captures over 97% of births in the province, as less than 3% of Ontario women deliver at home[62].

Infants were followed up until March 31, 2018, for a minimum of 1 year to a maximum of 6 years, depending on their birth cohort. Specifically, children born on the last date of the study period (March 31, 2017) had 1 year of follow-up (from March 31, 2017 to March 31, 2018) and children born on the first date of the study period (April 1, 2012) had 6 years of follow-up (from April 1, 2012 to March 31, 2018) **(Figure 3-1)**. Follow-up time began on the date of birth and continued until the child emigrated from the province and was no longer eligible for Ontario health coverage, died, or reached the end of the study period, whichever occurred first. Study outcomes were ascertained from hospital admissions and emergency department visits within the province during the follow-up period.

Figure 3-1. Study design



3.2 Study population

Infants born between April 1, 2012 and March 31, 2017 were identified from the ICES MOMBABY database, along with their mother. We included births starting in 2012, as this was when universal Tdap immunization recommendations in the US and UK were implemented (in 2011-2012), and some maternity care providers in Canada initially began immunizing pregnant women against pertussis.

We excluded women who were not continuously eligible to receive health care in Ontario during their pregnancy to ensure that their immunization information was captured in our provincial datasets. We also excluded records that were missing gestational weeks at delivery (required to estimate when the woman became pregnant and therefore whether or not immunization was during pregnancy), records with maternal age <12 or >50 years, stillbirths, infants who died on their date of birth, and infants who did not have a record of becoming eligible to receive health

care in Ontario within 60 days of their birth. We conducted a complete case analysis, excluding records with missing covariate data.

3.3 Data sources

3.3.1 ICES MOMBABY Database

The ICES MOMBABY database links all inpatient admission records of delivering mothers and their newborns from the CIHI-DAD[63]. Linkages are made deterministically based on maternal and newborn chart numbers[63]. The database contains information on maternal and newborn characteristics at birth (e.g., maternal age, plurality, gestational age at delivery) and up to 25 diagnoses identified using the enhanced Canadian version of the 10th revision of International Classification of Diseases and Related Health Problems (ICD-10-CA)[63]. Diagnostic codes in the maternal portion of the hospitalization record were used to ascertain pre-existing maternal medical conditions and obstetrical complications (see Appendix A for codes used). Delivery by cesarean was ascertained using Canadian Classification of Health Interventions (CCI) code 5.MD.6.

3.3.2 ICES-linked Registered Persons Database (RPDB)

The Registered Persons Database (RPDB) is a population-based registry that is maintained by the Ministry of Health and Long-Term Care (MHLTC) in Ontario and used to manage health care services covered under the universal, publicly funded Ontario Health Insurance Plan (OHIP)[63]. It contains a complete listing of all OHIP numbers that have been issued to individuals in Ontario along with demographic information such as date of birth, date of death, and address[63]. At ICES, the RPDB is anonymously linked to other health services datasets which

may contain more up-to-date address and death data, improving the accuracy of the database[64]. The RPDB tracks changes in eligibility for Ontario health coverage over time and, therefore, was used in this study to determine the time period when each individual was eligible for health care coverage (i.e., follow-up time for infants)[63]. The database also contains information related to location of residence, defined according to postal code using Statistics Canada census data[63]. This includes neighbourhood income quintile, rural vs. non-rural area of residence, and public health unit region[63].

3.3.3 Ontario Health Insurance Plan (OHIP) claims database

The OHIP database contains billing information for outpatient services from the ~94% of physicians who submit claims to OHIP[65]. The database includes a unique identifier for the patient, service date, one diagnosis code (using modified ICD-9-CA diagnostic codes) to indicate the underlying reason for the visit, and a fee code for services delivered, which is where an administered vaccine would be specified[63].

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

The CIHI-DAD contains patient-level data on all discharges from acute- and chronic-care hospitals, rehabilitation hospitals, and day surgery clinics, abstracted from hospital records[66]. Each record in the database corresponds to a single hospitalization, including the date of admission, date of discharge, and up to 25 medical diagnoses associated with the hospitalization (classified using ICD-10-CA coding)[66].

3.3.5 CIHI National Ambulatory Care Reporting System (NACRS) Database

The CIHI National Ambulatory Care Reporting System Database contains patient-level data on emergency department (ED) visits[67]. Each entry includes the date of the visit and up to 10 medical diagnoses associated with the visit[67]. ED discharge diagnoses are indicated using a shortlist of more than 800 diagnoses in common terms, which are then mapped to ICD-10-CA codes[67].

3.3.6 ICES Ontario Asthma Dataset

The ICES-derived Ontario Asthma Dataset identifies incident cases of asthma using hospitalization records from the DAD, OHIP claims, and a validated algorithm[68]. An individual is flagged as having asthma if he or she has one hospitalization for asthma recorded in the DAD or two asthma OHIP claims within a three-year period, with hospitalizations and outpatient visits considered to be asthma-related if they included an asthma diagnostic code (J45 or J46)[68]. This algorithm has been validated against medical chart review for children in Ontario and found to have a sensitivity of 89% and specificity of 72%[69]. The Ontario Asthma Dataset also includes the date of the patient's first asthma-related healthcare contact[68].

3.4 Data linkage and access

Each record in the ICES databases is assigned an unique, confidential ICES Key Number (IKN) based on direct personal identifiers including health card number, first and last name, and date of birth[70]. This allows for individual records to be deterministically linked across datasets with personal identifiers removed[70]. For this study, the IKN for both the mother and the newborn in the MOMBABY database were used to link the cohort to additional demographic and health care

information for the mother and follow-up information for the newborn. The de-identified, linked data were stored, accessed, and analyzed within the secure research analytic environment at ICES, adhering to the strict privacy policies and procedures at ICES.

3.5 Exposure measurement

As pertussis vaccinations in Ontario are publicly-funded and administered almost exclusively through physicians' offices, we used the pertussis-specific vaccine fee code G847 (Tdap administered to adults) in the OHIP database to determine if a mother was immunized during pregnancy[71]. The pregnancy interval was defined as starting from the mother's derived last menstrual period (LMP) and ending one day prior to their newborn's date of birth. LMP was derived by subtracting the newborn's gestational age at birth (in days) from his or her date of birth. Vaccinations given during the first 14 days following the LMP were excluded in order to restrict the exposure group to women who were vaccinated after conception.

The ability of billing codes to correctly assess immunization status varies and a validation study of OHIP fee codes for Tdap immunization in adults has not been conducted[65,72]. In a recent study by Schwartz et al. (2016), influenza vaccine-specific OHIP fee codes were found to have 50% sensitivity and 96% specificity for determining influenza vaccination status when validated against self-report, suggesting that not all vaccinations are captured by the database[65]. However, we expect sensitivity to be higher for Tdap immunizations than influenza immunizations due to the significant proportion of individuals who get influenza vaccinations at alternate settings that are not captured in the OHIP database (e.g., temporary influenza vaccine clinic at work or school, public health clinic, pharmacy)[73].

3.6 Outcome measurement

Study outcomes were ascertained using diagnostic codes from hospitalization records (i.e., DAD) and emergency department visits (i.e., NACRS) from each infant's date of birth to a maximum of 6 years of age. We considered an outcome to have occurred if the corresponding ICD-10-CA code was present in any field position in either database (see Appendix B for specific diagnostic codes for each outcome). For outcomes that can occur many times in childhood (infections and urgent or in-patient health service utilization), we measured counts of events. For outcomes that typically occur once (asthma, sensory disorders, and neoplasm), we measured time to first event.

Although diagnostic codes are frequently used to measure study outcomes, they are not often validated for this purpose, and their accuracy varies depending on the condition[74]. Therefore, we used a validated case-finding algorithm to improve detection accuracy where possible. In the case of the outcomes assessed in this study, it was only possible to use a validated algorithm for asthma[68]. We chose to use diagnoses from hospitalisations and emergency department visits, and not from outpatient visits, to limit our outcomes to cases that were more serious, with more significant clinical implications, and better measurement. Diagnostic codes are not required for physician billing claims in Ontario and identifying diagnoses from administrative outpatient data alone may be unreliable[75].

3.6.1 Rationale for study outcomes

Standardized case definitions for monitoring longer term pediatric health outcomes following immunization during pregnancy have not been developed, and previous research on the safety of Tdap vaccination in pregnancy has focused on short-term outcomes[10,43,44,76]. With minimal

guidance available on the selection of outcomes to monitor, we selected childhood morbidity outcomes within two categories: (1) immune-related outcomes (infectious and atopic disease), as fetal immune development is thought to be influenced by exposures such as maternal immunization and infection, which could theoretically have immunological effects later in life, and (2) specific and non-specific safety outcomes, to address evidence gaps about the longer-term safety of the vaccine[56,58]. Our specific safety outcomes were chosen based on outcomes included in other recent safety studies conducted on pregnant women[77,78]. Although the biological plausibility for the association between maternal immunization and these safety outcomes is unclear, there may be concerns about long-term effects on infant health after any pregnancy exposure. Our non-specific safety outcome, urgent and in-patient health service utilization, was included to allow for a more comprehensive assessment of potential adverse events, which might be missed in analyses focusing only on specific end-points[79].

3.6.2 Infectious diseases

Upper respiratory infections, lower respiratory infections, gastrointestinal infections, and otitis media were identified using diagnostic codes from DAD and NACRS (see Appendix B). The number of infections per child was based on a definition in which an ED visit or hospitalization with the same specified diagnostic codes within 1 day of each other was counted as one infection, but those separated by more than 1 day were each counted separately. For example, if a child visited the emergency department for a gastrointestinal infection on day 100 of follow-up and was subsequently admitted to the hospital that same day or the following day, this would count as one gastrointestinal infection. We used this method of counting to reduce the chance of

the same infection being counted multiple times, compared to counting each ED visit or hospitalization as a unique infection[78,80].

3.6.3 Atopic disease

Incident cases of pediatric asthma were identified using the ICES-derived Ontario Asthma Dataset. The dataset specifies a date of diagnosis, which is given as either the first asthma hospitalization or the first of the two asthma OHIP claims, and this was used as the event of interest in our study[68]. As asthma is difficult to accurately diagnose in young children, only children with a minimum of three years of follow-up time available were included in the analysis for this particular outcome[68].

3.6.4 Specific morbidity outcomes

We looked at two non-immune related specific morbidity outcomes in this study: neoplasm and sensory disorders (defined as vision loss or hearing loss). Neoplasm was identified using the initial diagnostic code for a malignant neoplasm in either the DAD or NACRS databases (see Appendix B). Diagnostic codes for in situ neoplasms, benign neoplasms, and neoplasms of uncertain or unknown behaviour were not included. Sensory disorders were identified using the first occurrence of either a vision loss or hearing loss diagnostic code in either database (see Appendix B).

3.6.5 Non-specific morbidity outcome

The non-specific morbidity outcome, urgent and in-patient health services utilization, was measured by counting the total number of acute care hospitalizations and emergency department visits for any reason across total follow-up time for each infant.

3.6.6 Negative control outcome

Motor-vehicle related injuries were included as a negative control outcome to detect the presence of residual confounding. Negative control outcomes are used in epidemiological studies to reproduce a situation similar to the original association of interest, with the sources of bias likely the same, but where the hypothesized causal relationship cannot be present[81]. If a source of bias is responsible for the effect of the exposure on the outcome, it should have an effect even when the causal relationship is not present[81]. As motor vehicle-related injuries in children are not plausibly associated with Tdap vaccination during pregnancy, any measured association between the two could suggest that confounding may be responsible for associations seen between Tdap exposure and study outcomes. The first occurrence of a motor-vehicle related injury diagnostic code in either the DAD or NACRS databases was considered the event of interest for this outcome (see Appendix B for diagnostic codes).

3.7 Confounding adjustment

Women who were immunized against pertussis during their pregnancy were anticipated to be systematically different from women who were not immunized. Differences between exposure groups at baseline can lead to confounding and biased estimates if any of these characteristics are also associated with the outcomes. To adjust for these differences and balance the measured

baseline covariates between the Tdap-immunized and non-immunized subjects, we calculated propensity scores for the probability of having received the Tdap vaccine during pregnancy and then exposure-matched subjects based on this variable.

3.7.1 Variable selection for the propensity score

The baseline covariates included in the propensity score were pre-selected based on several factors: availability in our databases, whether they occurred "pre-treatment" (i.e., prior to Tdap immunization), and whether they were potentially associated with our outcomes or considered potential confounders in other studies on maternal vaccination[52,53,80]. Previous research has deemed it important to include all variables in the propensity score thought to be associated with the outcomes, regardless of whether they are associated with the exposure[82]. Excluding a potentially important confounder can bias the resulting estimate and, therefore, inclusion of more rather than fewer variables is generally recommended[83]. However, post-treatment variables should be excluded as they could theoretically be affected by the treatment, and consequently, including them in the propensity score would obscure part of the treatment effect being estimated[84]. Covariates were included in the model as continuous or categorical, depending on how they were present in the original dataset. A complete list of all covariates included in our propensity score models is provided in Appendix C.

3.7.2 Propensity score methods

Commonplace in pharmacoepidemiology studies over the last decade, propensity score methods are increasingly being used for other research using large healthcare databases, including maternal vaccine safety research[46,47,53,80]. Propensity score approaches optimize adjustment when

potential confounders are numerous and using propensity scores has been shown to reduce bias more effectively that conventional covariate adjustment techniques in studies using large databases[85,86]. Developed by Rosenbaum and Rubin (1983), the propensity score estimates the conditional probability of treatment based on a set of observed covariates, estimated using a logistic regression model[87]. Subjects with similar propensity scores therefore have a similar distribution of observed baseline covariates[87]. The propensity score is a balancing score: in a set of subjects with the same propensity score, the distribution of observed baseline covariates will be the same between the treated and untreated (or exposed and unexposed) subjects[87]. By balancing baseline covariates between exposure groups, confounding due to initial differences in the groups is attenuated[87]. In theory, propensity score methods aim to achieve some of the characteristics of a randomized control trial within an observational study, where randomization itself is not possible[87].

There are several methods of using propensity scores to balance baseline covariates, none of which is universally preferred. Among the most popular approaches are inverse probability of treatment weighting and propensity score-matching, each with advantages and disadvantages that must be weighed by the researcher[88]. We initially intended to use inverse probability of treatment weighting, where each subject is given a weight equal to the inverse of their probability of being in their exposure group. Individuals who received an "unexpected" treatment, based on their baseline covariates, are therefore given increased weight within their exposure group in order to balance covariate distribution between the two groups. However, this method gives unreliable estimates when the resulting weights are disproportionally large for a small set of individuals[89,90]. This can occur even after using stabilized weights and/or truncating extreme weights to reduce

weight variability. For a model to be correctly specified, the weights should have an approximate mean of one[91].

Matching based on the propensity score is another common method for confounding adjustment that has been implemented in numerous studies on pregnant women using large healthcare databases[80,92–94]. Matching is well suited to studies with a large number of unexposed subjects compared to exposed and where the distribution of propensity scores for the exposure groups overlaps[89]. This allows for each exposed subject to be matched to comparison subjects that are either identical or very similar in propensity score, avoiding bias induced by incomplete matching or matching to more dissimilar subjects[95]. Having a large pool of unexposed comparison subjects available also allows for one-to-many matching, which gives greater estimate precision than one-to-one matching[95]. We used greedy matching with a maximum caliper width of 0.2 times the standard deviation of the logit of the propensity score and matched at a ratio of 1 Tdap-exposed subject to 5 unexposed subjects. Using this caliper width has been shown to eliminate approximately 99% of the bias due to measured confounders and minimizes the mean squared error of the estimated treatment effect[95]. As pediatric asthma was assessed using a restricted cohort, we re-matched the exposed and unexposed groups for the analysis of this outcome.

