Health Outcomes in Young Children Following Pertussis Vaccination During Pregnancy

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abstract

BACKGROUND AND OBJECTIVES: Maternal immunization with tetanus, diphtheria, and acellular pertussis vaccine (Tdap) is routinely recommended in many countries as a strategy to protect young infants against severe pertussis infection; few studies have assessed whether prenatal exposure to the vaccine is associated with any longer-term adverse health effects in children. We evaluated the long-term safety of exposure to Tdap vaccination during pregnancy.

METHODS: Population-based retrospective cohort study conducted in Ontario, Canada using multiple linked province-wide health administrative databases. All live births between April 2012 and March 2017 were included, and children were followed for up to 6 years to ascertain study outcomes. Children exposed to prenatal Tdap were propensity score matched to unexposed children at a 1:5 ratio. Tdap vaccination during pregnancy was ascertained by using vaccine-specific fee codes. Immune-related (infectious diseases, asthma) and nonimmune-related (neoplasm, sensory disorders) outcomes and a nonspecific morbidity outcome (urgent or inpatient health service use) were evaluated from birth to end of follow-up.

RESULTS: Of 625 643 live births, 12 045 (1.9%) were exposed to Tdap in utero. There were no significant increased risks of adverse childhood outcomes and prenatal Tdap exposure; however, we observed inverse associations (adjusted incidence rate ratio [95% confidence interval]) with upper respiratory infections (0.94 [0.90–0.99]), gastrointestinal infections (0.85 [0.79–0.91]), and urgent and inpatient health service use (0.93 [0.91–0.96]).

CONCLUSIONS: Exposure to Tdap vaccination in pregnancy was not associated with any increased risk of adverse health outcomes in early childhood, supporting the long-term safety of Tdap administration in pregnancy.

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WHAT'S KNOWN ON THIS SUBJECT: Maternal immunization with tetanus, diphtheria, and acellular pertussis vaccine (Tdap) provides infants with passive immunity against pertussis during their first months of life; however few researchers have assessed longer-term health outcomes in young children.

WHAT THIS STUDY ADDS: Exposure to Tdap during pregnancy was not associated with any increased risk of adverse health outcomes or urgent and inpatient health service use in early childhood, supporting the long-term safety of Tdap administration in pregnancy.

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Pertussis, also known as whooping cough, is a highly contagious respiratory tract infection caused by *Bordetella pertussis*, from which young infants are at greatest risk of severe complications and death.[1] Maternal immunization during pregnancy with tetanus, diphtheria, and acellular pertussis-containing vaccine (Tdap) provides infants with passive immunity against pertussis during their first months of life by inducing the production of maternal antibodies that are transferred across the placenta to the fetus.[2] This strategy is highly protective, with an estimated vaccine effectiveness of 78% to 93% in infants <2 months of age.[3–7] Tdap vaccination during every pregnancy has been recommended since 2012 in the United Kingdom[8] and 2013 in the United States[9]; similar recommendations have since been adopted by other countries, including Canada in February 2018.[10]

A growing body of research has provided reassuring evidence that Tdap immunization is not associated with serious adverse events in the mother or clinically important adverse fetal or neonatal outcomes such as preterm birth, stillbirth, or small for gestational age birth.[11–13] However, evidence on longer-term pediatric health outcomes after Tdap vaccination during pregnancy is limited, with few studies extending beyond 18 months of age.[14,15] Because concerns about vaccine safety influence decisions about immunization during pregnancy, more evidence is needed about long-term safety of maternal vaccination for the child.[16–18] The objective of this study was to assess the association between Tdap vaccination during pregnancy and childhood health outcomes during the first 6 years of life.

