Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

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ABSTRACT

Background: In February 2018, Canada's National Advisory Committee on Immunization (NACI) recommended maternal immunization with Tetanus-diphtheria-acellular pertussis (Tdap) during every pregnancy as a strategy to prevent severe pertussis infection in young infants. This study assessed the relationship between maternal Tdap immunization with obstetric and perinatal outcomes in Ontario.

Methods: We performed a population-based cohort study of all live births prior to NACI's recommendation (April 2012 to March 2017), using multiple health administrative databases. We used extended Cox regression models with time-dependent exposures to estimate adjusted hazards ratios (aHR) for preterm and very preterm birth. Remaining outcomes (gestational hypertension, chorioamnionitis, postpartum hemorrhage, small-for-gestational-age [SGA] birth, neonatal intensive care unit [NICU] admissions >24 hours, neonatal morbidity composite outcome) were assessed using log-binomial regression to generate adjusted risk ratios (aRR). Estimates were adjusted using propensity score matching.

Results: We matched 11,750 Tdap-exposed pregnancies to 58,747 unexposed pregnancies and did not find increased risks (aHR/aRR [95% CI]) for preterm birth (0.95 [0.89-1.02]) or very preterm birth (1.15 [0.89-1.47]). Risk of SGA birth (0.91 [0.85-0.97]), NICU admission (0.84 [0.78-0.91]), and neonatal morbidity (0.79 [0.73-0.86]) were decreased. Maternal Tdap immunization was not associated with chorioamnionitis (0.98 [0.82-1.17]), postpartum hemorrhage (1.04 [0.92-1.17]), or severe postpartum hemorrhage (0.88 [0.60-1.30]), and we observed a reduced risk for gestational hypertension (0.82 [0.74-0.91]).

Interpretation: These results complement existing evidence that maternal Tdap vaccination is not associated with adverse outcomes in either mothers or infants. Ongoing evaluation in Canada is needed as maternal Tdap coverage increases in the coming years.

INTRODUCTION

Pertussis, an infectious vaccine-preventable illness, remains a public health challenge owing to repeated outbreaks in many countries, including Canada.[1–5] Infants under 1 year who have not completed their primary vaccine series are at highest risk for pertussis-related morbidity and mortality.[6,7] Pertussis vaccination during pregnancy with a reduced antigen acellular pertussis-containing vaccine (Tetanus-diphtheria-acellular pertussis [Tdap]) has been shown to convey passive immunity to newborns through transplacental transfer of maternal antibodies.[8,9]

In February 2018, Canada's National Advisory Committee on Immunization (NACI) joined countries such as the United States (US)[10] and United Kingdom (UK)[11] in recommending Tdap immunization during every pregnancy, ideally between 27 and 32 weeks' gestation.[12] During the 5 year-period preceding NACI's recommendation, some Canadian maternity care providers were already immunizing pregnant women against pertussis, likely on the basis of successful programs in the US and UK,[10,11] as well as earlier temporary provincial[13] and national[14] Canadian recommendations. With the release of the 2018 NACI recommendation,[12] a substantial increase in the number of Canadian women vaccinated with Tdap vaccine during pregnancy over the next few years is likely.

Despite a growing literature on safety of maternal pertussis vaccination,[15–28] studies currently available focus predominantly on the US and UK revealing a need for Canadian research, owing to differences in pertussis epidemiology, immunity profiles, historical vaccine formulations and schedules, recommended timing of Tdap during pregnancy, and health care system characteristics. Moreover, inconsistent findings from earlier studies suggesting possible associations with chorioamnionitis[16,25,28] and postpartum hemorrhage[28] warrant further investigation. To provide baseline evidence on maternal Tdap immunization in Canada in the pre-NACI policy era, we assessed whether receipt of Tdap during pregnancy was associated with any risk of adverse obstetric or perinatal outcomes in a large, population-based study in Ontario.

METHODS

Study design, data sources and study population

We conducted a population-based retrospective cohort study of all hospital live births in Ontario between April 1, 2012 and March 3, 2017. The MOMBABY database, containing linked maternal and newborn hospital records, was used to assemble the study cohort and provide additional information (e.g., gestational age, birth weight, maternal age, parity). We linked five other health administrative databases: Registered Persons Database, providing information on neighbourhood income, region of residence, and healthcare eligibility; Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), capturing hospital admissions (medical diagnoses and procedures); Ontario Health Insurance Plan (OHIP) Database, containing physician billing claims; Permanent Resident Database, with maternal country of birth; and the Ontario Marginalization Index (ON-Marg), which uses Census data to quantify the level of marginalization in Ontario. Further description of data sources is provided in Supplement Table A. Datasets were linked using unique encoded identifiers and analyzed at ICES. Diagnostic and procedural codes were from the Canadian implementation of the International Classification of Diseases, 10th Revision (ICD-10-CA) and the Canadian Classification of Health Interventions (CCI), respectively.

We excluded maternal-infant records for administrative reasons (e.g., invalid identifiers, duplicate records, linkage warnings) (Figure 1). To allow for complete exposure and outcome information, we excluded records belonging to non-Ontario residents or women who did not have continuous OHIP enrolment during pregnancy. As birth weight and gestational age were critical for defining our perinatal outcomes, we applied an algorithm[29,30] to exclude records with implausible birth weight and gestational age combinations, based on a Canadian reference standard.[31] We additionally excluded records belonging to women younger than 12 years or older than 50 years of age and those ending in stillbirth.

Exposure and outcome measurement

We ascertained Tdap during pregnancy using a billing code (G847) in the OHIP database. Tdap vaccination was classified as occurring during the pregnancy if administered 14 days after the last

menstrual period (estimated by subtracting gestational age from date of birth) through to 1 day before delivery. Obstetric outcomes included gestational hypertension, chorioamnionitis, postpartum hemorrhage, and severe postpartum hemorrhage (postpartum hemorrhage combined with hysterectomy, blood transfusion, or other procedures to control bleeding). These outcomes were identified using ICD-10-CA codes from any maternal hospitalization record during the pregnancy, including the delivery itself. Perinatal outcomes were chosen based on prior vaccine safety research, overall importance to perinatal health, and recommendations made by the Global Alignment of Immunization Safety Assessment in Pregnancy collaboration.[32] We examined five perinatal outcomes: preterm birth (<37 weeks' gestation), very preterm birth (<32 weeks' gestation), small-for-gestational-age [SGA] birth (<10th percentile for gestational age- and sex-specific birth weight based on a Canadian reference standard[31]), neonatal intensive care unit (NICU) admissions >24 hours, and an adaptation[33] of the composite neonatal adverse outcome indicator (NAOI)[34] (infants with ≥1 of 15 neonatal diagnoses or 7 procedures within 28 days following birth). Outcome definitions and associated database codes are presented in Supplement Tables B and C.

Statistical analyses

We used frequencies to describe the distribution of baseline categorical variables and standardized differences to compare the distributions between Tdap-exposed and unexposed women, with an absolute value above 0.10 considered indicative of an imbalanced covariate.[35,36] To address potential confounding, we matched five Tdap-unexposed women to each Tdap-exposed women based on the propensity score, computed using a logistic regression model that included all baseline covariates available in the databases, and an index for adequacy of prenatal care[37] (Supplement Tables D and E). We matched without replacement, using the greedy method and caliper width score of ±0.2 standard deviations.[36,38] Records missing covariate information were excluded; the percentage of records missing information across one or more covariates in the propensity score model was <1%.