3.7.3 Coarsened exact matching

To test the robustness of our primary findings, we also employed an alternate method of matching infants for comparison. Developed by Iacus, King, and Porro (2011), coarsened exact matching requires that the researcher "coarsens" or categorizes covariate data into groups they

consider sufficiently similar and applies exact matching to the categorized variables; matched subjects are then kept in the dataset and unmatched subjects are excluded[96]. This method of matching is beneficial in scenarios where it is difficult to achieve balance for all covariates simultaneously using propensity score matching[96]. Unlike propensity score matching, coarsened exact matching does not restrict the number of unexposed subjects that are matched to each exposed subject, but rather matches exposed subjects to as many unexposed subjects with identical covariate values as are available[96]. As the ratio of exposed to unexposed subjects is therefore uneven, for subsequent statistical analyses, exposed subjects are assigned a weight of 1 and unexposed subjects are assigned a weight of $m_C/m_T \times m_T^s/m_C^s$, where m_c represents the total number of matched unexposed subjects, m_T represents the total number of matched exposed subjects, m_T^s represents the number of matched exposed subjects for that "stratum" (or group of exact matched individuals), and m_C^s represents the number of matched comparison subjects for that strata[96].

3.8 Descriptive analyses

The characteristics of the study population were described using categorical variables and frequencies. To assess the balance of baseline covariates between the two exposure groups, before and after matching, we calculated standardized differences (SD), defined as

$$\text{SD}=\frac{(\hat{\text{p}}_{\text{exposed}}-\hat{\text{p}}_{\text{unexposed}})}{\sqrt{\frac{\hat{\text{p}}_{\text{exposed}}(1-\hat{\text{p}}_{\text{exposed}})+\hat{\text{p}}_{\text{unexposed}}(1-\hat{\text{p}}_{\text{unexposed}})}{2}}}$$

for categorical variables, where $\hat{\text{p}}_{\text{exposed}}$ and $\hat{\text{p}}_{\text{unexposed}}$ denote the prevalence of the variable in exposed and unexposed subjects, respectively[88]. We used an absolute SD of <0.10 as the threshold for indicating good covariate balance, as it has been taken to indicate a negligible

difference in prevalence between two groups[88]. Standardized differences were calculated before and after propensity score matching to evaluate the improvement in comparability of the exposure groups. We also computed standardized differences for the inverse probability of treatment weighted sample and the coarsened exact matched sample to assess the covariate balance achieved using these techniques.

3.9 Statistical models

3.9.1 Poisson regression

We used Poisson regression models for the analyses of the infectious outcomes and for urgent and in-patient health services utilization, which were all count outcomes. Crude incidence rates were computed as the number of occurrences of each outcome divided by the sum of each child's total follow-up time, stratified by maternal vaccination status, and expressed per 1000-person days of follow-up. To compare rates of outcomes between the vaccinated and unvaccinated groups, we calculated unadjusted and adjusted incidence rate ratios (IRR) and 95% confidence intervals using Poisson regression models with an offset equal to the natural logarithm of the sum of each child's total follow-up time in days. Poisson regression models estimate the incidence of events over a specified follow-up period, based on the predictor variables (typically, the exposure variable and confounding variables)[97]. Since potential confounding was accounted for in the design by way of propensity score matching, we only included the exposure variable (maternal Tdap vaccination status) in the main adjusted models. Weighting was employed in the secondary models for the inverse probability of treatment weighted and coarsened exact matched samples.

3.9.2 Cox proportional hazards regression

Cox proportional hazards models were used for asthma, neoplasm, sensory loss, and our negative control outcome, motor vehicle-related injuries; these are outcomes in which we were interested in the time to first event. Cox models use time-to-event data to compare the hazards of disease according to exposure status, considering not only whether an outcome occurred but also the varying amount of time until it occurred[98]. Survival analyses, including Cox proportional hazards regression, also take into account incomplete follow-up and varying lengths of follow-up for each subject[98]. In this study, follow up time for each time-to-event outcome was measured in days from birth until the event of interest, with censoring occurring if the child died, emigrated from the province, or reached the end of the study period without experiencing the outcome under consideration. Crude incidence rates for the time-to-event outcomes were computed as the number of infants who were diagnosed with the disease divided by the sum of each child's follow-up time, calculated as described. Crude incidence rates were stratified by maternal vaccination status and expressed per 1000-person days of follow-up. To compare the risk of an outcome between the two exposure groups, we estimated unadjusted and adjusted hazard ratios (HR) using Cox proportional hazards models, with weighting employed for the inverse probability of treatment weighted and coarsened exact matched samples.

Cox regression models rely on the proportional hazards assumption (i.e. that the hazard ratio remains constant over time)[99]. To check this assumption, we used both statistical testing and graphical procedures, and assessed the proportional hazards assumption for exposure status only, as it was the only independent variable in the models. We conducted two statistical tests: (1) a Wald test for interaction between the exposure variable and time, and (2) a test for

nonproportionality developed by Lin, Wei, and Ying (1993) that compares Martingale-based residuals of the model with 1000 stimulations of the null distribution[100,101]. We considered a p-value <0.05 suggestive of a possible violation of the assumption, requiring further investigation[101]. To assess the assumption graphically, we (1) inspected the Schoenfeld residual plots, considering the proportional hazards assumption to hold if the residuals appeared uncorrelated with time and (2) produced plots of the log(-log(survival) versus the log of survival time, considering the assumption to hold if the curves were reasonably parallel[101]. As recommended by Kleinbaum and Klein (2012), we used a conservative strategy when testing the proportional hazard assumption, assuming it was satisfied unless there was strong evidence of a violation[101].

3.10 Sensitivity analyses

3.10.1 Probable Tdap vaccinations

It is possible that the majority of the maternal records with a general immunization code during their pregnancy (but outside of the influenza vaccine season), also received the Tdap vaccine. Newer vaccine-specific codes, introduced in 2011, have been found to have lower sensitivity than previous general immunization codes[72]. Using both the vaccine-specific and general codes can increase sensitivity compared to using vaccine-specific codes alone[72]. In order to quantify the impact of not considering these women as Tdap-exposed in our main analyses, we conducted a sensitivity analysis where women with a general vaccine code (G840-G590) anytime during their gestation were also considered as having received a Tdap vaccine. General vaccine codes billed during the influenza season (October 1 to January 31 each year) were not considered Tdap vaccinations due to the increased likelihood that these represented influenza immunizations

during that time of year. The impact of including probable exposures on our estimates of association was then evaluated by comparing these estimates with our main findings.

3.10.2 Propensity to access the health care system

Two additional sensitivity analyses were conducted to assess whether an association between the exposure and outcomes might be due to maternal-infant pairs in the exposed group being more likely to access the healthcare system. This would confound our findings, as an increased propensity to access the healthcare system would affect both the mother's likelihood of receiving the Tdap vaccine and the infant's likelihood of having an illness captured by health administrative data (detection bias). For our first analysis, we additionally adjusted for the mother's likelihood to access care before pregnancy by adding the following two variables in our models: (1) number of outpatient visits in the 6 months before pregnancy and (2) number of non-obstetric related hospitalizations in the 2 years before pregnancy. The propensity score matched cohorts for these analyses were drawn from women who were eligible for OHIP for at least 6 months and at least 2 years before their pregnancy, respectively. The impact of including these covariates in our adjusted models was then evaluated.

For our second sensitivity analysis, we restricted the cohort to infants who had at least two well-baby visits and/or routine pediatric immunization visits in their first year of life. We then re-matched the restricted group of Tdap-exposed infants using the restricted group of unexposed infants and determined if this impacted our original estimates.

3.11 Ethical considerations

Ethics approval for this project was obtained from the ICES Privacy Office, the Children's Hospital of Eastern Ontario Research Ethics Board, and Ottawa Health Science Network Research Ethics Board. Under section 45 of Ontario's Personal Health Information Privacy Act, consent was not required for secondary use of personal health data.

To reduce the risk of identity disclosure, no dates of birth were supplied to the student. The infant's total follow-up time and dates of any health care encounters were given as the number of days following date of birth. If an infant was followed until the final date of the study (March 31, 2018), their total days of follow-up was randomly modified within a two-week period so that their date of birth could not be back calculated. All analyses were done using SAS version 9.4 within the secure Research Analytics Environment (RAE) at ICES.

CHAPTER 4. RESULTS

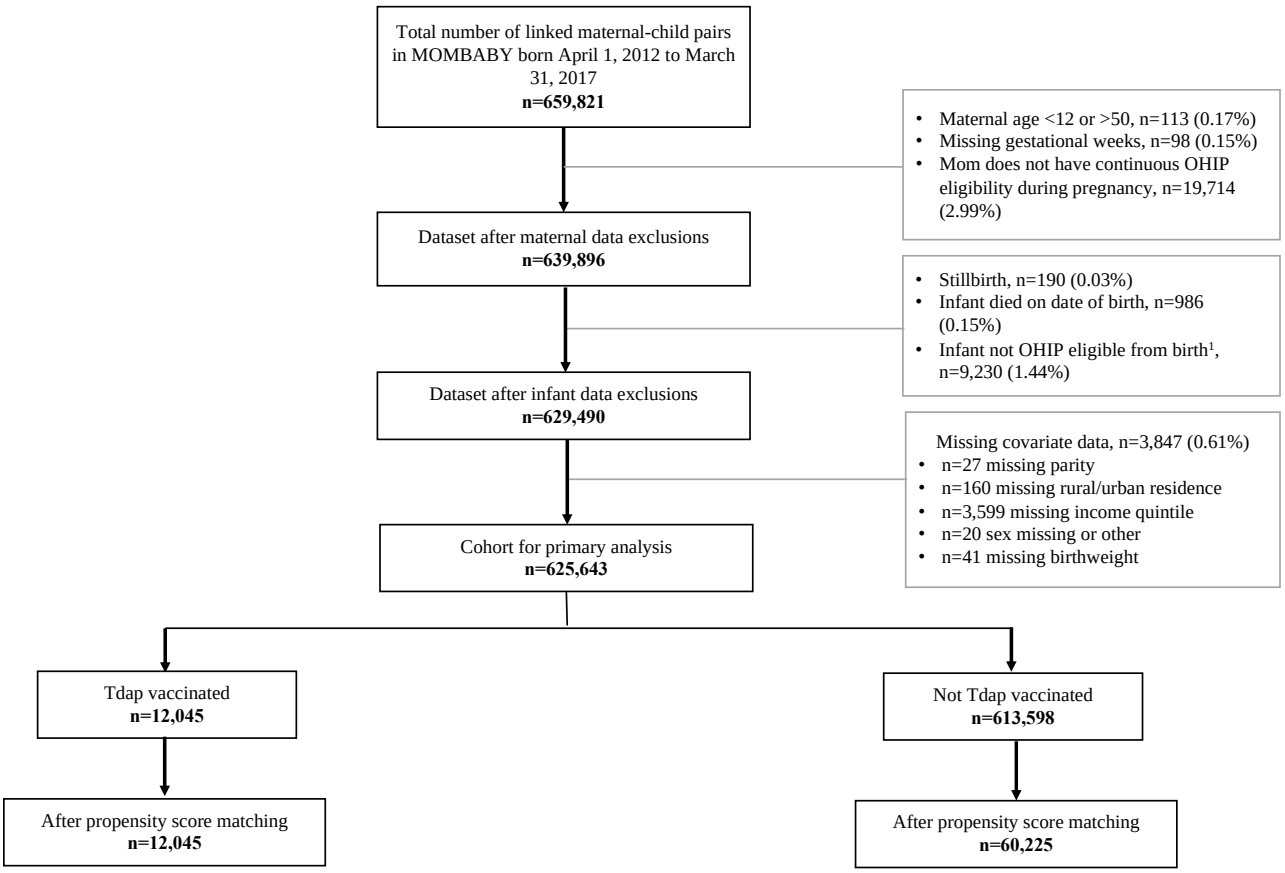
4.1 Primary analysis (propensity score matched cohort)

4.1.1 Descriptive characteristics

Between April 1, 2012 and March 31, 2017, there were 659,821 infants born in an Ontario hospital with a valid OHIP number that had a hospitalization record deterministically linked to that of their mother in the MOMBABY database **(Figure 4-1)**. We excluded 113 records with maternal age <12 or >50 years, 98 records missing gestational weeks at delivery, and 19,714 records where the mother did not have continuous OHIP eligibility during her pregnancy (3.02% of the total). We further excluded 190 stillbirths, 986 infants who died on their date of birth, and 9,230 infants who did not become OHIP-eligible within 60 days of birth (1.63% of the total). From the resulting cohort of 629,490 infants, we conducted a complete case analysis, excluding 3,847 records missing covariate data (0.61%). This resulted in a final cohort size of 625,643 infants for primary analysis. Of these, 12,045 infants were born to mothers immunized with Tdap during their pregnancy (1.9%) and were matched to 60,225 unexposed infants (a 1:5 ratio) based on their propensity score.

For the analysis of the association between Tdap immunization during pregnancy and pediatric asthma, the cohort was restricted to children with a minimum of three years of follow-up time. The 4,256 infants who had at least three years of follow-up time and were born to mothers immunized with Tdap during their pregnancy were matched to 21,280 unexposed infants who also had at least three years of follow-up time. We matched at a 1:5 ratio based on their propensity score.

Figure 4-1: Study flow diagram



[1]Infants were considered eligible from birth if they became OHIP-eligible within 60 days of their date of birth

The characteristics of the study population before and after matching are presented in **Table 4-1**. In the unmatched study cohort, the baseline characteristics that differed most notably between children born to Tdap-vaccinated and unvaccinated women were fiscal year of birth, maternal age, parity, and public health unit region, as indicated by a standardized difference >0.10. Children born to Tdap-vaccinated women were more likely to be born later in the study period (2017 vs. 2012), have a mother aged <25 years, have a mother who had never previously given birth, and live in the Eastern, Central East, or Toronto regions of Ontario (see Appendix D for map). Neighbourhood family income also differed, although to a slightly lesser extent, with

children born to vaccinated women being more likely to live in the one of the highest average income neighbourhoods in Ontario and less likely to live in one of the lowest average income neighbourhoods. Following matching based on the propensity scores, baseline characteristics that were initially imbalanced all had standardized differences <0.10, indicating an improved comparability of characteristics of infants born to women who were and were not vaccinated with Tdap during pregnancy.