METHODS

Study Design, Data Sources, and Study Population

This was a population-based retrospective cohort study of infants born to residents of Ontario, Canada between April 1, 2012, and March 31, 2017 (Supplemental Fig 2 depicting the study design is provided in the Supplemental Information). Although all live births included in this study occurred before the 2018 Canadian statement recommending Tdap immunization in pregnancy, some care providers had already adopted this practice, likely on the basis of international recommendations or previous Canadian recommendations to offer Tdap to pregnant women who had never received their adult booster or during pertussis outbreaks.[19] We used data from several health administrative databases, which were linked using unique encoded identifiers and analyzed at ICES, a not-for-profit provincial research institute (https://www.ices.on.ca/).

Maternal-infant pairs were identified using the MOMBABY database, which links the hospital delivery records of mothers with corresponding newborn records from the Canadian Institute for Health Information Discharge Abstract Database. The database contains information on maternal and newborn characteristics and up to 25 diagnoses identified using the Canadian version of the 10th revision of *International Classification of Diseases*. Diagnostic codes in the maternal hospitalization record were used to ascertain preexisting maternal medical conditions and obstetrical complications (see Supplemental Table 3 for codes). We additionally linked the following databases: Registered Persons Database to provide information on health care eligibility, region of residence, and neighborhood income; Ontario Health Insurance Plan (OHIP) Database to ascertain health care billing information made by physicians, including Tdap vaccination, receipt of prenatal care, and outpatient health care use; Ontario Asthma Dataset to identify cases of pediatric asthma and maternal preexisting asthma; and the Ontario Cancer Registry to identify diagnoses of pediatric cancer.

Infants were followed until March 31, 2018, resulting in a minimum of 1 year of follow-up to a maximum of 6 years. Follow-up began on the date of birth and continued until the child was no longer eligible for Ontario health coverage (because of emigration from the province or death) or reached the end of the study period, whichever occurred first.

To ensure that maternal immunization information was captured in the provincial data sets, women who were not continuously eligible for health care in Ontario throughout their pregnancy were excluded. We additionally excluded women younger than 12 years of age or older than 50, as well as infants who were missing gestational age information, who died on their date of birth, or who did not have a record of becoming eligible to receive provincial health care within 60 days of birth, because we could not track their health outcomes in the databases.

Exposures and Outcomes

We defined exposure as Tdap received between 14 days after the mother's last menstrual period to 1 day before the newborn's date of birth. The date of the last menstrual period was derived by subtracting the newborn's gestational age from the date of birth. Tdap vaccination was identified using a specific Tdap fee code (G847) in the OHIP database. Pertussis vaccinations in Ontario are almost exclusively administered through physician's offices, and ~94% of physicians submit claims to the province's universal health care plan.[20]

Three prespecified categories of childhood morbidity outcomes were assessed. We included immune-related outcomes (infections and asthma), because prenatal exposures

such as maternal immunization could theoretically have later immunologic effects on offspring.[21,22] Pediatric infections included upper and lower respiratory infections, gastrointestinal infections, and otitis media. We included 2 nonimmune-related morbidity outcomes (sensory disorders [hearing loss and vision loss], neoplasm); these outcomes have been used as general safety outcomes in other studies of exposures during pregnancy.[23,24] Finally, we included a nonspecific outcome (urgent and inpatient health service use) to allow for a more comprehensive assessment of potential adverse events, which might be missed in analyses focusing only on specific outcomes.[25]

We searched for Canadian version of the 10th revision of *International Classification of Diseases* diagnostic codes (see Supplemental Table 4) within the Canadian Institute for Health Information Discharge Abstract Database and CIHI National Ambulatory Care Reporting System to ascertain most outcomes; these databases contain patient-level data from hospital admissions and emergency department visits, respectively. To reduce the chance of the same infection being counted multiple times, we used an episode of care in which an emergency department visit or hospitalization with the same specified diagnostic codes within 1 day of each other was counted as 1 infection, but those separated by >1 day were counted separately. Incident cases of asthma were identified from the Ontario Asthma Dataset, which uses a validated algorithm (sensitivity 81%–91% and specificity 83%–90% among children[26,27]) to identify cases from inpatient and outpatient health administrative databases.[28] Because asthma is difficult to diagnose in young children, only those with a minimum of 3 years of follow-up were assessed for this outcome.[29] We used the Ontario Cancer Registry to ascertain confirmed diagnoses of pediatric cancer (neoplasm). Finally, to detect possible residual confounding as an alternate explanation for any observed associations, we included a negative control outcome (all-cause injuries).