We used Cox regression with a time-dependent exposure variable to generate hazard ratios (HR) and 95% confidence intervals (CI) for preterm and very preterm birth, limiting analyses to women who received the Tdap vaccine before 37 weeks' gestation (preterm birth) or before 32 weeks' gestation (very preterm birth)[39] and censored ongoing gestations upon completing 37 weeks or 32 weeks for preterm birth and very preterm birth, respectively. Log-binomial regression was used to compute risk ratios (RR) and 95% CI for the remaining outcomes: gestational hypertension, chorioamnionitis, postpartum hemorrhage, severe postpartum hemorrhage, SGA, NICU admission >24 hours, and neonatal morbidity (NAOI). General estimating equations with an independent correlation structure were used to account for multiple deliveries to a unique woman. Statistical analyses were conducted using SAS version 9.4.

We assessed the potential impact of our analytical strategies on the findings through sensitivity analyses. First, we incorporated general OHIP vaccine codes (G538, G539) billed during pregnancy (but not between October 1 to January 31, as these were more likely to be influenza vaccinations) into an expanded exposure definition additionally capturing *possible* Tdap vaccination during pregnancy. Second, to account for potential differences in maternal healthcare seeking or access among exposed and unexposed subjects, we additionally adjusted for the number of maternal outpatient visits and non-obstetric hospital admissions within six months and two years before the index pregnancy, respectively. Lastly, we repeated our analyses using inverse probability of treatment weights—an alternative method of confounding adjustment using propensity scores.[40]

RESULTS

After exclusions, there were 621,903 eligible live births, of whom 11,750 (1.9%) were born to mothers who received Tdap vaccination during pregnancy (Figure 1). In the full unmatched population, vaccinated women were more likely to be nulliparous and live in higher-income neighbourhoods(Table 1). Following propensity score matching, 11,750 Tdap-exposed women were matched to 58,747

unexposed. Standardized differences for all baseline characteristics were attenuated following matching, with no values exceeding 0.1 (Supplement Figure).

In the unmatched population, the rate of chorioamnionitis was slightly higher among Tdap-vaccinated than unvaccinated women (1.23% vs. 0.99%); however, there was no increased risk of chorioamnionitis associated with Tdap vaccination during pregnancy in propensity-score matched analyses (aRR: 0.98; 95% CI: 0.82, 1.17; Table 2). Receipt of Tdap during pregnancy was not associated with postpartum hemorrhage (aRR: 1.04; 95% CI: 0.92, 1.17) or severe postpartum hemorrhage (aRR: 0.88; 95% CI: 0.60, 1.30), but we observed a significant inverse association between Tdap vaccination and gestational hypertension even after adjustment for confounding through propensity-score matching (aRR: 0.82; 95% CI: 0.74, 0.91).

In the unmatched population comparing Tdap-exposed infants with unexposed, the cumulative incidences were similar for preterm birth (6.03% vs. 7.93%) and there was no evidence of increased risk associated with vaccination (aHR: 0.95; 95% CI: 0.89, 1.02; Table 2). We observed reduced risks of SGA birth (aRR: 0.91; 95% CI: 0.85, 0.97), NICU admissions >24 hours (aRR: 0.84; 95% CI: 0.78, 0.91) and neonatal morbidity (aRR: 0.79; 95% CI: 0.73, 0.86) associated with Tdap vaccination during pregnancy.

In sensitivity analyses, the *possible* Tdap exposure definition additionally captured 2,845 records, bringing the number of exposed subjects to 14,595. Matching these subjects with 72,970 unexposed and repeating our analyses had minimal impact on the study outcomes (Supplement Table F), with the exception of SGA birth which was slightly attenuated in magnitude and no longer associated with Tdap during pregnancy (aRR: 0.94; 95% CI: 0.89, 1.01). Adjustment for maternal healthcare utilization before the index pregnancy and confounding adjustment through propensity score weighting, instead of matching, had little impact on our main findings (Supplement Table G).

INTERPRETATION

In this large population-based cohort study, we examined obstetric and perinatal outcomes among over 11,000 Ontario women who received Tdap vaccination during pregnancy. We found no association between vaccination and chorioamnionitis, postpartum hemorrhage, severe postpartum hemorrhage, preterm birth, or very preterm birth. We observed reductions in risk for gestational hypertension, SGA birth, NICU admissions >24 hours, and neonatal morbidity among Tdap-exposed subjects.

Our study results concur with a growing body of research providing reassuring evidence that Tdap immunization during pregnancy is not associated poor perinatal outcomes, such as preterm birth[15,17,19,20,23,25,26,41,42] and SGA birth.[17,20,25,41] While it is possible that the risk reductions we observed for SGA birth, NICU admissions >24 hours, and neonatal morbidity are due to non-specific beneficial effects of maternal Tdap vaccination (i.e., vaccine protection beyond the targeted disease[43]), there is limited evidence supporting this concept in the context of maternal immunization. Given known biases in observational studies on immunization,[44] we also cannot rule out the possibility of residual confounding inducing a healthy vaccinee bias.

Although this is the first maternal Tdap study that has utilized the NAOI composite outcome, to our knowledge, others have examined individual components of the composite. A large US cohort study by Layton et al. consisting of over 1 million pregnant women (148,817 immunized with Tdap during pregnancy) found no increased risks of adverse newborn outcomes, such as respiratory distress or seizures, but reported a reduced risk of neonatal sepsis among infants born to Tdap-vaccinated women.[28] DeSilva et al. did not observe any associations between Tdap vaccination during pregnancy and transient tachypnea, neonatal sepsis, neonatal pneumonia, respiratory distress syndrome, or newborn convulsions.[16] A smaller single-centre cohort study by Morgan et al.[17] found similar rates of neonatal complications including ventilation requirement, sepsis and intraventricular hemorrhage between Tdap-exposed and unexposed infants. A recent New Zealand cohort study, comprising approximately 70,000 infants, found a reduced risk of respiratory distress syndrome (aOR: 0.65; 95 CI: 0.52, 0.81) among Tdap-exposed infants compared with unexposed.[20]

Current evidence on Tdap vaccination during pregnancy and chorioamnionitis has been inconsistent. Three studies have reported an increased risk of chorioamnionitis among women vaccinated with Tdap during pregnancy; reassuringly, none demonstrated any increased risks for adverse infant outcomes typically associated with chorioamnionitis, such as preterm birth.[16,25,28] Similar to other studies by Morgan et al.[17] and Berenson et al.,[15] we did not find any association with chorioamnionitis after adjustment for potential confounding through our propensity-score matched analyses. Moreover, this result was robust throughout all sensitivity analyses. Our finding that Tdap was also not associated with risk of postpartum hemorrhage aligns with two previous studies.[21,23] In the UK, Donegan et al. reported on national surveillance data in the first six months of maternal Tdap program implementation and found no association with postpartum hemorrhage.[21] Similarly, receipt of Tdap in pregnancy was not associated with postpartum hemorrhage in a New Zealand cohort of 68,550 women.[23] Using a large insurance claims database in the US, Layton et al. observed an increased risk of postpartum hemorrhage following maternal Tdap vaccination during pregnancy, though the association was attenuated after they accounted for healthcare access and behaviours in sensitivity analyses.[28]