Table 4-1: Baseline characteristics of the study population before and after propensity score matching, Ontario, Canada

Characteristic	Unmatched cohort			Propensity-score matched cohort			Asthma propensity-score matched cohort[1]		
	No. (%) of births to Tdap-vaccinated women *n*=12,045	No (%) of births to Tdap-unvaccinated women *n*=613,598	Std Diff[2]	No (%) of births to Tdap-vaccinated women *n*=12,045	No (%) of births to Tdap-unvaccinated women *n*=60,225	Std Diff[2]	No (%) of births to Tdap-vaccinated women *n*=4,256	No (%) of births to Tdap-unvaccinated women *n*=21,280	Std Diff[2]
Fiscal year of birth									
2012-13	594 (4.9)	127,010 (20.7)	0.49	594 (4.9)	2,983 (5.0)	0.00	581 (13.7)	2,908 (13.7)	0.00
2013-14	1,634 (13.6)	124,291 (20.3)	0.18	1,634 (13.6)	8,233 (13.7)	0.00	1,608 (37.8)	8,029 (37.7)	0.00
2014-15	2,093 (17.4)	123,218 (20.1)	0.07	2,093 (17.4)	10,567 (17.5)	0.00	2,607 (48.6)	10,343 (48.6)	0.00
2015-16	2,899 (24.1)	121,299 (19.8)	0.10	2,899 (24.1)	14,629 (24.3)	0.01	0 (0.0)	0 (0.0)	0.00
2016-17	4,825 (40.1)	117,780 (19.2)	0.47	4,825 (40.1)	23,813 (39.5)	0.01	0 (0.0)	0 (0.0)	0.00
Maternal age (years)									
<20	186 (1.5)	14,415 (2.3)	0.06	186 (1.5)	995 (1.7)	0.01	83 (2.0)	427 (2.0)	0.00
20-24	808 (6.7)	66,293 (10.8)	0.15	808 (6.7)	4,023 (6.7)	0.00	294 (6.9)	1,466 (6.9)	0.00
25-29	3,388 (28.1)	164,953 (26.9)	0.03	3,388 (28.1)	17,101 (28.4)	0.01	1,239 (29.1)	6,141 (28.9)	0.01
30-34	4,775 (39.6)	224,765 (36.6)	0.06	4,775 (39.6)	23,886 (39.7)	0.00	1,646 (38.7)	8,288 (38.9)	0.01
≥35	2,888 (24.0)	143,172 (23.3)	0.02	2,888 (24.0)	14,220 (23.6)	0.01	994 (23.4)	4,958 (23.3)	0.00
Parity									
0 (nulliparous)	6,203 (51.5)	270,753 (44.1)	0.15	6,203 (51.5)	31,041 (51.5)	0.00	2,184 (51.3)	10,910 (51.3)	0.00
≥1 (multiparous)	5,842 (48.5)	342,845 (55.9)	0.15	5,842 (48.5)	29,184 (48.5)	0.00	2,072 (48.7)	2,072 (48.7)	0.00
Pre-existing maternal medical condition[3]									
No	11,873 (98.6)	602,136 (98.1)	0.03	11,873 (98.6)	59,693 (99.1)	0.05	4,200 (98.7)	21,090 (99.1)	0.04
Yes	172 (1.4)	11,462 (1.9)	0.03	172 (1.4)	532 (0.9)	0.05	56 (1.3)	190 (0.9)	0.04
Type of pre-existing maternal medical condition									
Asthma	25 (0.2)	1,502 (0.2)	0.01	25 (0.2)	85 (0.1)	0.02	10 (0.2)	29 (0.1)	0.02
Chronic hypertension	43 (0.4)	2,362 (0.4)	0.00	43 (0.4)	134 (0.2)	0.03	17 (0.4)	56 (0.3	0.02
Diabetes	62 (0.5)	5,076 (0.8)	0.04	62 (0.5)	171 (0.3)	0.03	14 (0.3)	55 (0.3)	0.01
Heart disease[4]	49 (0.4)	2,986 (0.5)	0.01	49 (0.4)	155 (0.3)	0.03	16 (0.4)	51 (0.2)	0.02
Obstetrical complication[5]									
No	10,486 (87.1)	534,237 (87.1)	0.00	10,486 (87.1)	52,844 (87.7)	0.02	3,796 (89.2)	19,074 (89.6)	0.01
Yes	1,559 (12.9)	79,361 (12.9)	0.00	1,559 (12.9)	7,381 (12.3)	0.02	460 (10.8)	2,206 (10.4)	0.01

Delivery by cesarean									
No	8,763 (72.7)	436,568 (71.1)	0.04	8,763 (72.7)	42,935 (71.3)	0.03	3,099 (72.8)	15,314 (72.0)	0.02
Yes	3,282 (27.3)	177,030 (28.9)	0.04	3,282 (27.3)	17,290 (28.7)	0.03	1,157 (27.2)	5,966 (28.0)	0.02
Multiple birth									
No	11,767 (97.7)	592,553 (96.6)	0.07	11,767 (97.7)	59,086 (98.1)	0.03	4,164 (97.8)	20,826 (97.9)	0.00
Yes	278 (2.3)	21,045 (3.4)	0.07	278 (2.3)	1,139 (1.9)	0.03	92 (2.2)	454 (2.1)	0.00
Neighbourhood median family income quintiles									
1 (Lowest)	2,096 (17.4)	129,239 (21.1)	0.09	2,096 (17.4)	10,488 (17.4)	0.00	722 (17.0)	3,582 (16.8)	0.00
2	2,442 (20.3)	122,321 (19.9)	0.01	2,442 (20.3)	12,337 (20.5)	0.01	852 (20.0)	4,330 (20.3)	0.01
3	2,364 (19.6)	124,701 (20.3)	0.02	2,364 (19.6)	11,783 (19.6)	0.00	809 (19.0)	4,033 (19.0)	0.00
4	2,679 (22.2)	134,188 (21.9)	0.01	2,679 (22.2)	13,346 (22.2)	0.00	961 (22.6)	4,760 (22.4)	0.01
5 (Highest)	2,464 (20.5)	103,1429 (16.8)	0.09	2,464 (20.5)	12,271 (20.4)	0.00	912 (21.4)	4,575 (21.5)	0.00
Rural residence									
No	10,914 (90.6)	550,586 (89.7)	0.03	10,914 (90.6)	54,490 (90.5)	0.00	3,846 (90.4)	19,263 (90.5)	0.01
Yes	1,131 (9.4)	63,012 (10.3)	0.03	1,131 (9.4)	5,735 (9.5)	0.00	410 (9.6)	3,846 (90.4)	0.01
Public health unit region									
North West	131 (1.1)	10,855 (1.8)	0.06	131 (1.1)	651 (1.1)	0.00	18 (0.4)	104 (0.5)	0.01
North East	309 (2.6)	24,124 (3.9)	0.08	309 (2.6)	1,542 (2.6)	0.00	64 (1.5)	340 (1.6)	0.01
Eastern	1,966 (16.3)	76,286 (12.4)	0.11	1,966 (16.3)	9,639 (16.0)	0.01	474 (11.1)	2,474 (11.6)	0.02
Central East	4,307 (35.8)	185,608 (30.3)	0.12	4,307 (35.8)	21,478 (35.7)	0.00	1,741 (40.9)	8,552 (40.2)	0.01
Toronto	3,503 (29.1)	126,614 (20.6)	0.20	3,503 (29.1)	17,754 (29.5)	0.01	1,306 (30.7)	6,533 (30.7)	0.00
South West	528 (4.4)	69,380 (11.3)	0.26	528 (4.4)	2,632 (4.4)	0.00	185 (4.3)	935 (4.4)	0.00
Central West	1,301 (10.8)	120,731 (19.7)	0.25	1,301 (10.8)	6,529 (10.8)	0.00	468 (11.0)	2,342 (11.0)	0.00
Sex									
Female	5,858 (48.6)	299,118 (48.7)	0.00	5,858 (48.6)	29,378 (48.8)	0.00	2,043 (48.0)	10,274 (48.3)	0.01
Male	6,187 (51.4)	314,480 (51.3)	0.00	6,187 (51.4)	30.847 (51.2)	0.00	2,213 (52.0)	11,006 (51.7)	0.01
Birth weight (grams)									
<1500	44 (0.4)	5,316 (0.9)	0.06	44 (0.4)	425 (0.7)	0.05	19 (0.4)	139 (0.7)	0.03
1500-2499	545 (4.5)	33,866 (5.5)	0.05	545 (4.5)	2,943 (4.9)	0.02	184 (4.3)	950 (4.5)	0.01
2500-3499	6,752 (56.1)	332,489 (54.2)	0.04	6,752 (56.1)	33,434 (55.5)	0.01	2,335 (54.9)	11,749 (55.2)	0.01
≥3500	4,704 (39.0)	241,927 (39.4)	0.01	4,704 (39.0)	23,423 (38.9)	0.00	1,718 (40.4)	8,445 (39.7)	0.01
Gestational age at birth in weeks									
<31	56 (0.5)	6,134 (1.0)	0.06	56 (0.5)	497 (0.8)	0.05	21 (0.5)	167 (0.8)	0.04
32-33	63 (0.5)	5,687 (0.9)	0.05	63 (0.5)	413 (0.7)	0.02	24 (0.6)	136 (0.6)	0.01
34	88 (0.7)	5,990 (1.0)	0.03	88 (0.7)	515 (0.9)	0.01	39 (0.9)	168 (0.8)	0.01

35	152 (1.3)	10,020 (1.6)	0.03	152 (1.3)	813 (1.3)	0.01	61 (1.4)	298 (1.4)	0.00
36	366 (3.0)	20,119 (3.3)	0.01	366 (3.0)	1,797 (3.0)	0.00	121 (2.8)	604 (2.8)	0.00
≥37 (Term)	11,320 (94.0)	565,648 (92.2)	0.07	11,320 (94.0)	56,190 (93.3)	0.03	3,990 (93.8)	19,907 (93.5)	0.01
Median follow-up time in person-years (range)	2.3 (0.0-6.0)	3.5 (0.0-6.0)		2.3 (0.0-6.0)	2.5 (0.0-6.0)		4.0 (3.0-6.0)	4.0 (3.0-6.0)	

Abbreviations: Tdap, tetanus, diphtheria, and acellular pertussis; Std Diff, standardized difference

[1]Cohort for asthma is restricted to children with a minimum of 3 years of follow-up.
[2]Shaded cells represent standardized differences >0.10 indicating imbalance between Tdap-vaccinated and unvaccinated subjects.
[3]Asthma, chronic hypertension, diabetes, or heart disease
[4]Cardiac valvular disease, congenital heart disease, chronic congestive heart failure, hypertensive heart disease, or chronic ischemic heart disease
[5]Eclampsia, gestational diabetes, placenta previa, placental abruption, pre-eclampsia, or pregnancy-induced hypertension

4.1.2 Model fit evaluation

The c-statistic for the propensity score model was 0.718, indicating good predictive accuracy of the model. The distribution of the propensity scores for the exposed and unexposed infants also had a high degree of overlap (or "common support"), signifying that combinations of characteristics observed in the exposed group could also be observed among the unexposed group and the cohort was well-suited for propensity score matching (Appendix E). All exposed infants were matched to 5 unexposed infants using greedy matching without replacement; 94.7% were matched to an unexposed infant with an identical propensity score and the largest difference was 0.0013 (maximum caliper width of 0.0031). For the asthma propensity score matched cohort, 95.8% were matched to an identical propensity score and the largest difference was 0.000064 (maximum caliper width of 0.0015). Standardized differences were measured after matching and were <0.10 for all baseline characteristics.

For the Cox proportional hazards models, we evaluated the proportional hazards assumption using Wald tests for covariate-time interactions, tests of the cumulative sums of Martingale-based residuals, Schoenfeld residual plots, and log(-log(survival)) curves (see Appendix F for test outputs). There was no indication of a violation of the proportional hazards assumption for sensory loss. Although the Wald test p-value was significant at $p<0.05$ for neoplasm, asthma, and motor vehicle-related injuries, with such a large sample size, even a slight violation of the proportional hazards assumption may lead to a significant p-value. Visual inspection of the Schoenfeld residuals and log(-log(survival)) curves did not provide evidence of a strong departure from parallel hazards outside of the tail ends of the functions, where data points were sparse. A possible exception was motor-vehicle related injuries; however, as this was a negative

control outcome and not a primary outcome of interest, we did not make adjustments to the proportional hazards model for this outcome. Supremum tests comparing the cumulative sums of the model's Martingale residuals with 1000 stimulations of the null distribution (where the proportional hazards assumption held) found a significant departure from the assumption of proportional hazards at $p<0.05$ for motor-vehicle related injuries only.

4.1.3 Risk of pediatric adverse health outcomes following Tdap vaccination during pregnancy

Crude incidence rates were comparable between exposure groups for asthma, neoplasm, and sensory disorders. Crude incidence rates of upper respiratory tract infections, lower respiratory tract infections, gastrointestinal infections, otitis media, and rates of urgent and in-patient health service utilization were lower among infants whose mothers were vaccinated with Tdap during pregnancy **(Table 4-2)**.

In the propensity score matched sample, with balanced baseline covariates, Tdap vaccination during pregnancy was not associated with an increased risk for any of the study outcomes. For the immune-related outcomes, prenatal Tdap exposure was not associated with pediatric asthma (aHR: 0.93, 95% CI: 0.84-1.03) or otitis media (aIRR: 1.00, 95% CI: 0.95-1.05). There was a small inverse association with upper respiratory infections (aIRR: 0.96, 95% CI: 0.93-0.99) and lower respiratory infections (aIRR: 0.93, 95% CI: 0.89-0.98). We also observed an inverse association between prenatal Tdap exposure and gastrointestinal infections (aIRR: 0.88, 95% CI: 0.82-0.94). Prenatal Tdap was not associated with either of the specific non-immune related outcomes, neoplasm (aHR: 1.53, 95% CI: 0.83-2.86) or sensory disorders (aHR: 0.73, 95% CI: 0.35-1.53). However, there was a significant inverse association between prenatal Tdap and the

non-specific outcome, urgent and in-patient health service utilization (aIRR: 0.95, 95% CI: 0.94-0.97) **(Table 4-2)**.

Crude incidence rates were comparable between exposure groups for the negative control outcome, motor-vehicle related injuries. Analysis of the negative control outcome did not indicate the presence of residual confounding; in the propensity score matched sample, no association was found between maternal Tdap vaccination during pregnancy and motor-vehicle related injuries (aHR: 0.84, 95% CI:0.55-1.28) **(Table 4-2)**.

Table 4-2: Association between Tdap vaccination during pregnancy and pediatric health outcomes, Ontario, Canada

	Tdap vaccination during pregnancy		No Tdap vaccination during pregnancy		Crude estimate (95% CI)	Estimate from matched sample (95% CI)
	Number of events (%)	Incidence rate (95% CI) per 1000 person-years	Number of events (%)	Incidence rate (95% CI) per 1000 person-years		
Atopic disease						
Asthma[1,2]	461 (10.8)	28.2 (25.7-30.9)	43,757 (11.9)	28.4 (28.1-28.7)	0.95 (0.87-1.04)	0.93 (0.84-1.03)
Infectious disease						
Upper respiratory infections[3]	4,303	135.3 (131.3-139.4)	311,405	144.8 (144.3-145.3)	0.93 (0.91-0.96)	0.96 (0.93-0.99)
Lower respiratory infections[3]	1,787	56.2 (53.6-58.9)	129,960	60.4 (60.1-60.8)	0.93 (0.89-0.97)	0.93 (0.89-0.98)
Gastrointestinal infections[3]	1,077	33.9 (31.9-36.0)	77,783	36.2 (35.9-36.4)	0.94 (0.88-0.99)	0.88 (0.82-0.94)
Otitis media[3]	1,851	58.2 (55.6-60.9)	137,293	63.9 (63.5-64.2)	0.91 (0.87-0.95)	1.00 (0.95-1.05)
Non-immune related morbidity outcomes						
Neoplasm[2]	13 (0.11)	0.41 (0.24-0.70)	614 (0.10)	0.29 (0.26-0.31)	1.40 (0.81-2.43)	1.53 (0.83-2.86)
Sensory disorders[2]	8 (0.07)	0.25 (0.13-0.50)	764 (0.12)	0.36 (0.33-0.38)	0.70 (0.35-1.41)	0.73 (0.35-1.53)
Non-specific morbidity outcome						
Rates of urgent and in-patient health service utilization[3]	22,965	722.1 (712.8-731.5)	1,615,068	751.1 (749.9-752.3)	0.96 (0.95-0.97)	0.95 (0.94-0.97)
Negative-control outcome						
Motor-vehicle related injuries[2]	25 (0.21)	0.79 (0.53-1.16)	2,040 (0.33)	0.95 (0.91-0.99)	0.85 (0.57-1.26)	0.84 (0.55-1.28)

Abbreviations: Tdap, tetanus, diphtheria, and acellular pertussis; CI, confidence interval

[1]Cohort for asthma is restricted to children with a minimum of 3 years of follow-up.
[2]Number of events represents the total number of children diagnosed with the outcome. Incidence rates are based on the full study population. Point estimates are hazard ratios generated from a Cox proportional hazards model.
[3]Number of events represents the total number of occurrences for each outcome. Incidence rates are based on the full study population. Point estimates are incidence rate ratios generated from a Poisson regression model

4.1.4 Comparison of included and excluded subjects

Prior to matching, 10,216 infants were excluded from the eligible study cohort because they could not be followed up in the administrative databases past their date of birth. Excluded infants either died on their date of birth (n=986) or did not become OHIP-eligible within 60 days of their date of birth (n=9,230). It is possible that infants born without OHIP eligibility remained in Ontario and were assigned a health card number later in infancy, but for administrative reasons it was not linked to their birth record in the MOMBABY database, and therefore, they had no follow-up information available. To determine whether there were any systematic differences between included and excluded infants that might bias our results, we compared the maternal Tdap exposure status and other baseline characteristics of these excluded records with those records that were included in the study. We could not exclude infants who died on their date of birth from this analysis, and therefore, they were included in this comparison. The percentage of women immunized with Tdap during pregnancy was essentially the same for the infants who were included and excluded from the study population. Excluded infants were more likely to have very low birthweight and be preterm; however, this is most likely influenced by the infants who died on the first day after birth, who were not eligible for this study (which assessed outcomes in infants who survived >1 day; **Table 4-3).**

Table 4-4 presents the comparison of infant records that were included in the study population with records that were excluded due to missing covariate data. As only a small percentage of records had missing covariate data (n=3,847, 0.6%), we used complete cases analysis, rather than multiple imputation. We compared vaccination status and characteristics of included and excluded records to determine whether missing covariate information was systematically related

to exposure status or other baseline variables in a way that might affect the validity of our study findings. Nearly all exclusions were due to missing income quintile and therefore differences in baseline characteristics were primarily due to patterns in mother-child pairs that could not be assigned income information based on their place of residence. Infants excluded for missing covariate information were more likely to have a mother <25 years of age, have a mother with a pre-existing medical condition, and live in a rural setting **(Table 4-4)**. However, exclusion from the cohort was unrelated to the probability of receiving the Tdap vaccine **(Table 4-4)** and therefore exclusion of these records with missing covariate data was unlikely to have biased our results.