Statistical Analyses

Because only a small percentage of records were missing covariate information (0.6%), we conducted a complete case analysis, excluding records with missing covariates. We described the characteristics of the study population using frequencies; standardized differences assessed the balance of baseline covariates between the 2 exposure groups, with an absolute standardized difference <0.10 indicative of good covariate balance.[30]

To account for confounding, we matched 5 unexposed infants to each Tdap-exposed infant on the basis of the propensity score, estimated by using a logistic regression model containing the following baseline characteristics: maternal age, parity, year of delivery, rural residence, neighborhood income quintile, geographic region, preexisting maternal medical conditions, obstetrical complications, multifetal gestation, infant sex, and adequacy of prenatal care[31] (see Supplemental Table 5, Supplemental Information 1). Infants were matched without replacement by using the greedy method, with a caliper width score of ±0.2 SDs.[30]

Rates of outcomes were expressed per 1000 person-days of follow-up and stratified by maternal vaccination status. We used Poisson regression for analyses of infection-related outcomes, health service use, and all-cause injuries (negative control outcome) because they are likely to occur multiple times in early childhood and are, therefore, count outcomes. Incidence rate ratios and 95% confidence intervals (CIs), estimated from the Poisson models, compared incidence rates between the Tdap-vaccinated and unvaccinated groups. For asthma, neoplasm, and sensory disorders, we were interested in the first event in a child rather than the total volume of occurrences, because the duration of these illness would be expected to be longer or possibly even chronic (eg, asthma). Cox proportional hazards regression was, therefore, used to compute hazard ratios and 95% CI for these time-to-event outcomes. We found the proportional hazards assumption for the Cox models to be fulfilled on the basis of examination of log(−log(survival)) curves, Schoenfeld residual plots, and Wald tests for interaction between exposure status and time.

In sensitivity analyses, we expanded the exposure definition to include generic vaccine codes (G538, G539) documented during pregnancy to additionally capture possible maternal Tdap vaccination (generic vaccine codes billed during the usual seasonal influenza vaccine period from October 1 to January 31 were not included in this expanded definition because of the possibility that these represented influenza immunizations). We conducted other sensitivity analyses to account for any differences in health care seeking or access. First, we repeated our main analyses with additional adjustment for maternal health care seeking behaviors: (1) number of outpatient visits in the 6 months before pregnancy and (2) number of nonobstetric 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 pregnancy, respectively. Second, we restricted the cohort to infants who were accessing the health care system, specifically, those who had at least 2 well-baby visits and/or routine pediatric immunization visits recorded in their first year of life.

Ethics Approval

Ethics approval for this project was obtained from the Children's Hospital of Eastern Ontario Research Ethics Board (Protocol No. 18/10PE), the Ottawa Health Science Network Research Ethics Board (Protocol No. 20180432-01H), and the ICES Privacy Office (Project No. 2019-0901-171-000).

RESULTS

Of the 659 821 maternal–child pairs identified, 34 178 (5.2%) were excluded, primarily for lack of continuous OHIP eligibility during pregnancy (n = 19 714 [3.0%]) and missing follow-up information in OHIP for the child (n = 9230 [1.4%]) (Fig 1). Of the remaining 625 643 pairs, 12 045 infants born to mothers immunized with Tdap during their pregnancy (1.9%) were propensity score matched to 60 225 unexposed infants. For the analysis of pediatric asthma, 4256 Tdap-exposed infants were matched to 21 280 unexposed infants, all of whom had a minimum of 3 years of follow-up time (Fig 1, Supplemental Table 6). In the unmatched study cohort, children born to Tdap-vaccinated women were more likely to be born later in the study period and to have a mother ≥25 years of age, who received adequate prenatal care and who had never previously given birth (Table 1). After propensity score matching, all baseline covariates were well balanced with standardized differences <0.10 (Table 1, Supplemental Table 6).