We are unaware of any biological mechanism to explain the protective relationship we observed between Tdap vaccination and gestational hypertension; previous studies[23,25] have not reported any association between Tdap and this outcome. We believe our finding most likely reflects residual confounding and healthy vaccinee bias; compared to unvaccinated women, those vaccinated might represent a healthier population that engage in behaviours that also lower their risk for gestational hypertension. Additionally, the lack of information regarding the timing of disease onset precluded our ability to account for temporality of the association in our analyses. In contrast, Griffin et al., who were able to account for the timing of diagnosis in relation to timing of vaccination, found no association between Tdap vaccination and gestational hypertension.[23] Such temporal issues are known to be influential in studies of vaccination during pregnancy.[44,45]

Strengths of our study include its population-based design, comprising a source population of over 600,000 births. Despite achieving good balance of baseline covariates in our matched sample, the propensity scores were limited to measured variables available in the study databases. Importantly, there was no information about maternal smoking, alcohol and drug use, or body mass index; thus, we cannot dismiss the possibility of residual bias due to unmeasured potential confounders. Although timing of vaccination was available in the database, we lacked information on timing of disease onset for gestational hypertension and could not determine the temporality of the exposure-outcome relationship which may have affected our results. This was not a concern for other obstetric outcomes, such as chorioamnionitis and postpartum hemorrhage, as diagnosis typically occurs during the peripartum period. Ontario currently limits public funding for Tdap boosters in adults to one dose.[46] It is possible that care providers refrained from billing for the Tdap vaccine to avoid additional costs for the mother, who would thus be misclassified as unexposed. Further, vaccine-specific codes, including G847 for Tdap, were introduced only 7 months before the start of our study period and if not billed correctly, could have resulted in exposure misclassification.[47] However, our sensitivity analysis which additionally included *possible* Tdap vaccinations billed under a generic immunization code were essentially identical to our main analyses. Although the sensitivity of the Tdap vaccine code in our study population was unclear, specificity was likely high, as OHIP billing claims have previously demonstrated high specificity for immunization among children[47] and adults.[48] Because Tdap vaccination during pregnancy was uncommon in our study and specificity was high, any non-differential misclassification of the exposure likely had a small impact on the magnitude of our point estimates.[49]

CONCLUSION

Our findings corroborate existing literature and provide further support for the safety of Tdap immunization during pregnancy. Importantly, we found no indication of increased risk for postpartum hemorrhage or chorioamnionitis following Tdap immunization in the Ontario setting; earlier studies from other countries have reported equivocal results for these outcomes. This study provides preliminary safety

information on maternal Tdap vaccination in Canada, which is important for establishing baseline data to inform evolving maternal immunization initiatives and providing reassurance when discussing Tdap recommendations with pregnant women. Future studies using more contemporary data extending into the post-NACI policy time period will be important for further developing the evidence base in Canada.

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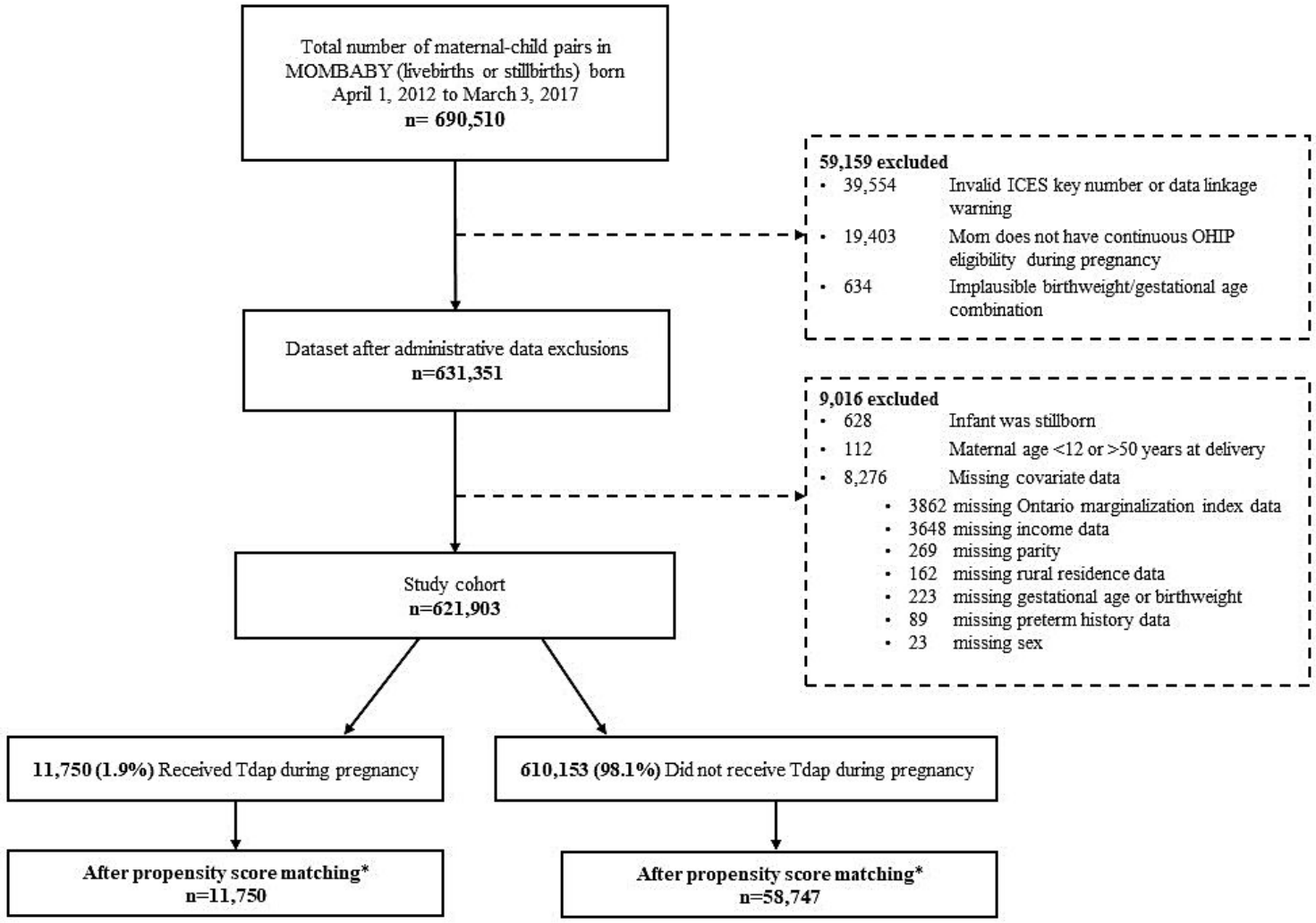


***Note: The ratio of matched exposed to unexposed pregnancies is not exactly 1:5, as some exposed cases were matched with fewer than five unexposed cases.**

Figure 1. Study flow diagram

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

Table 1. Baseline characteristics of the cohort, before and after propensity score matching, by Tdap vaccination status