Table 4-3: Characteristics of records included and excluded from the study cohort for infant eligibility reasons

Characteristic	Included (n=629,490)		Excluded (n=10,216)		Std Diff[1]
	n	%	n	%	
Tdap-vaccinated					
No	617,155	98.0	10,026	98.1	0.01
Yes	12,335	2.0	190	1.9	0.01
Maternal age (years)					
<20	14,932	2.4	457	4.5	0.12
20-24	67,952	10.8	1,406	13.8	0.09
25-29	169,356	26.9	2,627	25.7	0.03
30-34	230,596	36.6	3,297	32.3	0.09
≥35	146,654	23.3	2,429	23.8	0.01
Parity					
0 (nulliparous)	278,613	44.3	4,044	39.6	0.09
≥1 (multiparous)	350,850	55.7	5,864	57.4	0.03
Pre-existing maternal medical condition[2]					
No	617,710	98.1	9,988	97.8	0.03
Yes	9,988	1.9	228	2.2	0.03
Obstetrical complication[3]					
No	547,993	87.1	8,829	86.4	0.02
Yes	81,497	12.9	1,387	13.6	0.02
Delivery by cesarean					
No	448,024	71.2	7,413	72.6	0.03
Yes	181,466	28.8	2,803	27.4	0.03
Multiple birth					
No	608,054	96.6	9,585	93.8	0.13

Yes	21,436	3.4	631	6.2	0.13
Neighbourhood median family income quintiles					
1 (Lowest)	131,357	20.9	2,560	25.1	0.10
2	124,781	19.8	2,122	20.8	0.02
3	127,082	20.2	1,951	19.1	0.03
4	136,887	21.7	1,994	19.5	0.06
5 (Highest)	105,624	16.8	1,467	14.4	0.07
Rural residence					
No	563,309	89.5	9,080	88.9	0.02
Yes	66,021	10.5	1,129	11.1	0.02
Sex					
Female	306,861	48.7	4,904	48.0	0.01
Male	322,609	51.2	5,308	52.0	0.01
Birth weight (grams)					
<1500 g	5,459	0.9	1,273	12.5	0.48
1500-2499 g	34,590	5.5	779	7.6	0.09
2500-3499 g	341,012	54.2	4,851	47.5	0.13
≥3500 g	248,427	39.5	3,312	32.4	0.15
Gestational age at birth in weeks					
<28	2,040	0.3	1,150	11.3	0.48
28-31	4,223	0.7	155	1.5	0.08
32-33	5,786	0.9	166	1.6	0.06
34	6,125	1.0	160	1.6	0.05
35	10,235	1.6	199	1.9	0.02
36	20,625	3.3	386	3.8	0.03
≥37 (Term)	580,327	92.2	7,998	78.3	0.40

Abbreviations: Tdap, tetanus, diphtheria, and acellular pertussis; Std Diff, standardized difference

[1]Shaded cells represent standardized differences >0.10 indicating imbalance between vaccinated and unvaccinated subjects.
[2]Asthma, chronic hypertension, diabetes, or heart disease
[3]Eclampsia, gestational diabetes, placenta previa, placental abruption, pre-eclampsia, or pregnancy-induced hypertension

Table 4-4: Characteristics of records with and without missing covariate data

	Included (n=625,643)		**Excluded (n=3,847)**		**Std Diff[1]**
Characteristic	n	%	n	%	
Tdap-vaccinated					
No	613,598	98.1	3,830	98.9	0.07
Yes	12,045	1.9	42	1.1	0.07
Maternal age (years)					
<20	14,601	2.3	331	8.6	0.28
20-24	67,101	10.7	851	22.1	0.31
25-29	168,341	26.9	1,015	26.4	0.01
30-34	229,540	36.7	1,056	27.4	0.20
≥35	146,060	23.3	5948.6	15.4	0.20
Parity					
0 (nulliparous)	276,956	44.3	1,657	43.1	0.02

≥1 (multiparous)	348,687	55.7	2,163	56.2	0.01
Missing	0	0.0	27	0.70	0.12
Pre-existing maternal medical condition[2]					
No	614009	98.1	3701	96.2	0.12
Yes	11,643	1.9	146	3.8	0.12
Obstetrical complication[3]					
No	544,723	87.1	3,270	85.1	0.06
Yes	80,920	12.9	577	14.9	0.06
Delivery by cesarean					
No	445,331	71.2	2,693	70.0	0.03
Yes	180,312	28.8	1,154	30.0	0.03
Multiple birth					
No	604,320	96.6	3,734	97.1	0.03
Yes	21,323	3.4	113	2.9	0.03
Neighbourhood median family income quintiles					
1 (Lowest)	131,335	21.0	22	2.6	0.70
2	124,763	19.9	18	0.5	0.68
3	127,065	20.3	17	0.4	0.69
4	136,867	21.9	20	0.5	0.72
5 (Highest)	105,613	16.9	11	0.3	0.62
Missing	0	0.0	3,759	97.1	9.24
Rural residence					
No	561,500	89.7	1,809	47.0	0.29
Yes	64,143	10.3	1,878	48.8	1.03
Missing	0	0.0	160	4.2	0.93
Sex					
Female	304,976	48.7	1,885	49.0	0.01
Male	320,667	51.3	1,942	50.5	0.02
Missing or other	0	0.0	20	0.5	0.10
Birth weight (grams)					
<1500 g	5,360	0.9	60	1.6	0.06
1500-2499 g	34,411	5.5	179	4.7	0.04
2500-3499 g	339,241	54.2	1,771	46.0	0.16
≥3500 g	246,631	39.4	1,796	46.7	0.15
Missing	0	0.00	41	1.1	0.15
Gestational age at birth in weeks					
<28	2,000	0.3	41	1.1	0.09
28-31	4,190	0.7	33	0.9	0.02
32-33	5,750	0.9	36	0.9	0.00
34	6.078	1.0	49	1.	0.03
35	10,172	1.6	64	1.7	0.00
36	20,485	3.3	141	3.7	0.02
≥37 (Term)	576,968	92.2	3,483	90.5	0.06

Abbreviations: Tdap, tetanus, diphtheria, and acellular pertussis; Std Diff, standardized difference

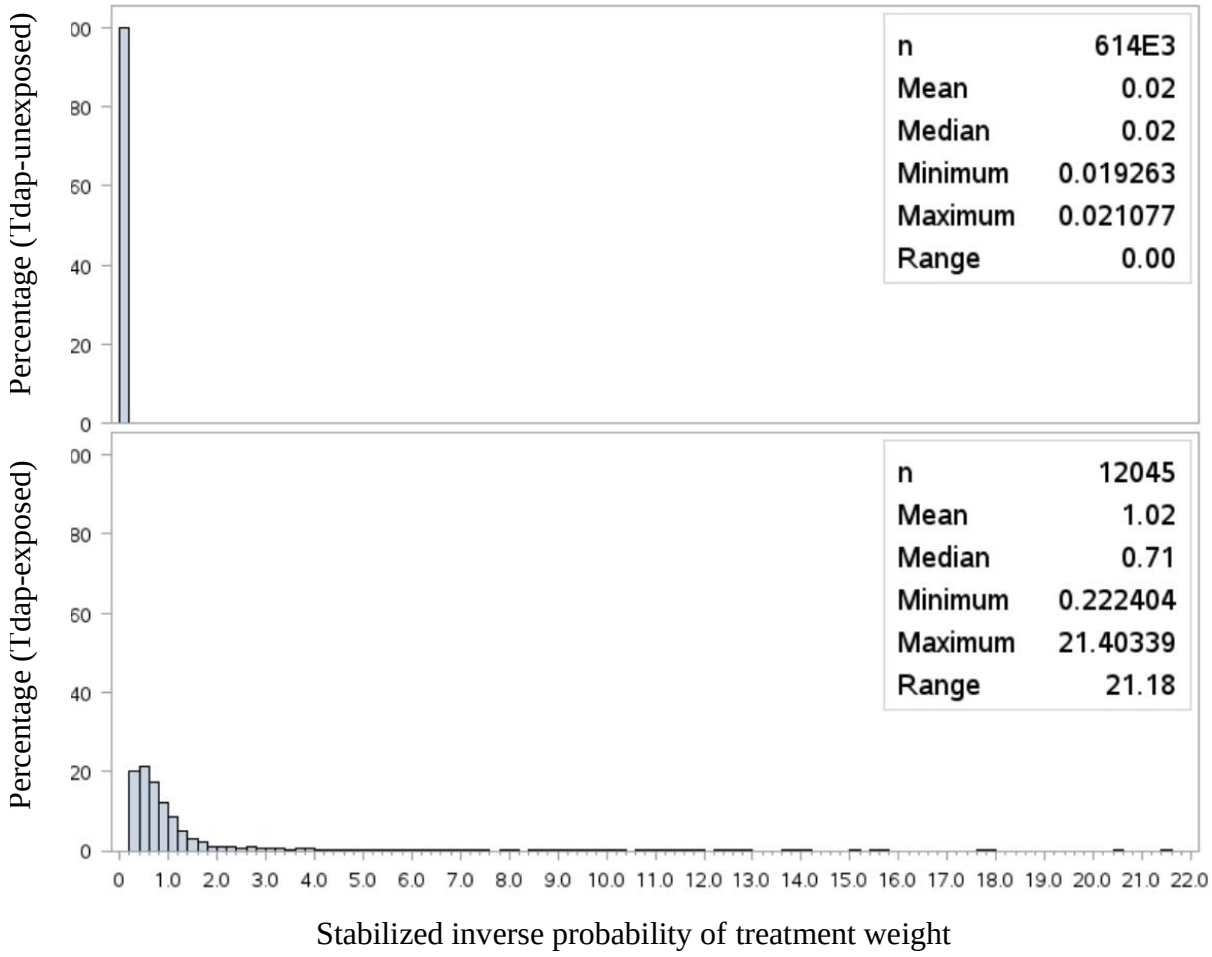
[1]Shaded cells represent standardized differences >0.10 indicating imbalance between vaccinated and unvaccinated subjects.
[2]Asthma, chronic hypertension, diabetes, or heart disease
[3]Eclampsia, gestational diabetes, placenta previa, placental abruption, pre-eclampsia, or pregnancy-induced hypertension

4.2 Alternate analytical approaches

4.2.1 Inverse probability of treatment weighted analysis

We initially planned to conduct an inverse probability of treatment weighted analysis as part of the original analysis plan. However, we found that despite using stabilized weights to contract the variance of the assigned weights, estimated weights for the subjects in the Tdap-vaccinated group were much larger than those for Tdap-unvaccinated group **(Figure 4-2)**. Highly variable weights indicate that the resulting effect estimates can be unreliable, with undue influence assigned to a small number of subjects. The mean weight for the study population was 0.039 with a standard deviation of 0.22; a mean close to 1.0 is required for correct model specification. Propensity score matching was, therefore, used instead of inverse probability of treatment weighting to adjust for confounding in the primary analyses. For completeness, baseline characteristics of the study population after weighting and the adjusted risks of pediatric adverse health outcomes following Tdap vaccination during pregnancy are presented in Appendix G.

Figure 4-2: Histogram of stabilized inverse probability of treatment weights



4.2.2 Coarsened exact matching analysis

After concluding that the stabilized inverse probability of treatment weighted approach was not feasible with our data, we also explored coarsened exact matching as an alternate method to propensity score matching. Using this approach, 11,776 of 12,045 Tdap-exposed infants were exactly matched to 419,779 controls based on the same variables that were included in the propensity score models (listed in Appendix C). The single continuous variable, maternal age, was coarsened into five categories: <20 years, 20-24 years, 25-29 years, 30-34 years, and ≥35 years. For analysis of pediatric asthma, 4,182 of the 4,256 Tdap-exposed infants were exactly

matched to 236,078 controls. Baseline characteristics of the study population after coarsened exact matching are presented in Appendix H1. No meaningful difference was noted between the estimates of association in the coarsened exact matched analysis compared to the propensity score matched analysis (Appendix H2). We chose to use the propensity score matched analysis as our primary analysis, and the coarsened exact matching analysis for comparison only, as propensity score matching is a more well-established, commonly used approach in vaccine and perinatal epidemiology research. Coarsened exact matching would have been preferable had we had difficulty balancing baseline covariates between the two exposure groups using propensity score matching; however, we achieved excellent covariate balance using this approach.

4.3 Sensitivity analyses

4.3.1 Inclusion of probable Tdap vaccinations (Sensitivity analysis #1)

To assess the impact of possible exposure misclassification (specifically, low sensitivity of the specific Tdap fee codes in the OHIP database), we conducted a pre-specified sensitivity analysis in which we expanded the Tdap exposure definition to additionally include women with a general vaccine code during their pregnancy, but outside of influenza vaccine season. Under the expanded exposure definition, 14,934 infants were considered exposed to prenatal Tdap and were matched to 74,640 unexposed infants (a 1:5 ratio) based on their propensity score. For the analysis of pediatric asthma, 5,867 exposed infants were matched to 29,334 unexposed infants.

Expanding the exposure definition had a negligible impact on the magnitude of most of the point estimates. However, the estimates for the infectious outcomes were slightly attenuated, resulting in non-significant associations between Tdap vaccination during pregnancy and upper respiratory

(aIRR: 0.98, 95% CI: 0.96-1.01) and lower respiratory infections (aIRR: 0.96, 95% CI: 0.91-1.00). The estimates for gastrointestinal infections (aIRR: 0.90, 95% CI: 0.85-0.96) along with rates of urgent and in-patient health service utilization (aIRR: 0.96, 95% CI: 0.95-0.98) were also slightly attenuated but remained statistically significant. Using the expanded exposure definition, we did find a statistically significant association between Tdap vaccination during pregnancy and neoplasm, which was not present in the primary analysis (aHR: 1.79, 95% CI: 1.03-3.11). All estimates are presented in **Table 4-5**.