Crude incidence rates in the unmatched study sample were comparable between exposure groups for asthma; lower rates of respiratory tract infections, gastrointestinal infections, otitis media, and urgent and inpatient health service use were observed among Tdap-exposed infants (Table 2). In the propensity score–matched sample, we observed inverse associations with rates of upper respiratory infections (adjusted incidence rate ratio [aIRR], 0.94 [95% CI, 0.90–0.99]) and gastrointestinal infections (aIRR, 0.85; [95% CI, 0.79–0.91]), as well as with urgent and inpatient health service use (aIRR, 0.93 [95% CI, 0.91–0.96]) (Table 2). Tdap exposure was not associated with neoplasm (adjusted hazard ratio, 1.36 [95% CI, 0.76–2.44]) or with the negative control outcome, all-cause injuries (adjusted hazard ratio, 0.99 [95% CI, 0.95–1.03]), in the propensity score–matched sample, despite higher crude rates in exposed infants.

In sensitivity analyses, we expanded the Tdap exposure definition to include women with a generic vaccine code during their pregnancy but outside of influenza season (n = 14 934 Tdap-exposed infants matched to n = 29 334 unexposed). This had a negligible impact on our estimates (Supplemental Table 7). Additional sensitivity analyses accounting for maternal propensity to access health care for themselves before pregnancy (Supplemental Table 8) and for their infants in the first year of life (Supplemental Table 9) also had minimal impact on the point estimates and did not alter the interpretation of the main findings.

DISCUSSION

In this population-based retrospective cohort study, we did not observe any increased risk of adverse health outcomes in early childhood

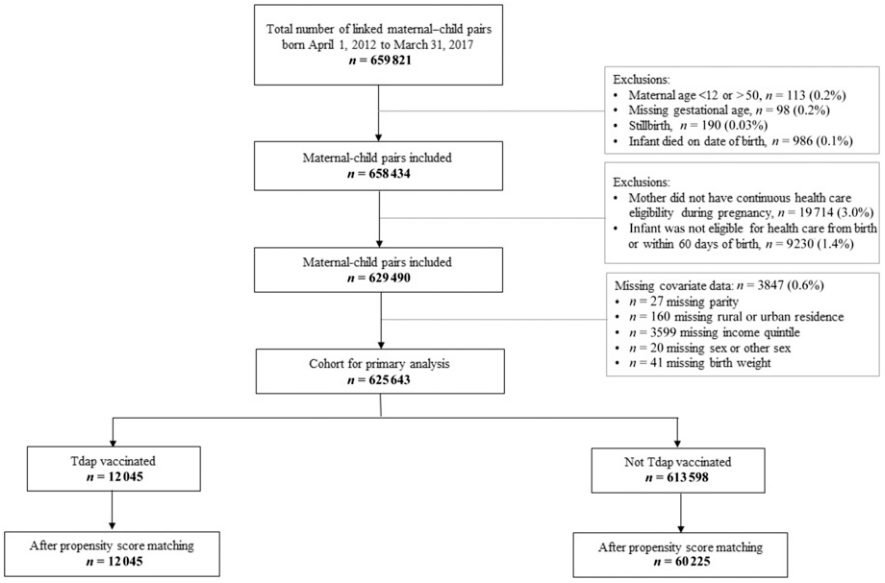

FIGURE 1
Study flow diagram.