Characteristic	Unmatched cohort (n=621,903)			Propensity score-matched cohort (n=70,497)		
	Tdap vaccinated women, N (%) [a] (n=11,750)	Tdap unvaccinated women, N (%) [a] (n=610,153)	Stand Diff [b]	Tdap vaccinated women, % [a] (n=11,750)	Tdap unvaccinated women, % [a] (n=58,747)	Stand Diff [b]
Gestational age at vaccination (week)						
<20	2,641 (22.5)	-	-	-	-	-
20-26	1,153 (9.8)	-	-	-	-	-
27-32	4,903 (41.7)	-	-	-	-	-
33+	3,053 (26.0)	-	-	-	-	-
Maternal age (years)						
<20	179 (1.5)	14,080 (2.3)	0.06	1.5	1.5	0.01
20–24	787 (6.7)	65,615 (10.8)	0.14	6.7	6.5	0.01
25–29	3,305 (28.1)	163,942 (26.9)	0.03	28.1	28.1	0
30–34	4,659 (39.7)	223,707 (36.7)	0.06	39.7	39.8	0
≥35	2,820 (24.0)	142,809 (23.4)	0.01	24.0	24.1	0
Birth year (in fiscal year)						
2012-13	594 (5.1)	127,585 (20.9)	0.49	5.1	5.4	0.02
2013-14	1,628 (13.9)	124,744 (20.4)	0.18	13.9	13.6	0.01
2014-15	2,099 (17.9)	123,945 (20.3)	0.06	17.9	17.8	0
2015-16	2,903 (24.7)	122,767 (20.1)	0.11	24.7	24.9	0.01
2016-17	4,526 (38.5)	111,112 (18.2)	0.46	38.5	38.3	0.01
Parity						
0 (nulliparous)	6,066 (51.6)	269,466 (44.2)	0.15	51.6	51.7	0
≥1 (multiparous)	5,684 (48.4)	340,687 (55.8)	0.15	48.4	48.3	0
Multiple birth						
No	11,474 (97.7)	589,055 (96.5)	0.07	97.7	97.8	0.01
Yes	276 (2.3)	21,098 (3.5)	0.07	2.3	2.2	0.01
Baby's sex						
Female	5,706 (48.6)	297,283 (48.7)	0	48.6	48.8	0
Male	6,044 (51.4)	312,870 (51.3)	0	51.4	51.2	0
History of preterm birth						
Nulliparous	6,066 (51.6)	269,466 (44.2)	0.15	51.6	51.7	0

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

Parous – no history of preterm birth	5,352 (45.5)	316,038 (51.8)	0.13	45.5	44.8	0.01
Parous – history of preterm birth	332 (2.8)	24,649 (4.0)	0.07	2.8	3.5	0.04
Pre-existing maternal medical condition [c]						
No	11,399 (97.0)	592,496 (97.1)	0.01	97.0	97.1	0
Yes	351 (3.0)	17,657 (2.9)	0.01	3.0	2.9	0
Type of pre-existing maternal medical condition						
Asthma	25 (0.2)	1,508 (0.2)	0.01	0.2	0.2	0
Chronic hypertension	41 (0.3)	2,327 (0.4)	0.01	0.3	0.3	0
Diabetes	55(0.5)	4,779(0.8)	0.01	0.5	0.5	0
Heart disease	51 (0.4)	2,986 (0.5)	0.01	0.4	0.4	0
Thyroid disease						
No	11,548 (98.3)	602,995 (98.8)	0.05	98.3	98.3	0
Yes	202 (1.7)	7,158 (1.2)	0.05	1.7	1.7	0
Obstetrical complication [d]						
No	9,096 (77.4)	482,522 (79.1)	0.04	77.4	78.7	0.02
Yes	2,654 (22.6)	127,631 (20.9)	0.04	22.6	21.3	0.02
Type of obstetrical complication [e]						
Preeclampsia and eclampsia	247 (2.1)	11,839 (1.9)	0.01	2.1	2.1	0
Gestational diabetes	771 (6.6)	38,483 (6.3)	0.01	6.6	6.5	0
Placenta previa	82 (0.7)	4,369 (0.7)	0.01	0.7	0.7	0
Placental abruption	112 (1.0)	6,253 (1.0)	0.01	1.0	0.9	0
PROM	1,599 (13.6)	74,941 (12.3)	0.04	13.6	12.5	0.3
Type of delivery						
Vaginal	8,558 (72.8)	434,154 (71.2)	0.04	72.8	70.7	0.04
Cesarean	3,192 (27.2)	175,999 (28.8)	0.04	27.2	29.3	0.04
Previous cesarean delivery						
Nulliparous	6,066 (51.6)	269,466 (44.2)	0.15	51.6	51.7	0

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

Parous – no previous cesarean section	4,615 (39.3)	271,605 (44.5)	0.11	39.3	37.9	0.03
Parous – previous cesarean section	1,069 (9.1)	69,082 (11.3)	0.07	9.1	10.4	0.04
UTI during pregnancy	10 (0.1)	1,068 (0.2)	0.02	0.1	0.1	0
Neighborhood median family income quintiles						
1 (Lowest)	2,030 (17.3)	126,778 (20.8)	0.09	17.3	17.2	0
2	2,377 (20.2)	122,298 (20.0)	0	20.2	20.3	0
3	2,297 (19.5)	124,419 (20.4)	0.02	19.5	19.4	0
4	2,624 (22.3)	134,002 (22.0)	0.01	22.3	22.7	0.01
5 (Highest)	2,422 (20.6)	102,656 (16.8)	0.11	20.6	20.4	0.01
Rural residence						
No	10,666 (90.8)	550,396 (90.2)	0.02	90.8	90.7	0
Yes	1,084 (9.2)	59,757 (9.8)	0.02	9.2	9.3	0
Public health unit region						
North West	114 (1.0)	8,823 (1.4)	0.04	1.0	1.0	0
North East	286 (2.4)	23,203 (3.8)	0.08	2.4	2.4	0
Eastern	1,905 (16.2)	76,058 (12.5)	0.11	16.2	16.1	0
Central East	4,240 (36.1)	185,512 (30.4)	0.12	36.1	36.1	0
Toronto	3,439 (29.3)	126,977 (20.8)	0.20	29.3	29.4	0
South West	521 (4.4)	68,837 (11.3)	0.26	4.4	4.3	0.01
Central West	1,245 (10.6)	120,743 (19.8)	0.26	10.6	10.7	0
Birth weight						
<1500 g	48 (0.4)	6,081 (1.0)	0.07	0.4	0.9	0.06
1500-2500 g	533 (4.5)	33,998 (5.6)	0.05	4.5	5.3	0.03
2500-3500 g	6,575 (56.0)	330,647 (54.2)	0.04	56.0	56.2	0
≥3500 g	4,594 (39.1)	239,427 (39.2)	0	39.1	37.6	0.01
Gestational weeks at delivery						
<28	9 (0.1)	2,717 (0.4)	0.07	0.1	0.4	0.06
28-31	50 (0.4)	4,145 (0.7)	0.03	0.4	0.6	0.02
32-33	62 (0.5)	5,725 (0.9)	0.05	0.5	0.8	0.03
34	82 (0.7)	6,006 (1.0)	0.03	0.7	0.9	0.02