Table 4-5: Sensitivity analysis for association between Tdap vaccination during pregnancy and pediatric health outcomes, Ontario, Canada

Outcome	Original results from Table 4-2 (Tdap definite)[1]	Sensitivity analysis (Tdap probable)[2]
	Estimate from propensity score-matched sample (95% CI)	Estimate from propensity score-matched sample (95% CI)
Atopic disease		
Asthma[3,4]	0.93 (0.84-1.03)	0.96 (0.88-1.04)
Infectious disease		
Upper respiratory infections[5]	0.96 (0.93-0.99)	0.98 (0.96-1.01)
Lower respiratory infections[5]	0.93 (0.89-0.98)	0.96 (0.91-1.00)
Gastrointestinal infections[5]	0.88 (0.82-0.94)	0.90 (0.85-0.96)
Otitis media[5]	1.00 (0.95-1.05)	0.99 (0.95-1.04)
Non-immune related morbidity outcomes		
Neoplasm[4]	1.53 (0.83-2.86)	1.79 (1.03-3.11)
Sensory disorders[4]	0.73 (0.35-1.53)	0.54 (0.27-1.08)
Non-specific morbidity outcome		
Rates of urgent and in-patient health service utilization[5]	0.95 (0.94-0.97)	0.96 (0.95-0.98)
Negative-control outcome		
Motor-vehicle related injuries[4]	0.84 (0.55-1.28)	0.87 (0.60-1.25)

Abbreviations: Tdap, tetanus, diphtheria, and acellular pertussis; CI, confidence interval

[1]Exposure to Tdap vaccination defined as pertussis-specific fee code during pregnancy.
[2]Exposure to Tdap vaccination defined as pertussis-specific or general vaccine fee code (outside of flu season) during pregnancy.
[3]Cohort for asthma is restricted to children with a minimum of 3 years of follow-up.
[4]Point estimates are hazard ratios generated from a Cox proportional hazards model.
[5]Point estimates are incidence rate ratios generated from a Poisson regression model.

4.3.2 Propensity to access the health care system (Sensitivity analysis #2)

To account for the impact that maternal propensity to access the health care system might have on estimates of association between Tdap vaccination during pregnancy and pediatric health outcomes, we (1) additionally adjusted for number of outpatient visits in the 6 months before pregnancy and number of non-obstetric hospitalizations in the 2 years before pregnancy and (2) restricted the analysis to children with at least 2 well-baby or routine immunization visits in their first year. Before adjusting for number of health care visits, we excluded women from the sensitivity analyses unless they were eligible for OHIP for the entire 6-month and 2-year period prior to the start of their pregnancy and used 1:5 propensity score matching to balance the baseline covariates between the remaining eligible Tdap-exposed and unexposed infants. For the 6-month lookback, 11,708 Tdap-exposed infants (of the 12,045 in the original study cohort) were matched to 58,540 controls, and for the 2-year lookback, 10,979 Tdap-exposed infants were matched to 54,895 controls. The estimates of association in the slightly reduced propensity score matched cohorts were mostly comparable to those in the primary analysis, although there was some variation **(Table 4-6)**. The impact of additionally adjusting for the number of outpatient visits in the 6 months prior to pregnancy and non-obstetric hospitalizations in the 2 years prior to pregnancy on the estimates of association was negligible **(Table 4-6)**. After restricting the analysis to children with at least 2 well-baby or routine immunization visits in their first year, we matched 11,745 Tdap-exposed infants to 58,725 controls using 1:5 propensity score matching. Using this restricted cohort also had a minimal impact on the estimates of association **(Table 4-7)**. The most notable effect was on asthma, where the inverse association between vaccination and asthma was slightly stronger than in the primary analysis **(Table 4-7)**.

Table 4-6: Sensitivity analyses for association between Tdap vaccination during pregnancy and pediatric health outcomes, Ontario, Canada

Outcome	Original results from Table 4-2	6-month lookback[1]		2-year lookback[2]	
	Estimate from propensity score-matched sample (95% CI)	Estimate from propensity score-matched sample (95% CI)	Estimate from propensity score-matched sample (95% CI), adjusted for health care visits[3]	Estimate from propensity score-matched sample (95% CI)	Estimate from propensity score-matched sample (95% CI), adjusted for health care visits[4]
Atopic disease					
Asthma[5,6]	0.93 (0.84-1.03)	0.88 (0.80-0.98)	0.89 (0.81-0.99)	0.89 (0.81-0.99)	0.89 (0.91-0.99)
Infectious disease					
Upper respiratory infections[7]	0.96 (0.93-0.99)	0.95 (0.92-0.98)	0.95 (0.92-0.98)	0.95 (0.92-0.99)	0.95 (0.92-0.99)
Lower respiratory infections[7]	0.93 (0.89-0.98)	0.92 (0.87-0.96)	0.92 (0.88-0.97)	0.94 (0.89-0.99)	0.94 (0.89-0.99)
Gastrointestinal infections[7]	0.88 (0.82-0.94)	0.88 (0.82-0.94)	0.89 (0.83-0.95)	0.87 (0.81-0.93)	0.87 (0.81-0.93)
Otitis media[7]	1.00 (0.95-1.05)	0.97 (0.93-1.02)	0.98 (0.93-1.03)	0.97 (0.93-1.03)	0.97 (0.93-1.03)
Non-immune related morbidity outcomes					
Neoplasm[6]	1.53 (0.83-2.86)	1.17 (0.62-2.19)	1.16 (0.62-2.18)	1.33 (0.71-2.50)	1.33 (0.71-2.50)
Sensory disorders[6]	0.73 (0.35-1.53)	0.71 (0.34-1.48)	0.72 (0.35-1.52)	0.87 (0.41-1.85)	0.88 (0.41-1.85)
Non-specific morbidity outcome					
Rates of urgent and in-patient health service utilization[7]	0.95 (0.94-0.97)	0.94 (0.93-0.96)	0.95 (0.94-0.96)	0.95 (0.93-0.96)	0.95 (0.93-0.96)
Negative-control outcome					
Motor-vehicle related injuries[6]	0.84 (0.55-1.28)	0.95 (0.62-1.46)	0.96 (0.63-1.47)	1.02 (0.67-1.57)	1.02 (0.67-1.57)

Abbreviations: Tdap, tetanus, diphtheria, and acellular pertussis; CI, confidence interval

[1]Analysis limited to mothers continuously eligible for provincial healthcare in the 6 months before pregnancy
[2]Analysis limited to mothers continuously eligible for provincial healthcare in the 2 years before pregnancy
[3]Additionally adjusted for maternal propensity to use health care (# of outpatient visits in the 6 months before pregnancy).
[4]Additionally adjusted for maternal propensity to use health care (# of non-obstetric related hospitalizations in the 2 years before pregnancy).
[5]Cohort for asthma is restricted to children with a minimum of 3 years of follow-up.
[6]Point estimates are hazard ratios generated from a Cox proportional hazards model.
[7]Point estimates are incidence rate ratios generated from a Poisson regression model.

Table 4-7: Sensitivity analysis for association between Tdap vaccination during pregnancy and pediatric health outcomes, Ontario, Canada

Outcome	Original results from Table 4-2	Sensitivity analysis[1]
	Estimate from propensity score-matched sample (95% CI)	Estimate from propensity score-matched sample (95% CI)
Atopic disease		
Asthma[2,3]	0.93 (0.84-1.03)	0.89 (0.81-0.99)
Infectious disease		
Upper respiratory infections[4]	0.96 (0.93-0.99)	0.95 (0.92-0.99)
Lower respiratory infections[4]	0.93 (0.89-0.98)	0.94 (0.89-0.99)
Gastrointestinal infections[4]	0.88 (0.82-0.94)	0.90 (0.84-0.96)
Otitis media[4]	1.00 (0.95-1.05)	0.98 (0.93-1.03)
Non-immune related morbidity outcomes		
Neoplasm[3]	1.53 (0.83-2.86)	1.27 (0.68-2.40)
Sensory disorders[3]	0.73 (0.35-1.53)	0.79 (0.38-1.67)
Non-specific morbidity outcome		
Rates of urgent and in-patient health service utilization[3]	0.95 (0.94-0.97)	0.94 (0.93-0.96)
Negative-control outcome		
Motor-vehicle related injuries[3]	0.84 (0.55-1.28)	0.92 (0.59-1.42)

Abbreviations: Tdap, tetanus, diphtheria, and acellular pertussis; CI, confidence interval

[1]Analysis limited to children with at least 2 well-baby and/or routine pediatric immunization visits in the first year.
[2]Cohort for asthma is restricted to children with a minimum of 3 years of follow-up.
[3]Point estimates are hazard ratios generated from a Cox proportional hazards model.
[4]Point estimates are incidence rate ratios generated from a Poisson regression model.

CHAPTER 5. DISCUSSION

5.1 Statement of principal findings

In this population-based retrospective cohort study of Ontario infants, we did not observe any increased risk of adverse health outcomes in infants exposed to Tdap vaccine in utero. Specifically, no association was found between Tdap vaccination and asthma, otitis media, neoplasm, or vision or hearing loss in the first 6 years of life. Weak but statistically significant inverse associations were observed between Tdap vaccination and upper respiratory infections, lower respiratory infections, and urgent and in-patient health service utilization; the magnitude of these risk reductions ranged from 4% to 7%. A slightly stronger inverse association was noted between Tdap vaccination and gastrointestinal infections (12% reduction in Tdap-exposed compared with unexposed infants). Point estimates remained largely unchanged in several sensitivity analyses adjusting for possible differential access to healthcare by the exposure group.

5.2 Interpretation of findings

The Developmental Origins of Health and Disease Hypothesis postulates that exposure to environmental influences during critical periods of fetal development can have significant, lasting consequences on an individual's short- and long-term health[54]. Adverse intrauterine environments may have programming effects on the developing fetal immune system, which can permanently alter offspring immune function and lead to an increased susceptibility to inflammatory and immune diseases[58]. Activation of the immune system during pregnancy due to maternal infection has been correlated with adverse health outcomes including psychiatric and neurodevelopmental disorders, type I diabetes, and atopic disease[102–107]. Although vaccination induces an inflammatory response, it is lower in magnitude and shorter in duration compared to

infection itself[108]. Whether maternal immune activation caused by vaccination could be associated with later poor outcomes is unknown.

Research to date on the safety of maternal Tdap vaccination in pregnancy has focused largely on obstetric and neonatal outcomes[10,43,44]. Findings have been reassuring, with studies finding no increased risk of hypertensive disorder, preterm birth, small-for-gestational-age birth, stillbirth, or neonatal death following maternal Tdap vaccination in pregnancy; however, three studies have reported a small increase in the risk of chorioamnionitis among pregnant women vaccinated with Tdap[10,43–47]. Studies that have included longer-term adverse health outcomes have focused on the first 12 to 18 months of life, finding no increased risk of growth or developmental delays in the first 18 months, mortality or hospitalization in the first 6 months, or complex chronic disease in the first year[24,37,50–53]. Only one study on Tdap vaccination in pregnancy has followed infants for a longer period: Becerra-Culqui et al. (2018) compared the incidence of ASD between children exposed and unexposed to prenatal Tdap up to 6.5 years of age[53]. Using a similar methodology as our study, Becerra-Culqui et al. (2018) conducted a large, retrospective cohort study of mother-child pairs, used electronic medical records to ascertain vaccination history and the development of ASD, and employed propensity score methods (inverse probability of treatment weighting) to adjust for confounding[53]. They did not find maternal Tdap vaccination to be associated with any increased risk of ASD[53]. The results of our study are in line with other research that has been conducted on Tdap immunization in pregnancy and infant or childhood health outcomes, in that we did not observe any increased risks to offspring of women vaccinated with Tdap during their pregnancy[24,37,50–53].

Outside of maternal Tdap vaccination research, two studies have been conducted which examined the risk of similar longer-term childhood morbidity outcomes following maternal pandemic H1N1 influenza immunization in pregnancy. Hviid et al. (2017) conducted a cohort study of singleton children in Denmark with 5 years of follow-up, assessing the incidence rates of hospital admissions, infectious diseases, and neurologic, autoimmune, and behavioural conditions[80]. Walsh et al. (2019) similarly assessed immune related, non-immune related, and non-specific morbidity outcomes, along with childhood mortality, in children from birth to age 5 years in Ontario, Canada[78]. Like our study, these studies were large, retrospective population-based cohort studies which obtained exposure and outcome information from health administrative databases and used propensity score methods to adjust for confounding[78,80]. Specifically, Hviid et al. (2017) used 1:4 propensity score matching and Walsh et al. (2019) used stabilized inverse probability of treatment weighting[78,80]. Specific comparison of study outcomes with these studies is presented below.

5.2.1 Immune related outcomes

For our immune-related outcomes, no association was found between Tdap vaccination during pregnancy and pediatric asthma or otitis media. We observed an inverse association with rates of upper respiratory infection, lower respiratory infection, and gastrointestinal infection. The reduced risk of upper and lower respiratory tract infections (aIRR: 0.96, 95% CI: 0.93-0.99 and 0.93, 95% CI: 0.89-0.98, respectively) could be attributable to a reduction in pertussis disease in maternal Tdap-exposed infants. Pertussis is an upper respiratory tract infection; however, misdiagnosis of pertussis as another respiratory infection may account for some of the protective

association seen between maternal Tdap vaccination and lower respiratory infections. Pertussis can be difficult to diagnose, and the disease is both under-diagnosed and under-reported[109–111].

Our findings are comparable to those of a large, American case-control study by Sukumaran et al. (2018)[52]. This study assessed the association between both maternal Tdap vaccination and maternal influenza vaccination and all-cause hospitalization, hospitalization due to respiratory causes, and mortality in the first 6 months of life[52]. They also observed a protective association between maternal Tdap during pregnancy and infant hospitalizations due to respiratory causes (adjusted odds ratio [aOR]: 0.79, 95% CI: 0.67-0.94), but noted that only 3% of infants hospitalized for respiratory causes had a pertussis ICD code[52]. They posited that the observed protective effect might be due to infants with pertussis not being appropriately tested and diagnosed[52]. A protective effect against hospitalization due to respiratory causes was not seen in children exposed to prenatal influenza vaccination (aOR: 1.08, 95% CI: 0.97-1.19)[52]. Studies by Hviid et al. (2017) and Walsh et al. (2017) similarly did not find an association between maternal influenza vaccination and lower respiratory tract infections in the first 5 years of life, though an inverse association between maternal influenza vaccination and upper respiratory tract infection (adjusted rate ratio [RR]: 0.92, 95% CI: 0.85-0.99) was observed in the Hviid et al. (2017) study[78,80].

There is also the possibility that residual confounding is contributing to the observed inverse association between maternal Tdap vaccination and upper and lower respiratory infections. In particular, mothers who were vaccinated may also be healthier (i.e., have fewer pre-existing medical comorbidities) and be more likely to engage in other healthy behaviours that influence

outcomes, such as hand washing or other actions that might prevent infection transmission to their infants ("healthy vaccinee bias")[112,113].

As previously mentioned, we also found an inverse association between maternal Tdap vaccination during pregnancy and gastrointestinal infection (aIRR: 0.88, 95% CI: 0.82-0.94). Inverse associations between H1N1 vaccination during pregnancy and gastrointestinal infections were also seen in the Walsh et al. (2019) study (aIRR: 0.94, 95% CI: 0.91-0.98) and in the Hviid et al. (2017) study for vaccinations in the second or third (but not first) trimester (aRR: 0.84, 95% CI: 0.74-0.94)[78,80]. Walsh et al. (2019) hypothesized that this association could be due to residual confounding by an increased likelihood of vaccinated mothers to ensure rotavirus vaccination in their children, as rotavirus is a common cause of gastroenteritis[78]. No rotavirus specific vaccine codes were available to allow for specific adjustment in our statistical models, but we attempted to account for rotavirus immunization in our sensitivity analysis restricting the cohort to infants who had at least 2 well-baby or routine immunization visits during the first year. Following this restriction, our estimate of association was slightly attenuated, but still statistically significant (aIRR: 0.90, 95% CI: 0.84-0.96).

5.2.2 Non-immune related outcomes

No association was found between Tdap vaccination during pregnancy and either of our non-immune related outcomes, neoplasm and sensory disorders (vision or hearing loss). Our results are comparable to those of Walsh et al. (2019), who also found no association between H1N1 influenza vaccination during pregnancy and neoplasm or sensory disorders[78]. Shakib et al. (2013) conducted a retrospective cohort study using health administrative data to compare the incidence

of a complex chronic condition, a composite outcome that included neoplasm, between a small number of Utah infants born to Tdap-vaccinated and Tdap-unvaccinated women and also found no difference between the two groups of infants within the first year[50].