TABLE 1 Baseline Characteristics of the Study Population before and after Propensity Score Matching, Ontario, Canada

Characteristic	Unmatched Cohort			Propensity Score–Matched Cohort		
	No. (%) of Births to Tdap-Vaccinated Women, *n* = 12 045	No (%) of Births to Tdap-Unvaccinated Women, *n* = 613 598	Std Diff[a]	No (%) of Births to Tdap-Vaccinated Women, *n* = 12 045	No (%) of Births to Tdap-Unvaccinated Women, *n* = 60 225	Std Diff[a]
Fiscal year of birth						
2012–2013	594 (4.9)	127 010 (20.7)	0.49	594 (4.9)	2984 (5.0)	0.00
2013–2014	1634 (13.6)	124 291 (20.3)	0.18	1634 (13.6)	8481 (14.1)	0.01
2014–2015	2093 (17.4)	123 218 (20.1)	0.07	2093 (17.4)	10 620 (17.6)	0.01
2015–2016	2899 (24.1)	121 299 (19.8)	0.10	2899 (24.1)	14 538 (24.1)	0.00
2016–2017	4825 (40.1)	117 780 (19.2)	0.47	4825 (40.1)	23 602 (39.2)	0.02
Maternal age, y						
<20	186 (1.5)	14 415 (2.3)	0.06	186 (1.5)	887 (1.5)	0.01
20–24	808 (6.7)	66 293 (10.8)	0.15	808 (6.7)	4004 (6.6)	0.00
25–29	3388 (28.1)	164 953 (26.9)	0.03	3388 (28.1)	17 204 (28.6)	0.01
30–34	4775 (39.6)	224 765 (36.6)	0.06	4775 (39.6)	23 940 (39.8)	0.00
≥35	2888 (24.0)	143 172 (23.3)	0.02	2888 (24.0)	14 190 (23.6)	0.01
Parity						
0 (nulliparous)	6203 (51.5)	270 753 (44.1)	0.15	6203 (51.5)	31 009 (51.5)	0.00
≥1 (multiparous)	5842 (48.5)	342 845 (55.9)	0.15	5842 (48.5)	29 216 (48.5)	0.00
Preexisting maternal medical condition[b]						
No	11 873 (98.6)	602 136 (98.1)	0.03	11 873 (98.6)	59 589 (98.9)	0.03
Yes	172 (1.4)	11 462 (1.9)	0.03	172 (1.4)	636 (1.1)	0.03
Type of preexisting maternal medical condition						
Asthma	1815 (15.1)	95 998 (15.6)	0.02	1815 (15.1)	8662 (14.4)	0.02
Chronic hypertension	43 (0.4)	2362 (0.4)	0.00	43 (0.4)	128 (0.2)	0.03
Diabetes	62 (0.5)	5076 (0.8)	0.04	62 (0.5)	210 (0.3)	0.03
Heart disease[c]	49 (0.4)	2986 (0.5)	0.01	49 (0.4)	165 (0.3)	0.02
Obstetrical complication[d]						
No	10 486 (87.1)	534 237 (87.1)	0.00	10 486 (87.1)	53 550 (88.9)	0.06
Yes	1559 (12.9)	79 361 (12.9)	0.00	1559 (12.9)	6675 (11.1)	0.06
Delivery by cesarean						
No	8763 (72.7)	436 568 (71.1)	0.04	8763 (72.8)	42 552 (70.7)	0.05
Yes	3282 (27.3)	177 030 (28.9)	0.04	3282 (27.2)	17 673 (29.3)	0.05
Multiple birth						
No	11 767 (97.7)	592 553 (96.6)	0.07	11 767 (97.7)	59 086 (98.1)	0.03
Yes	278 (2.3)	21 045 (3.4)	0.07	278 (2.3)	1156 (1.9)	0.03
Prenatal care index[e]						
Adequate	6445 (53.5)	251 492 (41.0)	0.25	6445 (53.5)	32 677 (54.3)	0.02
Inadequate	732 (6.1)	73 510 (12.0)	0.21	732 (6.1)	3607 (6.0)	0
Intensive	912 (7.6)	36 870 (6.0)	0.06	912 (7.6)	4187 (7.0)	0.02
Intermediate	3661 (30.4)	209 362 (34.1)	0.08	3661 (30.4)	18 369 (30.5)	0
No care	295 (2.4)	42 364 (6.9)	0.21	295 (2.4)	1385 (2.3)	0.01
Neighborhood median family income quintiles						
1 (Lowest)	2096 (17.4)	129 239 (21.1)	0.09	2096 (17.4)	10 585 (17.6)	0.00
2	2442 (20.3)	122 321 (19.9)	0.01	2442 (20.3)	12 497 (20.5)	0.01
3	2364 (19.6)	124 701 (20.3)	0.02	2364 (19.6)	11 726 (19.5)	0.00
4	2679 (22.2)	134 188 (21.9)	0.01	2679 (22.2)	13 375 (22.2)	0.00
5 (Highest)	2464 (20.5)	103 1429 (16.8)	0.09	2464 (20.5)	12 042 (20.0)	0.01
Rural residence						
No	10 914 (90.6)	550 586 (89.7)	0.03	10 914 (90.6)	54 928 (91.2)	0.02
Yes	1131 (9.4)	63 012 (10.3)	0.03	1131 (9.4)	5297 (8.8)	0.02
Public health unit region						
North west	131 (1.1)	10 855 (1.8)	0.06	131 (1.1)	516 (0.9)	0.02
North east	309 (2.6)	24 124 (3.9)	0.08	309 (2.6)	1341 (2.2)	0.02
Eastern	1966 (16.3)	76 286 (12.4)	0.11	1966 (16.3)	9705 (16.1)	0.01
Central east	4307 (35.8)	185 608 (30.3)	0.12	4307 (35.8)	21 536 (35.8)	0.00
Toronto	3503 (29.1)	126 614 (20.6)	0.20	3503 (29.1)	17 940 (29.8)	0.02
South west	528 (4.4)	69 380 (11.3)	0.26	528 (4.4)	2645 (4.4)	0.00
Central west	1301 (10.8)	120 731 (19.7)	0.25	1301 (10.8)	6542 (10.9)	0.00