35	154 (1.3)	9,919 (1.6)	0.03	1.3	1.5	0.02
36	352 (3.0)	19,902 (3.3)	0.02	3.0	3.1	0.01
≥37	11,041 (94.0)	561,739 (92.1)	0.07	94.0	92.6	0.05
Maternal world region of origin						
North America	9,075 (77.2)	477,882 (78.3)	0.03	77.2	77.6	0.01
Asia	2,090 (17.8)	83,018 (13.6)	0.12	17.8	17.6	0.01
Europe	163 (1.4)	12,060 (2.0)	0.05	1.4	1.3	0.01
Africa	157 (1.3)	11,512 (1.9)	0.04	1.3	1.3	0.01
Caribbean	73 (0.6)	8,224 (1.3)	0.07	0.6	0.6	0.01
Yugoslavia & USSR	89 (0.8)	7,684 (1.3)	0.05	0.8	0.8	0
South America	69 (0.6)	6,428 (1.1)	0.05	0.6	0.6	0
Central America	25 (0.2)	3,059 (0.5)	0.05	0.2	0.2	0
Oceania	9 (0.1)	286 (0.0)	0.01	0.1	0.1	0
Marginalization Indices [f]						
Residential instability quintile						
1	2,574 (21.9)	138,078 (22.6)	0.02	21.9	22.2	0.01
2	2,205 (18.8)	118,780 (19.5)	0.02	18.8	19.3	0.01
3	2,181 (18.6)	113,027 (18.5)	0	18.6	18.1	0.01
4	2,153 (18.3)	115,549 (18.9)	0.02	18.3	18.6	0.01
5	2,637 (22.4)	124,719 (20.4)	0.05	22.4	21.9	0.01
Material deprivation quintile						
1	2,000 (17.0)	94,889 (15.6)	0.04	17.0	16.7	0.01
2	2,267 (19.3)	116,036 (19.0)	0.01	19.3	20.1	0.02
3	2,358 (20.1)	120,708 (19.8)	0.01	20.1	20.6	0.01
4	2,456 (20.9)	126,083 (20.7)	0.01	20.9	21.4	0.01
5	2,669 (22.7)	152,437 (25.0)	0.05	22.7	21.2	0.04
Dependency quintile						
1	3,861 (32.9)	212,799 (34.9)	0.04	32.9	35.3	0.04
2	2,426 (20.6)	122,966 (20.2)	0.01	20.6	19.8	0.02
3	2,105 (17.9)	105,041 (17.2)	0.02	17.9	16.8	0.03
4	1,772 (15.1)	91,485 (15.0)	0	15.1	14.4	0.02
5	1,586 (13.5)	77,862 (12.8)	0.02	13.5	13.7	0.01

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

Ethnic concentration quintile						
1	1,479 (12.6)	85,842 (14.1)	0.04	12.6	12.1	0.02
2	1,702 (14.5)	90,458 (14.8)	0.01	14.5	12.6	0.05
3	1,939 (16.5)	102,531 (16.8)	0.01	16.5	16.2	0.01
4	2,361 (20.1)	126,466 (20.7)	0.02	20.1	22.5	0.02
5	4,269 (36.3)	204,856 (33.6)	0.06	36.3	36.7	0.01
Prenatal care index [g]						
Intensive	247 (2.1)	8,933 (1.5)	0.05	2.1	2.0	0.01
Adequate	4,493 (38.2)	162,460 (26.6)	0.25	38.2	38.5	0
Intermediate	5,780 (49.2)	302,356 (49.6)	0.01	49.2	49.3	0
Inadequate	898 (7.6)	86,139 (14.1)	0.21	7.6	7.4	0.01
No care	332 (2.8)	50,265 (8.2)	0.24	2.8	2.8	0

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

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

Table 2. Association between receipt of Tdap vaccination during pregnancy and obstetrical and perinatal outcomes

Outcome	Unmatched Cohort Analysis (n=621,903)			Propensity Score-Matched Analysis (n=70,497)		
	Tdap Vaccinated (n=11,750)	Tdap Unvaccinated (n=610,153)	Crude Estimate (RR/HR [95% CI])	Tdap Vaccinated (n=11,750)	Tdap Unvaccinated (n=58,747)	Adjusted Estimate (RR/HR [95% CI])
	N (%)	N (%)		N (%)	N (%)	
Chorioamnionitis [a]	145 (1.23)	6,069 (0.99)	1.24 (1.05,1.46)	145 (1.23)	741 (1.26)	0.98 (0.82,1.17)
Gestational hypertension [a]	399 (3.40)	23,698 (3.88)	0.87 (0.79,0.96)	399 (3.40)	2,434 (4.14)	0.82 (0.74,0.91)
Postpartum hemorrhage [a]	324 (2.76)	16,804 (2.75)	1.00 (0.90, 1.12)	324 (2.76)	1,561 (2.66)	1.04 (0.92, 1.17)
Severe postpartum hemorrhage [a, b]	30 (0.26)	1,974 (0.32)	0.79 (0.55, 1.13)	30 (0.26)	170 (0.29)	0.88 (0.60, 1.30)
Small-for-gestational-age birth [a]	1,089 (9.27)	59,697 (9.78)	0.95 (0.89,1.00)	1,089 (9.27)	5,991 (10.20)	0.91 (0.85,0.97)
NICU admission >24 hours [a]	759 (6.46)	50,676 (8.31)	0.78 (0.73,0.83)	759 (6.46)	4,496 (7.65)	0.84 (0.78,0.91)
NAOI composite outcome [a]	670 (5.70)	44,717 (7.33)	0.78 (0.72,0.84)	670 (5.70)	4,240 (7.22)	0.79 (0.73,0.86)
Preterm birth, <37 weeks [c,d]	709 (6.03)	48,414 (7.93)	0.94 (0.87,1.01)	709 (6.03)	4,328 (7.37)	0.95 (0.89,1.02)
Very preterm birth, <32 weeks [c,d]	59 (0.50)	6,862 (1.12)	1.06 (0.82,1.37)	59 (0.50)	595 (1.01)	1.15 (0.89,1.47)

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

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

[b] Postpartum hemorrhage in conjunction with a procedure code for hysterectomy, blood transfusion, or other procedures to control bleeding.

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

[d] We limited analyses to Tdap administration at 36 weeks' gestation or earlier (N=69,620) and 31 weeks' or earlier (N=65,824) for preterm birth outcome and very preterm outcome respectively.

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

SUPPLEMENTARY MATERIALS:

Table A: Description & purpose of each data source utilized in the study

Database	Description	Information collected
MOMBABY Database	Contains inpatient admission records of delivering mothers and their respective newborns (including stillbirths), which are linked by a unique matching identifier on each hospitalization record. This administrative dataset, maintained and annually updated at ICES, links approximately 98% of maternal-infant records for in-hospital deliveries in Ontario.	This database was used to assemble our study cohort, as well as collect maternal and newborn information such as gestational age at birth, maternal age, birth weight, baby's sex, parity and plurality.
Registered Persons Database (RPDB)	Demographic repository containing information on all Ontario residents eligible for publicly funded health care in the province.	Was used to establish the duration for which each participant was eligible to receive health care services, as well as obtain demographic information regarding neighbourhood income quintiles and region of residence.
Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD)	Captures demographic and clinical information regarding hospital admissions from all acute care institutions throughout Canada.	We used this database to collect information from both the mothers and newborns regarding medical diagnoses (e.g., gestational diabetes), interventions (e.g., neonatal ventilatory support), number of previous preterm deliveries, as well as admissions and discharges to any special care units (e.g., neonatal intensive care unit).
Ontario Health Insurance Plan (OHIP) Database	Contains health care billing information made by physicians, or other health care providers, for service reimbursement. This database includes information on the diagnosis (i.e., reason for the visit), type of service received, and the associated billing code.	Specific OHIP fee codes are used when a vaccine is administered, which provided the information to identify our exposure group. In addition, we identified prenatal care visits (via OHIP fee codes) and health care provider specialties (via SPEC variable) through from this database.