5.2.3 Non-specific morbidity outcome

We observed a statistically significant inverse association between Tdap vaccination during pregnancy and our non-specific morbidity outcome, urgent and in-patient health service utilization (aIRR: 0.95, 95% CI: 0.92-0.97), which persisted after several sensitivity analyses adjusting for potential differential access to the healthcare system between the exposure groups. Similar analyses in pandemic H1N1-vaccinated women had varying results: Hviid et al. (2017) also observed an association between H1N1 vaccination during pregnancy in the second or third trimester and all-cause pediatric hospitalizations in the first 5 years of life (aRR: 0.93, 95% CI: 0.87-0.99); however, Walsh et al. (2019) found no association between H1N1 vaccination during pregnancy and urgent and in-patient health service utilization[78,80]. It is possible that Tdap vaccination during pregnancy could have a beneficial impact on infant health beyond the direct protection against pertussis infection (called non-specific effects); however, evidence on non-specific vaccine effects is inconclusive and the mechanism by which Tdap vaccine might induce non-specific protective effects is unknown[114,115]. Although we adjusted for confounding using propensity score matching, there may be remaining differences (residual confounding) between mothers who were vaccinated and mothers who were not that could explain this protective association, including differences in the baseline health of the mother and in healthy behaviours that may have impacted the health of the child ("healthy vaccinee bias")[112,113].

5.2 Strengths and limitations

The main strength of this study was the availability of population-based health administrative databases that contained sociodemographic, clinical, and vaccination information in pregnant women linked with up to six years of follow-up information on health outcomes in their infants. Using this large study population allowed for a large sample of mother-child pairs to be analyzed, giving the study power to detect associations between our exposure and outcomes, despite the rarity of pregnant women being vaccinated with Tdap during this time period. These datasets have low rates of loss to follow up and few patients were excluded due to missing data, with close to 95% of live born infants during the study period included in the study cohort.

We used propensity score methods to adjust for confounding, which optimize adjustment when potential confounders are numerous and have been shown to reduce bias more effectively than conventional adjustment techniques in studies using large databases[85,86]. Using propensity score matching, we were able to compare Tdap-exposed infants with Tdap-unexposed infants that were similar with respect to the distribution of a large number of baseline covariates. Furthermore, we increased the precision of our estimates by matching each exposed infant to multiple controls (vs. one control)[95]. Despite the strengths of using propensity scores for confounding adjustment, a general limitation of any covariate adjustment method in an observational study is that it can only account for measured variables[95]. Our datasets did not contain information on potentially influential socioeconomic variables like race and education level, and data on pre-existing maternal medical conditions were limited to diagnoses available on the mother's delivery record. Without randomization, we could not adjust for unmeasured or unknown confounders, and thus there remains the possibility of residual confounding. We used a negative control outcome,

motor vehicle-related injuries, as a method of detecting the presence of residual confounding. Although we did not observe any statistically significant associations between Tdap vaccination during pregnancy and rates of motor vehicle-related injuries in infants in our analyses, due to the small number of events, the confidence intervals for these associations were wide. The point estimate of association between Tdap vaccination during pregnancy and motor vehicle-related injuries for the propensity score matched analysis was 0.84 (a protective association), suggesting that protective associations observed between exposure to Tdap during pregnancy and respiratory tract infections or urgent and in-patient health service utilization could be attributable to residual confounding.

Another potential limitation of our study was information bias arising from the misclassification of exposure and outcome variables. We expected less-than-perfect sensitivity as outcome diagnoses were obtained from emergency department visits and hospitalizations, and therefore milder cases and those not seeking medical care were not captured. We used a validated algorithm for asthma diagnoses, however, we still expected some misclassification as the sensitivity and specificity of the algorithm were 89% and 72% respectively[69]. Additionally, it is difficult for medical professionals to accurately diagnosis asthma in young children[116]. Other research utilizing the Ontario Asthma Cohort classified asthma cases diagnosed at less than six months of age only if they had at least one more diagnosis code for asthma between age one and five[116]. Although we included all cases in our analysis, the distribution of cases diagnosed <6 months of age was comparable between Tdap-exposed and unexposed infants. Therefore, we expect any resulting misclassification to be nondifferential and to bias our estimate toward the null. For asthma and the majority of our other outcomes, bias toward the null due to

nondifferential misclassification could have masked a stronger inverse association than what was observed. This is less of a concern as this study is focused on increased risks to the child following exposure to vaccination in utero. The exception is for neoplasm, where bias toward the null could have led to an underestimation of a potentially harmful relationship.

It is also possible there was some misclassification of our exposure variable, which would most likely be nondifferential by study outcomes. When exposure prevalence is low, as was the case in this study, bias from nondifferential misclassification is most pronounced when specificity is low[117]. We expected specificity to be high, as research validating vaccine-specific OHIP fee codes for determining vaccination status have consistently shown codes to have high specificity (e.g., 96% for influenza immunizations and 89 to 92% for infant immunizations)[65,118]. Sensitivity may be low; influenza-specific OHIP fee codes have been found to have 50% sensitivity for determining influenza vaccination status, although unlike Tdap vaccinations, flu shots are commonly administered outside of a physician's office and would therefore not be captured in the OHIP database[65]. However, OHIP claims for the Tdap vaccine may still be missed for several reasons: physicians may not bill because remuneration per vaccination is low (physicians receive as little as $0.68 per vaccine billing claim), the vaccine may be administered by a nurse and not billed for, or a physician may have used an older, general vaccine code in place of the Tdap-specific fee code[118]. Nondifferential misclassification due to low sensitivity would result in some bias toward the null; however, as the exposure in this case is rare, we expect the magnitude of the impact to be minimal[117].

5.3 Implications for public health and areas for future research

Although our results support the long-term safety of Tdap administration in pregnancy, this is the first such study to our knowledge of longer-term pediatric safety outcomes. Additional research is needed to corroborate these findings and as immunization with Tdap in pregnancy becomes more common in Canada, the long-term outcomes of children exposed to the vaccine in utero should continue to be monitored. Although vaccine safety is a major concern for pregnant women considering whether or not to get immunized, the longer-term effects in children of vaccination in pregnancy is an area that has received little research focus to date. Our results should provide reassurance about the long-term safety of the Tdap vaccine to both pregnant women and their healthcare providers.

To support future high-quality research on this subject, there is a need to identify core pediatric health outcomes that should be evaluated following maternal immunization and to standardize the definitions of those outcomes to facilitate comparison across studies, similar to what the Global Alignment of Immunization safety Assessment in pregnancy (GAIA) project has done for maternal and newborn safety outcomes following vaccination in pregnancy[76]. This will continue to be important with the ongoing efforts to develop new vaccines specifically for pregnant women, including vaccines against respiratory syncytial virus (RSV) and group B streptococcus[2]. Further research is also needed to better understand possible biological mechanisms, if any, between vaccination in pregnancy, infection in pregnancy, and long-term pediatric health outcomes.

There is also a need for a high-quality electronic immunization registry in the province of Ontario specifically, but across other provinces and territories in Canada as well, that can be linked to other health data in women and their children. In the absence of an immunization registry, research validating the use of OHIP billing codes for identifying Tdap vaccinations, which are typically administered in physician's offices in Ontario, would greatly enhance efforts to evaluate vaccine coverage and safety in the province. This is particularly important as differing estimates of association were seen in this study depending on whether we used Tdap-specific fee codes only or additionally included general vaccine codes outside of influenza season to identify women who received the vaccine in pregnancy.

As several studies have now identified a protective association between maternal vaccination in pregnancy and gastrointestinal infection, this relationship warrants further investigation[78,80]. Specifically, research should be done to investigate whether this association is due to confounding by rotavirus vaccination status of the children.

5.4 Conclusion

Our study aimed to assess the association between maternal Tdap vaccination during pregnancy and the risk of adverse health outcomes in early childhood, both immune-related and non-immune related. Monitoring infants exposed to Tdap during pregnancy for adverse outcomes is an important part of vaccine safety surveillance, particularly as concerns about vaccine safety are one of the main reasons for pregnant women not becoming immunized and for health care providers choosing not to recommend vaccination to their pregnant patients[7–9].

Our results did not indicate any association between exposure to Tdap vaccine during pregnancy and an increased risk of infection, asthma, neoplasm, vision or hearing loss, or urgent and in-patient health service utilization, supporting the long-term safety of Tdap administration in pregnancy. This research is timely, as Tdap has recently been recommended to women in Canada in every pregnancy, regardless of their immunization history[5]. Results will be of interest to clinicians when informing and counselling their patients, pregnant women when making decisions regarding Tdap immunization in pregnancy, and policy makers when considering the available evidence in their recommendations.

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APPENDICES

Appendix A: Diagnostic codes for pre-existing maternal medical conditions and obstetrical complications

Condition or complication	ICD-10-CA diagnostic codes
Pre-existing condition	
Maternal asthma	J45-46
Chronic hypertension	I10, I15, O10.0
Diabetes	O24.0, O24.1 O24.3, O24.5, O24.6, O24.7, E10, E11, E13, E14
Heart disease	O10.1, I05-I09, I34-I39, I150.0, I20, I25, Q20-26, O99.4
Obstetrical complication	
Pre-eclampsia	O11, O14
Eclampsia	O15
Gestational diabetes	O24.4, O24.8
Placenta previa	O44
Placental abruption	O45
Pregnancy-induced hypertension	O13, O16

Appendix B: Diagnostic codes for study outcomes

Study outcome	ICD-10-CA diagnostic codes
Infectious diseases	
Upper respiratory infections	A36.0, A36.1, A36.2, A36.8, A36.9, J01-06, J35-37
Lower respiratory infections	A37, A42.0, A48.1, A70, J09-18, J20-22, J85-86
Gastrointestinal infections	A00, A01, A02.0, A02.2-A02.9, A03-09, A42.1
Otitis media	H65-67
Atopic disease	
Pediatric asthma	J45-46[1]
Non-immune related specific morbidity outcomes	
Neoplasm	C00-97
Vision loss	H47, H48.8, H53-54
Hearing loss	H90-91
Negative control outcome	
Motor vehicle-related injuries	V20-69

[1]Pediatric asthma was measured using the ICES-derived Ontario Asthma Cohort algorithm, which requires one hospitalization with a J45 or J46 diagnostic code or two outpatient visits with J45 or J46 diagnostic codes within a three-year period.

Appendix C: Baseline covariates included in the propensity scores

- Year of birth
- Maternal age
- Parity
- Type of pre-existing maternal medical condition (asthma, chronic hypertension, diabetes, heart disease)
- Type of obstetrical complication (eclampsia or pre-eclampsia, gestational diabetes, placenta previa, placental abruption, pregnancy-induced hypertension)
- Multifetal gestation
- Neighbourhood median income quintile
- Rural or urban residence
- Public health unit region
- Infant sex

Appendix D: Map of public health unit regions in Ontario

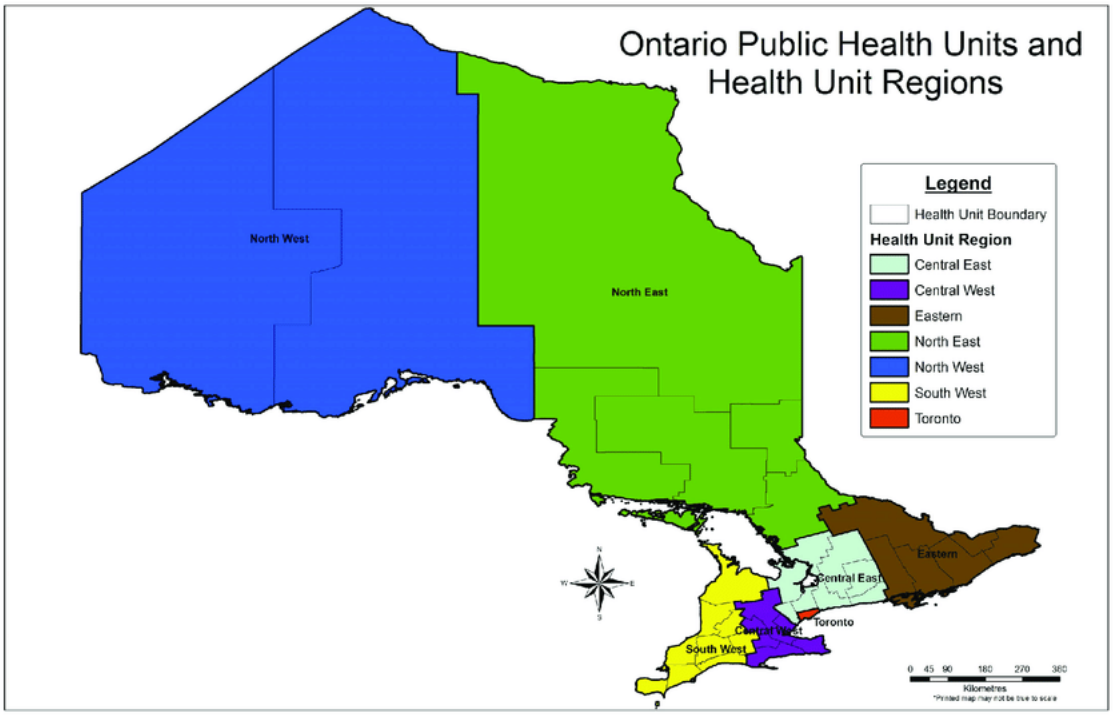
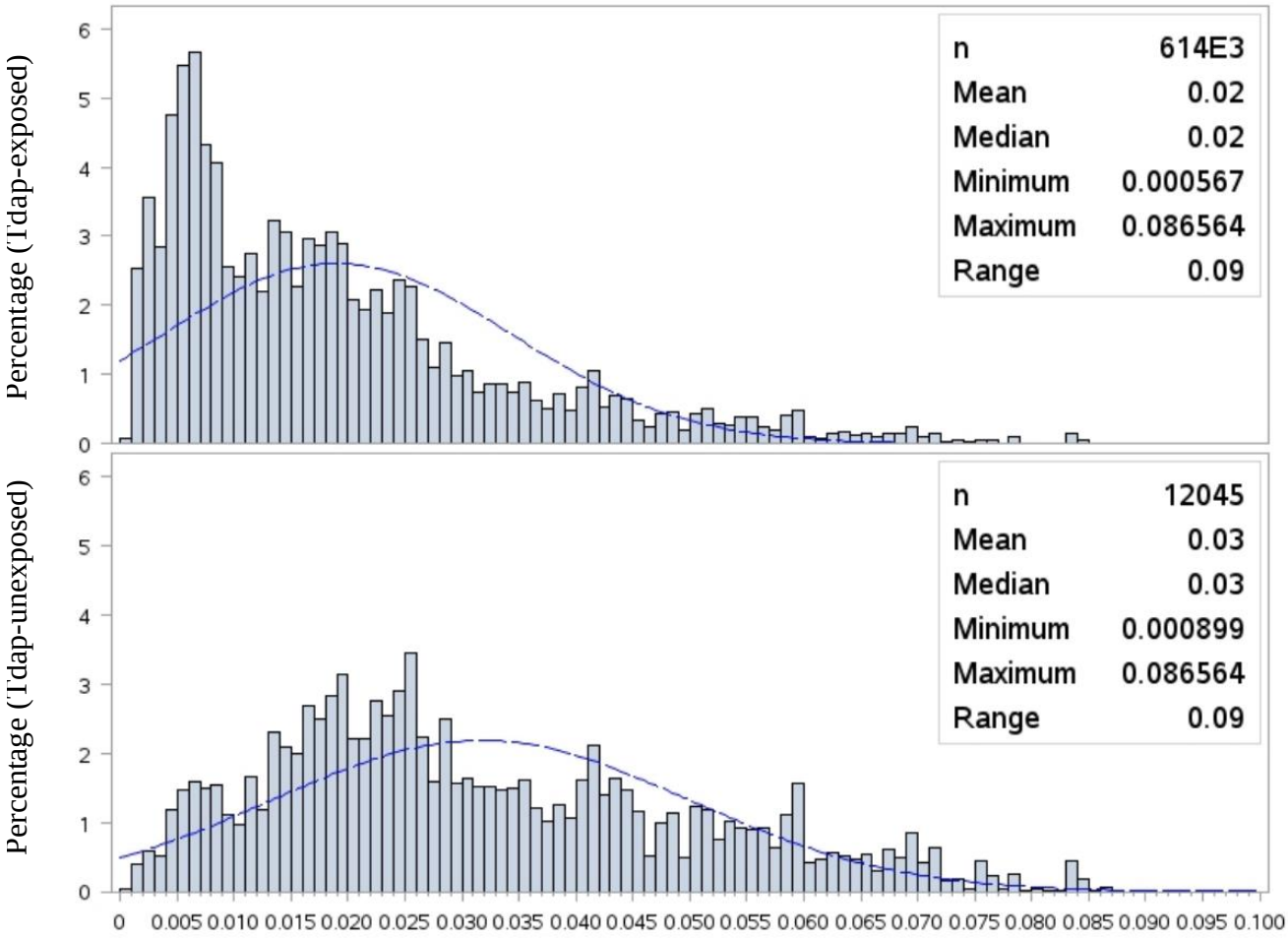


Image from: Bolotin, S. *et al.* Population-based estimate of hepatitis C virus prevalence in Ontario, Canada. *PLoS One* **13**, 1–10 (2018).