TABLE 1 Continued

Characteristic	Unmatched Cohort			Propensity Score–Matched Cohort		
	No. (%) of Births to Tdap-Vaccinated Women, *n* = 12 045	No (%) of Births to Tdap-Unvaccinated Women, *n* = 613 598	Std Diff[a]	No (%) of Births to Tdap-Vaccinated Women, *n* = 12 045	No (%) of Births to Tdap-Unvaccinated Women, *n* = 60 225	Std Diff[a]
Sex						
Female	5858 (48.6)	299 118 (48.7)	0.00	5858 (48.6)	29 594 (49.1)	0.01
Male	6187 (51.4)	314 480 (51.3)	0.00	6187 (51.4)	30 631 (50.9)	0.01
Birth wt, g						
<1500	44 (0.4)	5316 (0.9)	0.06	44 (0.4)	489 (0.8)	0.06
1500–2499	545 (4.5)	33 866 (5.5)	0.05	545 (4.5)	3058 (5.1)	0.03
2500–3499	6752 (56.1)	332 489 (54.2)	0.04	6752 (56.1)	33 876 (56.2)	0.00
≥3500	4704 (39.0)	241 927 (39.4)	0.01	4704 (39.1)	22 802 (37.9)	0.02
Gestational age at birth in wk						
<31	56 (0.5)	6134 (1.0)	0.06	56 (0.5)	557 (0.9)	0.05
32–33	63 (0.5)	5687 (0.9)	0.05	63 (0.5)	464 (0.8)	0.03
34	88 (0.7)	5990 (1.0)	0.03	88 (0.7)	503 (0.8)	0.01
35	152 (1.3)	10 020 (1.6)	0.03	152 (1.3)	888 (1.5)	0.02
36	366 (3.0)	20 119 (3.3)	0.01	366 (3.0)	1869 (3.1)	0.00
≥37 (term)	11 320 (94.0)	565 648 (92.2)	0.07	11 320 (94.0)	55 944 (92.9)	0.04
Median follow-up time in person-yr (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)	—

Std Diff, standardized difference; —, not applicable.

[a] Standardized difference >0.10 indicates imbalance between Tdap-vaccinated and unvaccinated subjects.