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

Ontario Marginalization Index (ON-Marg)	Data tool that quantifies the level of marginalization occurring in Ontario. This multifaceted index uses data from Statistics Canada's Census and consists of four dimensions that indicate marginalization: residential instability, material deprivation, dependency and ethnic concentration. Scores corresponding to each of these four dimensions were previously divided into quintiles, where quintile 1 represents areas that are the least marginalized and quintile 5 represents the most marginalized areas.	Collected information regarding the four indices of marginalization.
Permanent Resident Database (PRD) led by Immigration, Refugee and Citizenship Canada (IRCC)	Contains records of permanent residents that immigrated to Canada.	Was used to collect information regarding maternal country of birth.

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

Table B. Study outcome definitions and diagnostic codes

Study Outcome	Definition	Data source, ICD10 Diagnostic Code, and/or CCI procedure code
Obstetrical Outcomes		
Gestational hypertension	Hypertension in pregnant women (blood pressure >140/90mmHg) after 20 weeks of gestation without presence of proteinuria or preeclampsia.	O13, O16
Chorioamnionitis	Acute inflammation of the chorion and membranes of the placenta due to bacterial infection.	O41.12, O41.13, O41.19
Postpartum hemorrhage	Blood loss of ≥ 500 mL following vaginal delivery or ≥ 1000 mL following Caesarean section, or diagnosis as noted by a health care provider.	O720-O723
Severe postpartum hemorrhage	Postpartum hemorrhage in conjunction with one of the following procedures to control bleeding: blood transfusion, hysterectomy, and other procedures to control bleeding.	
-Hysterectomy		5MD60KE; 5MD60RC; 5MD60CB; 5MD60RD; 1RM87LAGX; (1RM89LA without 1PL74;1RS80; 1RS74)
-Other procedures to control bleeding		5PC91LA, 1RM13, 1KT51;5PC91HT
-Blood transfusion		Measured using DAD variable: BTANY.
Perinatal Outcomes		
Small-for-gestational-age birth	Birth weight <10th percentile for gestational age and sex.	Measured using infant sex, gestational age, and birth weight variables in MOMBABY.

NICU Admission >24 hours	Intensive care unit admission lasting >24 hours	Measured using DAD variables (special care unit admission and discharge dates) from infant records.
NAOI composite outcome	The NAOI is a validated composite outcome that will be utilized to identify neonatal morbidity. It combined ICD-based codes relating to treatments of severe events.	Refer to **Appendix III** for a complete list of the diagnostic and procedural codes included.
Preterm birth	Live birth prior to 37 weeks of gestation.	Measured using gestational age variable in MOMBABY.
Very preterm birth	Live birth prior to 32 weeks of gestation.	Measured using gestational age variable in MOMBABY.

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

Table C. Components of the Neonatal Adverse Outcome Indicator (NAOI) composite outcome

Components of Variable	MOMBABY Variable	DAD Variable	Diagnosis Code (ICD-10)
Gestational age <32 weeks	B_GESTWKS_DEL (or M_GESTWKS_DEL)		
Birth weight <1500grams	B_WEIGHT		
Respiratory distress syndrome			P22.0
Seizures			P90, R56
Intraventricular hemorrhage (grades 2,3, or 4)			P52.1, P52.2
Cerebral infarction			I63
Periventricular leukomalacia			P91.2
Birth trauma (intracranial hemorrhage paralysis due to brachial plexus injury, skull or long bone fracture)			P10.0 to P10.3, P13.0, P13.2, P13.3, P14.0, P14.1
Hypoxic ischemic encephalopathy			P91.5, P91.81, P91.6
Necrotizing enterocolitis			P77
Bronchopulmonary dysplasia			P27.1
Sepsis/septicemia			P36, A40, A41.5, A41.9, B95.1, B96.2
Pneumonia			P23, J12 to J18

Primary atelectasis			P28.0
Respiratory failure			P28.5
	MOMBABY Variable	**DAD Variable**	**Procedure code (CCI)**
Resuscitation			1.GZ.30
Ventilatory support (mechanical ventilation and/or CPAP)			1.GZ.31
Central venous or arterial catheter			1.IS.53, 1.KV.53
Transfusion of blood or blood products		BTANY, BTOTHER	
Pneumothorax requiring an intercostal catheter			1.GT.33

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

Table D. Baseline characteristics included in propensity score model

Variables included
Maternal age (continuous variable)
Parity
Multiple birth
Baby's sex
Pre-existing maternal medical conditions (chronic hypertension, diabetes, asthma, heart disease, thyroid disease)
Obstetrical complications (placenta previa, placental abruption, preeclampsia, eclampsia, gestational diabetes, PROM)
UTI during pregnancy
Fiscal year of delivery
Maternal world region of birth
Marginalization indices from Ontario Marginalization (ONMARG) database (residential instability, material deprivation, dependency, ethnic concentration) (continuous variable)
Rural residency
Neighborhood income quintile
Public health unit region of residence
Revised Graduated Adequacy of Prenatal Care Index (R-GINDEX) (6 categories of prenatal care: inadequate, intermediate, adequate, intensive, no care, and missing)

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

Table E. OHIP fee codes associated with a prenatal visit

OHIP fee code	Description
A920	Medical management of early pregnancy, initial visit
A921	Medical management of early pregnancy, subsequent visit
A005	Consultation
A006	Re-consultation
A665	Prenatal consult
Q606	Prenatal care - gen. Assess - major prenatal visit
Q607	Prenatal care - min. Assess - subsequent prenatal visit
P002	High risk prenatal assessment
P003	Obs.-prenatal care-general assess - major prenatal visit
P004	Obs.-prenatal care-minor prenatal assess - subsequent prenatal visit
P005	Antenatal health screen

* Prenatal visits were defined by limiting to one record per person per type of doctor per day. Only visits with an associated OHIP fee code related to prenatal care were included in this definition.