Appendix E: Distribution of the propensity score



Appendix F: Proportional hazards assumption

F1. Sensory disorders

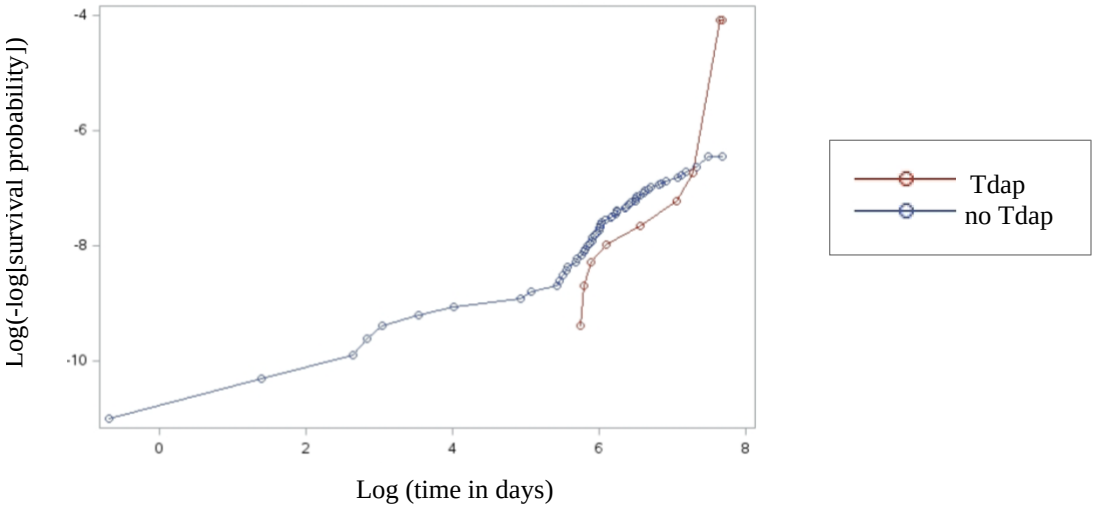
(1) Wald test

Outcome	Exposure*time interaction p-value
Sensory disorders	0.11

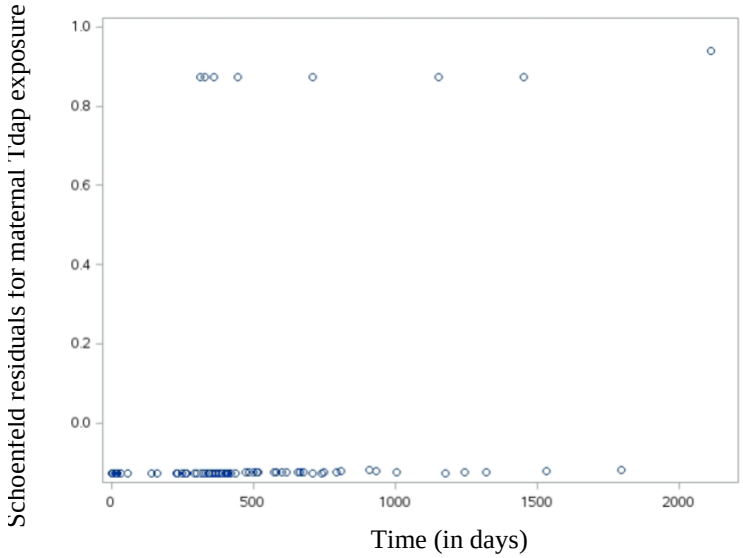
(2) Supremum test for non-proportionality based on Martingale residuals (ASSESS statement)

Outcome	Supremum test p-value
Sensory disorders	0.44

(3) Log (-log) survival curve



(4) Schoenfeld residuals



F2. Neoplasm

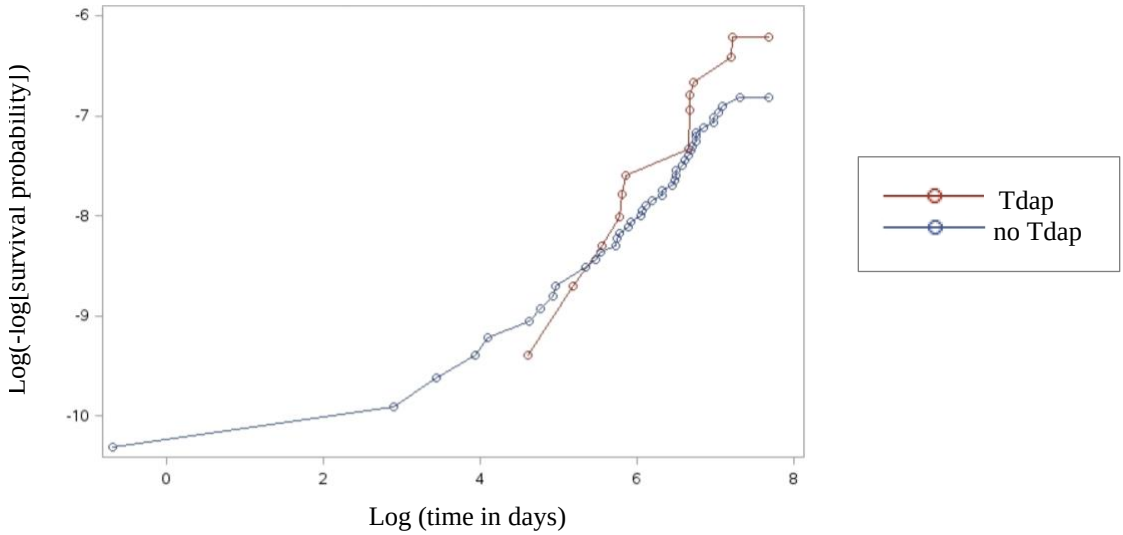
(1) Wald test

Outcome	Exposure*time interaction p-value
Neoplasm	<0.001

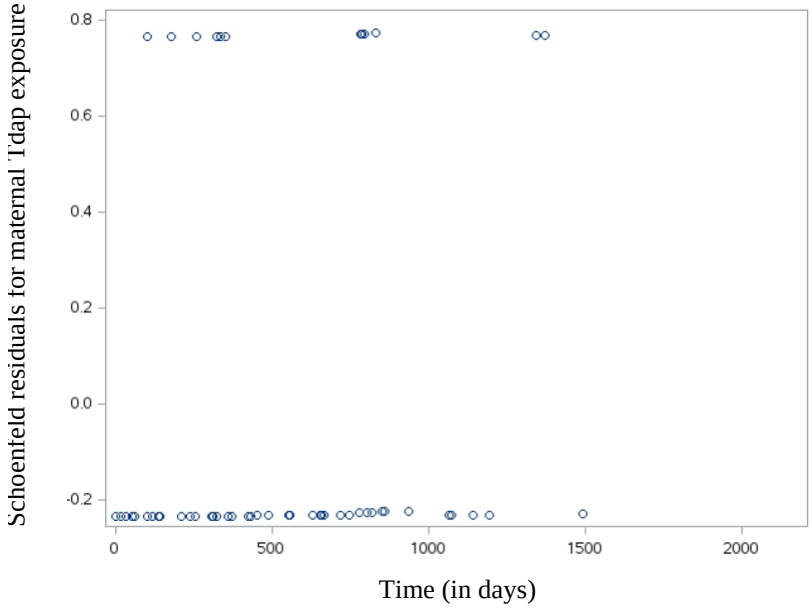
(2) Supremum test for non-proportionality based on Martingale residuals (ASSESS statement)

Outcome	Supremum test p-value
Neoplasm	0.26

(3) Log (-log) survival curve



(4) Schoenfeld residuals



F3. Asthma

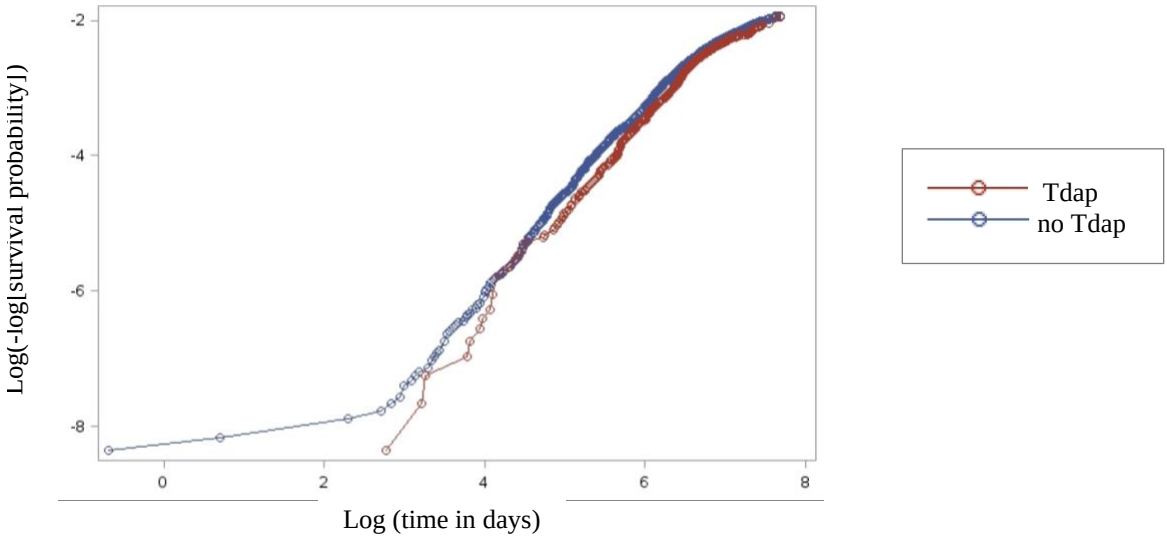
(1) Wald test

Outcome	Exposure*time interaction p-value
Asthma	<0.001

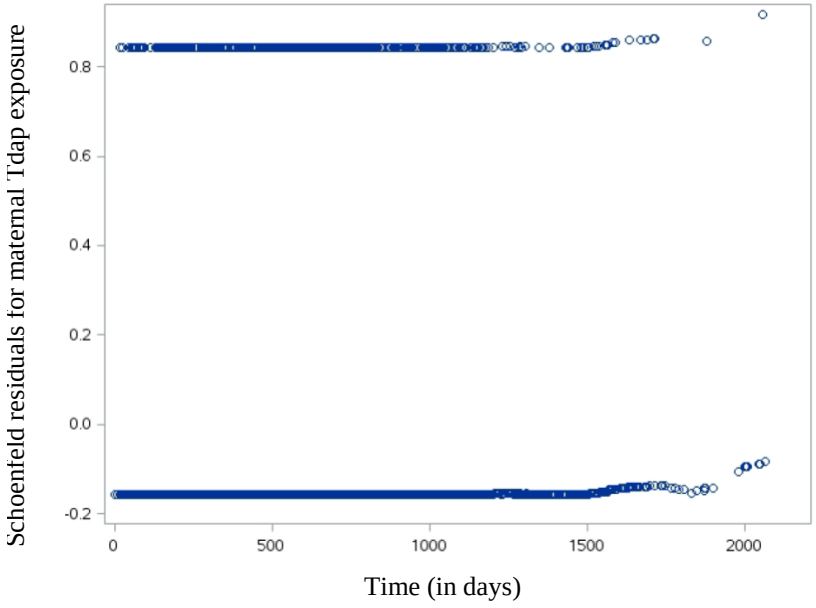
(2) Supremum test for non-proportionality based on Martingale residuals (ASSESS statement)

Outcome	Supremum test p-value
Asthma	0.06

(3) Log (-log) survival curve



(4) Schoenfeld residuals



F4. Motor-vehicle related injuries (negative control outcome)

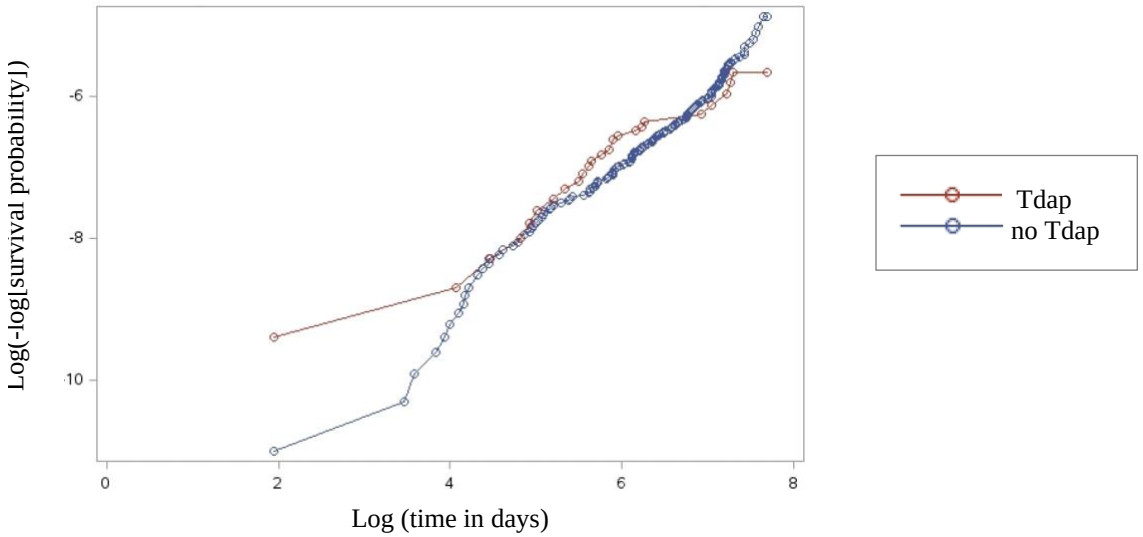
(1) Wald test

Outcome	Exposure*time interaction p-value
Motor-vehicle related injuries	<0.001

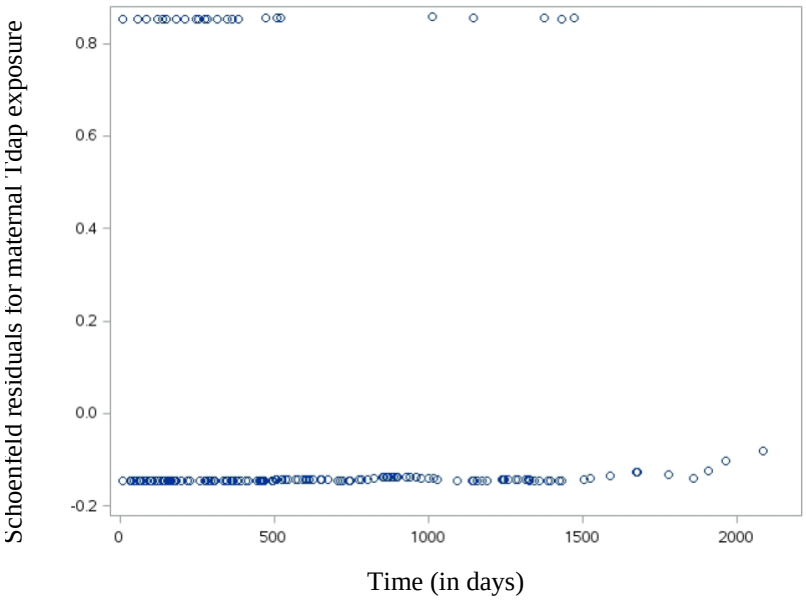
(2) Supremum test for non-proportionality based on Martingale residuals (ASSESS statement)

Outcome	Supremum test p-value
Motor-vehicle related injuries	0.03

(3) Log (-log) survival curve



(4) Schoenfeld residuals



Appendix G: Results of the inverse probability of treatment weighted analyses

G1. Baseline characteristics of the study population after inverse probability of treatment weighting, Ontario, Canada

Characteristic	IPTW-weighted cohort		
	% of births to Tdap-vaccinated women *n*=12,045	% of births to Tdap-unvaccinated women *n*=613,598	Std Diff[1]
Fiscal year of birth			
2012-13	23.5	20.4	0.11
2013-14	18.6	20.1	0.05
2014-15	19.1	20.0	0.03
2015-16	19.4	19.9	0.02
2016-17	19.4	19.6	0.01
Maternal age (years)			
<20	2.9	2.3	0.05
20-24	9.9	10.7	0.04
25-29	28.5	26.9	0.05
30-34	35.5	36.7	0.04
≥35	23.3	23.3	0.00
Parity			
0 (nulliparous)	43.4	44.3	0.02
≥1 (multiparous)	56.6	55.7	0.02
Pre-existing maternal medical condition[3]			
No	98.1	98.1	0.00
Yes	1.9	1.9	0.00
Type of pre-existing maternal medical condition			
Asthma	0.2	0.2	0.01
Chronic hypertension	0.4	0.4	0.00
Diabetes	0.8	0.8	0.00
Heart disease[4]	0.5	0.5	0.01
Obstetrical complication[5]			
No	87.0	87.1	0.00
Yes	13.0	12.9	0.00
Delivery by cesarean			
No	73.3	71.1	0.07
Yes	26.7	28.9	0.07
Multiple birth			
No	96.7	96.6	0.01
Yes	3.3	3.4	0.01
Neighbourhood median family income quintiles			
1 (Lowest)	22.8	21.0	0.06
2	19.2	19.9	0.03
3	19.6	20.3	0.02
4	22.1	21.9	0.01
5 (Highest)	16.2	16.9	0.02
Rural residence			
No	89.7	89.7	0.00
Yes	10.3	10.3	0.00
Public health unit region			

North West	1.4	1.8	0.04
North East	3.1	3.9	0.06
Eastern	10.6	12.5	0.09
Central East	31.7	30.4	0.04
Toronto	19.9	20.8	0.03
South West	12.7	11.2	0.06
Central West	20.6	19.5	0.04
Sex			
Female	47.9	48.7	0.02
Male	52.1	51.3	0.02
Birth weight (grams)			
<1500 g	0.5	0.9	0.07
1500-2499 g	5.0	5.5	0.03
2500-3499 g	54.3	54.2	0.00
≥3500 g	40.3	39.4	0.03
Gestational age at birth in weeks			
<28	<0.1	0.3	0.07
28-31	0.5	0.7	0.04
32-33	0.5	0.9	0.07
34	0.8	1.0	0.03
35	1.7	1.6	0.01
36	3.0	3.3	0.03
≥37 (Term)	93.5	92.2	0.07
Median follow-up time in person-years (range)	3.5 (0.0-6.0)	3.5 (0.0-6.0)	

Abbreviations: IPTW, inverse probability of treatment weight; Tdap, tetanus, diphtheria, and acellular pertussis; Std Diff, standardized difference

[1]Shaded cells represent standardized differences >0.10 indicating imbalance between vaccinated and unvaccinated subjects.
[2]Asthma, chronic hypertension, diabetes, or heart disease
[3]Cardiac valvular disease, congenital heart disease, chronic congestive heart failure, hypertensive heart disease, or chronic ischemic heart disease
[4]Eclampsia, gestational diabetes, placenta previa, placental abruption, pre-eclampsia, or pregnancy-induced hypertension

G2. Association between Tdap vaccination during pregnancy and pediatric health outcomes, Ontario, Canada

Outcome	IPTW-adjusted estimate (95% CI)
Atopic disease	
Asthma[1,2]	1.04 (0.94-1.14)
Infectious disease	
Upper respiratory infections[3]	1.07 (1.04-1.11)
Lower respiratory infections[3]	1.01 (0.96-1.07)
Gastrointestinal infections[3]	0.90 (0.84-0.97)
Otitis media[3]	1.07 (1.02-1.13)
Non-immune related morbidity outcomes	
Neoplasm[2]	1.07 (0.49-2.34)
Sensory disorders[2]	1.05 (0.50-2.20)
Non-specific morbidity outcome	
Rates of urgent and in-patient health service utilization[3]	1.02 (0.99-1.03)
Negative-control outcome	
Motor-vehicle related injuries[2]	0.65 (0.39-1.06)

Abbreviations: Tdap, tetanus, diphtheria, and acellular pertussis; IPTW, inverse probability of treatment weight; CI, confidence interval

[1]Cohort for asthma is restricted to children with a minimum of 3 years of follow-up.
[2]Point estimates are hazard ratios generated from a Cox proportional hazards model.
[3]Point estimates are incidence rate ratios generated from a Poisson regression model.

Appendix H: Results of the coarsened exact matching analyses

H1. Baseline characteristics of the study population before and after coarsened exact matching, Ontario, Canada

Characteristic	Unmatched cohort			Coarsened exact matched cohort			Asthma coarsened exact matched cohort[1]		
	No. (%) of births to Tdap-vaccinated women *n*=12,045	No (%) of births to Tdap-unvaccinated women *n*=613,598	Std Diff[2]	% of births to Tdap-vaccinated women *n*=11,776	% of births to Tdap-unvaccinated women *n*=419,779	Std Diff[2]	% of births to Tdap-vaccinated women *n*=4,182	% of births to Tdap-unvaccinated women *n*=236,078	Std Diff[2]
Fiscal year of birth									
2012-13	594 (4.9)	127,010 (20.7)	0.49	4.9	4.9	0.00	13.5	13.5	0.00
2013-14	1,634 (13.6)	124,291 (20.3)	0.18	13.6	13.6	0.00	37.8	37.8	0.00
2014-15	2,093 (17.4)	123,218 (20.1)	0.07	17.5	17.5	0.00	48.7	48.7	0.00
2015-16	2,899 (24.1)	121,299 (19.8)	0.10	24.1	24.1	0.00	0.0	0.0	0.00
2016-17	4,825 (40.1)	117,780 (19.2)	0.47	39.9	39.9	0.00	0.0	0.0	0.00
Maternal age									
<20	186 (1.5)	14,415 (2.3)	0.06	1.5	1.5	0.00	1.9	1.9	0.00
20-24	808 (6.7)	66,293 (10.8)	0.15	6.6	6.6	0.00	6.9	6.9	0.00
25-29	3,388 (28.1)	164,953 (26.9)	0.03	2.8	2.8	0.00	29.2	29.2	0.00
30-34	4,775 (39.6)	224,765 (36.6)	0.06	39.7	39.7	0.00	38.8	38.8	0.00
≥35	2,888 (24.0)	143,172 (23.3)	0.02	23.8	23.8	0.00	23.2	23.2	0.00
Parity									
0 (nulliparous)	6,203 (51.5)	270,753 (44.1)	0.15	51.4	51.4	0.00	51.3	51.3	0.00
≥1 (multiparous)	5,842 (48.5)	342,845 (55.9)	0.15	48.6	48.6	0.00	48.7	48.7	0.00
Pre-existing maternal medical condition[3]									
No	11,873 (98.6)	602,136 (98.1)	0.03	99.2	99.2	0.00	99.1	99.1	0.00
Yes	172 (1.4)	11,462 (1.9)	0.03	0.8	0.8	0.00	0.9	0.9	0.00
Type of pre-existing maternal medical condition									
Asthma	25 (0.2)	1,502 (0.2)	0.01	0.1	0.1	0.00	0.1	0.1	0.00
Chronic hypertension	43 (0.4)	2,362 (0.4)	0.00	0.2	0.2	0.00	0.2	0.2	0.00
Diabetes	62 (0.5)	5,076 (0.8)	0.04	0.3	0.3	0.00	0.2	0.2	0.00
Heart disease[4]	49 (0.4)	2,986 (0.5)	0.01	0.2	0.2	0.00	0.3	0.3	0.00
Obstetrical complication[5]									

No	10,486 (87.1)	534,237 (87.1)	0.00	88.5	88.5	0.00	90.3	90.3	0.00
Yes	1,559 (12.9)	79,361 (12.9)	0.00	11.5	11.5	0.00	9.7	9.7	0.00
Delivery by cesarean									
No	8,763 (72.7)	436,568 (71.1)	0.04	73.2	71.7	0.05	73.0	72.1	0.03
Yes	3,282 (27.3)	177,030 (28.9)	0.04	26.8	28.3	0.05	27.0	27.9	0.03
Multiple birth									
No	11,767 (97.7)	592,553 (96.6)	0.07	98.2	98.2	0.00	98.2	98.2	0.00
Yes	278 (2.3)	21,045 (3.4)	0.07	1.8	1.8	0.00	1.8	1.8	0.00
Neighbourhood median family income quintiles									
1 (Lowest)	2,096 (17.4)	129,239 (21.1)	0.09	17.3	17.3	0.00	16.8	16.8	0.00
2	2,442 (20.3)	122,321 (19.9)	0.01	20.4	20.4	0.00	20.1	20.1	0.00
3	2,364 (19.6)	124,701 (20.3)	0.02	19.6	19.6	0.00	19.0	19.0	0.00
4	2,679 (22.2)	134,188 (21.9)	0.01	22.3	22.3	0.00	22.6	22.6	0.00
5 (Highest)	2,464 (20.5)	103,1429(16.8)	0.09	20.4	20.4	0.00	21.5	21.5	0.00
Rural residence									
No	10,914 (90.6)	550,586 (89.7)	0.03	91.0	91.0	0.00	90.7	90.7	0.00
Yes	1,131 (9.4)	63,012 (10.3)	0.03	9.0	9.0	0.00	9.3	9.3	0.00
Public health unit region									
North West	131 (1.1)	10,855 (1.8)	0.06	1.0	1.0	0.00	0.4	0.4	0.00
North East	309 (2.6)	24,124 (3.9)	0.08	2.4	2.4	0.00	1.5	1.5	0.00
Eastern	1,966 (16.3)	76,286 (12.4)	0.11	16.1	16.1	0.00	11.1	11.1	0.00
Central East	4,307 (35.8)	185,608 (30.3)	0.12	35.9	35.9	0.00	40.8	40.8	0.00
Toronto	3,503 (29.1)	126,614 (20.6)	0.20	29.4	29.4	0.00	30.9	30.9	0.00
South West	528 (4.4)	69,380 (11.3)	0.26	4.3	4.3	0.00	4.3	4.3	0.00
Central West	1,301 (10.8)	120,731 (19.7)	0.25	10.8	10.8	0.00	11.0	11.0	0.00
Sex									
Female	5,858 (48.6)	299,118 (48.7)	0.00	48.7	48.7	0.00	48.2	48.2	0.00
Male	6,187 (51.4)	314,480 (51.3)	0.00	51.3	51.3	0.00	51.8	51.8	0.00
Birth weight									
<1500 g	44 (0.4)	5,316 (0.9)	0.06	0.3	0.7	0.07	0.4	0.7	0.05
1500-2500 g	545 (4.5)	33,866 (5.5)	0.05	4.2	4.8	0.04	4.0	4.6	0.04
2500-3500 g	6,752 (56.1)	332,489(54.2)	0.04	56.1	55.7	0.01	55.0	55.4	0.01
≥3500 g	4,704 (39.0)	241,927 (39.4)	0.01	39.4	38.8	0.02	40.7	39.4	0.04
Gestational age at birth in weeks									
<28	5 (<0.1)	1,995 (0.3)	0.07	<0.1	0.3	0.09	0.1	0.2	0.06

28-31	51 (0.4)	4,139 (0.7)	0.03	0.4	0.5	0.02	0.4	0.5	0.03
32-33	63 (0.5)	5,687 (0.9)	0.05	0.5	0.7	0.05	0.5	0.7	0.04
34	88 (0.7)	5,990 (1.0)	0.03	0.7	0.8	0.02	0.8	0.8	0.00
35	152 (1.3)	10,020 (1.6)	0.03	1.2	1.4	0.02	1.3	1.3	0.00
36	366 (3.0)	20,119 (3.3)	0.01	2.8	2.9	0.01	2.8	2.8	0.00
≥37 (Term)	11,320 (94.0)	565,648 (92.2)	0.07	94.5	93.5	0.06	94.1	93.6	0.03
Median follow-up time in person-years (range)	2.3 (0.0-6.0)	3.5 (0.0-6.0)		2.3 (0.0-6.0)	2.5 (0.00-6.0)		4.0 (3.0-6.0)	4.0 (3.0-6.0)	

Abbreviations: Tdap, tetanus, diphtheria, and acellular pertussis; Std Diff, standardized difference

[1]Cohort for asthma is restricted to children with a minimum of 3 years of follow-up.
[2]Shaded cells represent standardized differences >0.10 indicating imbalance between vaccinated and unvaccinated subjects.
[3]Asthma, chronic hypertension, diabetes, or heart disease
[4]Cardiac valvular disease, congenital heart disease, chronic congestive heart failure, hypertensive heart disease, or chronic ischemic heart disease
[5]Eclampsia, gestational diabetes, placenta previa, placental abruption, pre-eclampsia, or pregnancy-induced hypertension

H2. Association between Tdap vaccination during pregnancy and pediatric health outcomes in propensity score-matched and coarsened exact-matched samples, Ontario, Canada

Outcome	Estimate from propensity score-matched sample (95% CI)	Estimate from coarsened exact-matched sample (95% CI)
Atopic disease		
Asthma[1,2]	0.93 (0.84-1.03)	0.91 (0.83-1.00)
Infectious disease		
Upper respiratory infections[3]	0.96 (0.93-0.99)	0.95 (0.92-0.98)
Lower respiratory infections[3]	0.93 (0.89-0.98)	0.93 (0.92-0.98)
Gastrointestinal infections[3]	0.88 (0.82-0.94)	0.88 (0.83-0.94)
Otitis media[3]	1.00 (0.95-1.05)	0.98 (0.93-1.03)
Non-immune related morbidity outcomes		
Neoplasm[2]	1.53 (0.83-2.86)	1.14 (0.63-2.08)
Sensory disorders[2]	0.73 (0.35-1.53)	0.69 (0.34-1.39)
Non-specific morbidity outcome		
Rates of urgent and in-patient health service utilization[3]	0.95 (0.94-0.97)	0.94 (0.93-0.96)
Negative-control outcome		
Motor-vehicle related injuries[2]	0.84 (0.55-1.28)	0.88 (0.59-1.32)

Abbreviations: Tdap, tetanus, diphtheria, and acellular pertussis; CI, confidence interval

[1]Cohort for asthma is restricted to children with a minimum of 3 years of follow-up.
[2]Point estimates are hazard ratios generated from a Cox proportional hazards model.
[3]Point estimates are incidence rate ratios generated from a Poisson regression model.