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

Table F. Association between receipt of Tdap (main exposure + *possible* Tdap) vaccination during pregnancy and obstetrical and perinatal outcomes using propensity-score matching

Outcome	Unmatched Cohort Analysis (n=621,903)			Propensity Score-Matched Analysis (n=87,565)		
	Tdap Vaccinated (n=14,595) N (%)	Tdap Unvaccinated (n=607, 308) N (%)	Crude Estimate (RR/HR [95% CI])	Tdap Vaccinated (n=14,595) N (%)	Tdap Unvaccinated (n=72,970) N (%)	Adjusted Estimate (RR/HR [95% CI])
Chorioamnionitis [a]	184 (1.26)	6,030 (0.99)	1.27 (1.10,1.47)	184 (1.26)	899 (1.23)	1.02 (0.87, 1.20)
Gestational hypertension [a]	506 (3.47)	23,591 (3.88)	0.89 (0.82,0.97)	506 (3.47)	2,897 (3.97)	0.87 (0.80, 0.96)
Postpartum hemorrhage [a]	403 (2.76)	16,725	1.00 (0.91, 1.11)	403 (2.76)	1,932 (2.65)	1.04 (0.94, 1.16)
Severe post-partum hemorrhage [a,b]	41 (0.28)	1,963 (0.32)	0.87 (0.64, 1.18)	41 (0.28)	220 (0.30)	0.93 (0.67, 1.30)
Small-for-gestational-age birth [a]	1,381 (9.46)	59,405 (9.78)	0.97 (0.92,1.02)	1,381 (9.46)	7,324 (10.0)	0.94 (0.89, 1.01)
NICU admission >24 hours [a]	962 (6.59)	50,473 (8.31)	0.79 (0.75,0.84)	962 (6.59)	5,645 (7.74)	0.85 (0.80, 0.91)
NAOI composite outcome [a]	858 (5.88)	44,529 (7.33)	0.80 (0.75,0.86)	858 (5.88)	5,341 (7.32)	0.80 (0.75, 0.86)
Preterm birth, <37 weeks [c,d]	901 (6.17)	48,222 (7.94)	0.94 (0.88,1.00)	901 (6.17)	5,409 (7.41)	0.94 (0.89, 1.01)
Very preterm birth, <32 weeks [c,d]	83 (0.57)	6,838 (1.13)	1.09 (0.88,1.34)	83 (0.57)	724 (0.99)	1.18 (0.96, 1.46)

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

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

[b] Postpartum hemorrhage in conjunction with a procedure code for hysterectomy, blood transfusion, or other procedures to control bleeding.

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

[d] We limited analyses to Tdap administration at 36 weeks' gestation or earlier (N=86,577) and 31 weeks' or earlier (N=82,424) for preterm birth outcome and very preterm outcome respectively.

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

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

	Original Propensity Score Matched Results	Maternal Outpatient Visits (6 months before pregnancy)	Maternal Non-Obstetric Hospitalization (2 years before pregnancy)	Propensity Score Weighting
	Adjusted estimate (RR/HR [95% CI]) [a] (n=621,903)	Adjusted estimate (RR/HR [95% CI]) [a,b] (n=609,916)	Adjusted estimate (RR/HR [95% CI]) [a,c] (n=579,768)	Adjusted estimate (RR/HR [95% CI]) [d] (n=621,903)
Obstetrical Outcomes				
Chorioamnionitis [e]	0.98 (0.82,1.17)	0.94 (0.78, 1.12)	0.98 (0.82, 1.18)	0.95 (0.79,1.14)
Gestational hypertension [e]	0.82 (0.74,0.91)	0.84 (0.75, 0.93)	0.83 (0.75, 0.93)	0.81 (0.73,0.89)
Postpartum hemorrhage	1.04 (0.92, 1.17)	1.02 (0.91, 1.15)	0.98 (0.86, 1.10)	1.03 (0.93,1.14)
Severe postpartum hemorrhage	0.88 (0.60, 1.30)	0.78 (0.52, 1.16)	0.70 (0.46, 1.05)	0.98 (0.71, 1.34)
Perinatal Outcomes				
Small-for-gestational-age birth [e]	0.91 (0.85,0.97)	0.89 (0.84, 0.95)	0.91 (0.85, 0.97)	0.96 (0.91,1.01)
NICU admission >24 hours [e]	0.84 (0.78,0.91)	0.85 (0.79, 0.92)	0.86 (0.80, 0.93)	0.98 (0.92,1.04)
NAOI composite outcome [e]	0.79 (0.73,0.86)	0.79 (0.73, 0.85)	0.78 (0.72, 0.85)	0.86 (0.80,0.92)
Preterm birth, <37 weeks [f]	0.95 (0.89,1.02)	0.96 (0.89, 1.03)	0.95 (0.88, 1.03)	0.94 (0.87,1.02)
Very preterm birth, <32 weeks [f]	1.15 (0.89,1.47)	1.11 (0.86, 1.43)	1.10 (0.85, 1.44)	1.06 (0.82,1.37)

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

[a] Adjusted using propensity score matching.

[b] Adjusted for number of outpatient visits during the 6-month period prior to the index pregnancy. This sub-cohort was restricted to women with continuous Ontario insurance eligibility for the 6 months prior to pregnancy.

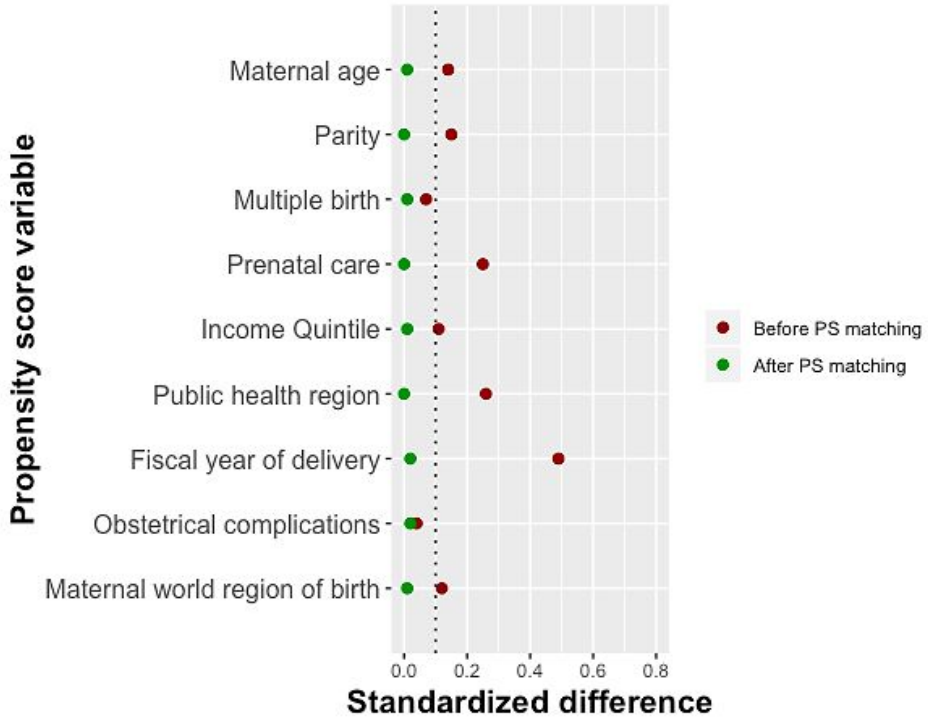
[c] Adjusted for number of non-obstetric hospitalization during the 2-year period prior to the index pregnancy. This sub-cohort was restricted to women with continuous Ontario insurance eligibility for the 2 years prior to pregnancy.

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

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

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

Figure. Comparison of standardized difference scores before and after propensity score (PS) matching



Supplementary Methods—Coding algorithm for Revised Graduated Prenatal Care Utilization Index (R-GINDEX)

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

Key Variables:
GEST = Gestational Age (18-45 weeks based on LMP)
PCV = Number of Prenatal Care Visits (0 = None)
TPCB = Trimester Prenatal Care Began (0 = None, 1-3 trimesters) *
GINDEX = Graduated Prenatal Care Utilization Index

***NOTE:** Trimester 1 = (0-13 weeks or 1-91 days)
Trimester 2 = (14-27 weeks or 92-189 days)
Trimester 3 = (28+ weeks or 190+ days)

INTENSIVE PRENATAL CARE UTILIZATION;

```
IF (TPCB=1) &
      (((18<=GEST<=21) & (11=<PCV))       |  ((22<=GEST<=25) & (13=<PCV))
      | ((26<=GEST<=29) & (14=<PCV))      |  ((30<=GEST<=31) & (15=<PCV))
      | ((32<=GEST<=36) & (16=<PCV))      |  ((37<=GEST<=40) & (17<=PCV))
      | ((41<=GEST<=42) & (18=<PCV))      |  ((43<=GEST<=45) & (19<=PCV)))
THEN GINDEX = 'INTENSIVE (1st Trimester)';
IF (TPCB=2) &
      (((18<=GEST<=21) & (10=<PCV))       |  ((22<=GEST<=25) & (11=<PCV))
      | ((26<=GEST<=31) & (12=<PCV))      |  ((32<=GEST<=35) & (13=<PCV))
      | ((36<=GEST<=37) & (14=<PCV))      |  ((38<=GEST<=40) & (15=<PCV))
      | ((41<=GEST<=42) & (16=<PCV))      |  ((43<=GEST<=45) & (17<=PCV)))
THEN GINDEX = 'INTENSIVE (2nd Trimester)';
IF (TPCB=3) &
      (((GEST=25) & (9=<PCV))           |  ((26<=GEST<=31) & (10=<PCV))
      | ((32<=GEST<=35) & (11=<PCV))     |  ((36<=GEST<=37) & (12=<PCV))
      | ((38<=GEST<=40) & (13=<PCV))     |  ((41<=GEST<=42) & (14=<PCV))
      | ((43<=GEST<=45) & (15=<PCV)))
 THEN GINDEX = 'INTENSIVE (3rd Trimester)';
```

ADEQUATE PRENATAL CARE UTILIZATION CRITERIA;

```
IF (TPCB=1) &
      (((18<=GEST<=21) & (3=<PCV<=10))    |  ((22<=GEST<=25) & (4=<PCV<=12))
      | ((26<=GEST <=29) & (5=<PCV<= 13))  |  ((30<=GEST<=31) & (6=<PCV<= 14))
```

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

```
      | ((32<=GEST<=33)  & (7=<PCV<=15))    |       ((34<=GEST<=35) & (8=<PCV<=15))
      | ((GEST=36)       & (9=<PCV<=15))    |       ((GEST =37) & (10<=PCV<=16))
      | ((GEST=38)       & (11=<PCV<=16))   |       ((GEST =39) & (12<=PCV<=16))
      | ((GEST=40) & (13=<PCV<=16))         |       ((GEST =41) & (14<=PCV<=17))
      | ((GEST=42) & (15=<PCV<=17))         |       ((43<=GEST<=45) & (16<=PCV<=18)))
THEN GINDEX = 'ADEQUATE (1st Trimester)';

INTERMEDIATE PRENATAL CARE UTILIZATION CRITERIA;

IF (TPCB=1) &
      (((18<=GEST<=21) & (1<=PCV<=2))       |    ((22<=GEST<=25) & (2=<PCV<=3))
      | ((26<=GEST<=29) & (2=<PCV<=4))      |     ((30<=GEST<=31) & (3=<PCV<=5))
      | ((32<=GEST<=33) & (4=<PCV<=6))      |     ((34<=GEST<=35) & (5=<PCV<=7))
      | ((GEST=36) & (5=<PCV<=8))           |    ((GEST=37) & (6=<PCV<=9))
      | ((GEST=38) & (7=<PCV<=10))          |     ((GEST=39) & (7=<PCV<=11))
      | ((GEST=40) & (8=<PCV<=12))          |     ((GEST=41) & (8=<PCV<=13))
      | ((GEST=42) & (9=<PCV<=14))          |     ((43<=GEST<=45) & (9=<PCV<=15)))
THEN GINDEX = 'INTERMEDIATE (1st Trimester)';
IF (TPCB=2) &
      (((18<=GEST<=21) & (1=<PCV<=9))       | ((22<=GEST<=25) & (2=<PCV<=10))
      | ((26<=GEST<=29) & (2=<PCV<=11))     | ((30<=GEST<=31) & (3=<PCV<=11))
      | ((32<=GEST<=33) & (4=<PCV<=12))     | ((34<=GEST<=35) & (5=<PCV<=12))
      | ((36<=GEST<=37) & (6=<PCV<=13))     | ((38<=GEST<=39) & (7=<PCV<=14))
      | ((GEST=40) & (8=<PCV<=14))          | ((GEST =41)     & (8=<PCV<=15))
      | ((GEST=42) & (9=<PCV<=15))          | ((43<=GEST<=45) & (9=<PCV<=16)))
THEN GINDEX = 'INTERMEDIATE (2nd Trimester)';

INADEQUATE PRENATAL CARE UTILIZATION CRITERIA;

IF (TPCB=1) &
      (((22<=GEST<=29) & (PCV=1))           |    ((30<=GEST<=31) & (1<=PCV<=2))
      | ((32<=GEST<=33) & (1<=PCV<=3))      |    ((34<=GEST<=36) & (1<=PCV<=4))
      | ((GEST=37) & (1<=PCV<=5))           |    ((38<=GEST<=39) & (1<=PCV<=6))
      | ((40<=GEST<=41) & (1<=PCV<=7))      |    ((42<=GEST<=45) & (1<=PCV<=8)))
THEN GINDEX = 'INADEQUATE (1St Trimester)';
IF (TPCB=2) &
```

Obstetric and perinatal health outcomes following pertussis immunization during pregnancy in Ontario, Canada

```
      (((22<=GEST<=29) & (PCV=1))          |     ((30<=GEST<=31) & (1<=PCV<=2))
      | ((32<=GEST<=33) & (1<=PCV<=3))     |     ((34<=GEST<=35) & (1<=PCV<=4))
      | ((36<=GEST<=37) & (1<=PCV<=5))     |     ((38<=GEST<=39) & (1<=PCV<=6))
      | ((40<=GEST<=41) & (1<=PCV<=7))     |     ((42<=GEST<=45) & (1<=PCV<=8)))
THEN GINDEX = 'INADEQUATE (2nd Trimester)';
IF (TPCB=3) &
      (((GEST =25) & (1<=PCV<=8))          |    ((26<=GEST<=31) & (1<=PCV<=9))
      | ((32<=GEST<=35) & (1<=PCV<=10))    |    ((36<=GEST<=37) & (1<=PCV<=11))
      | ((38<=GEST<=40) & (1<=PCV<=12))    |    ((41<=GEST<=42) & (1<=PCV<=13))
      | ((43<=GEST<=45) & (1<=PCV<=14)))
THEN GINDEX = 'INADEQUATE (3rd Trimester)';

MISSING PRENATAL CARE CRITERIA;

IF (((PCV=.) & (TPCB^=0))                  | ((TPCB=3) & (1<=GEST<=24))
|  ((TPCB=2) & (1<=GEST<=11))              |  ((GEST=.) & (PCV^=0))
|  ((TPCB=.) & (PCV^=0))                   | (TPCB=0 & (PCV>0)))
THEN GINDEX = 'MISSING';

NO PRENATAL CARE UTILIZATION;

IF (PCV=0)                                 |     (TPCB=0 & PCV=.)
THEN GINDEX = 'NOCARE';
```