[b] Asthma, chronic hypertension, diabetes, or heart disease.

[c] Cardiac valvular disease, congenital heart disease, chronic congestive heart failure, hypertensive heart disease, or chronic ischemic heart disease.

[d] Eclampsia, gestational diabetes, placenta previa, placental abruption, pre-eclampsia, or pregnancy-induced hypertension.

[e] Adequacy of prenatal care characterized using the Revised-Graduated Prenatal Care Use Index (see Supplemental Information 1 for description).

among infants born to mothers who were immunized with Tdap during pregnancy. Specifically, there was no association between Tdap vaccination during pregnancy and asthma, otitis media, neoplasm, or sensory disorders. We observed statistically significant reductions in rates of upper respiratory infections, gastrointestinal infections, and urgent and inpatient health service use; the magnitude of these reductions ranged from 6% to 15%.

Research to date on the safety of maternal Tdap vaccination during pregnancy has been focused on obstetric and neonatal outcomes; findings have been reassuring, with studies reporting no increased risk of preterm birth or small for gestational age birth after Tdap vaccination in pregnancy.[32–40] Three studies reported a small increased risk of chorioamnionitis among Tdap-vaccinated pregnant women, although no increases in sequelae of chorioamnionitis, such as preterm birth, were observed.[37,41,42] The few studies in which longer-term health outcomes were assessed have mostly been 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 (a composite outcome that includes neoplasm) in the first year.[14,40,43–46] In 2 studies of Tdap vaccination in pregnancy, researchers followed infants for a longer period. Becerra-Culqui et al[14] compared the incidence of autism spectrum disorder in children followed up to 6.5 years of age and found no difference between those exposed and unexposed to prenatal Tdap. Authors of a subsequent study of the same cohort reported no association between Tdap during pregnancy and attention-deficit/hyperactivity disorder in offspring.[15] A related body of research on long-term pediatric health outcomes after influenza immunization during pregnancy has some relevance to this discussion. In a recent systematic review, just 9 such studies were identified, the majority of which were conducted to assess early childhood outcomes after prenatal vaccination with 2009 influenza A virus subtype H1N1 (A/H1N1) pandemic monovalent influenza vaccines.[47] No meta-analysis was possible owing to variability in outcomes assessed; 2 studies recorded risk reductions for upper respiratory tract infection, all-cause hospitalization, and gastrointestinal infection in offspring exposed to maternal 2009 A/H1N1 pandemic influenza vaccination. Although there were singular findings of increased risk of asthma, sepsis, Sjögren syndrome, and autism, none were significant after accounting for multiplicity of outcomes assessed.[47]

We observed a small inverse association between Tdap vaccination during pregnancy and rates of upper and lower respiratory infections. In a case-control study, Sukumaran et al[46] observed a lower odds of maternal Tdap vaccination among infants with a respiratory-related

TABLE 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)	Adjusted Estimate From Matched Sample (95% CI)
	No. Events	Incidence Rate (95% CI) per 1000 Person-Years	No. Events	Incidence Rate (95% CI) per 1000 Person-Years		
Atopic disease						
Asthma[a,b]	461	28.2 (25.7–30.9)	43 757	28.4 (28.1–28.7)	0.95 (0.87–1.04)	0.93 (0.82–1.04)
Infectious disease						
Upper respiratory infections[c]	4303	135.3 (129.7–141.1)	311 405	144.8 (144.0–145.6)	0.93 (0.90–0.97)	0.94 (0.90–0.99)
Lower respiratory infections[c]	1787	56.2 (53.0–59.6)	129 960	60.4 (60.0–60.9)	0.93 (0.88–0.99)	0.94 (0.88–1.00)
Gastrointestinal infections[c]	1077	33.9 (31.7–36.2)	77 783	36.2 (35.9–36.5)	0.94 (0.88–1.00)	0.85 (0.79–0.91)
Otitis media[c]	1851	58.2 (54.8–61.8)	137 293	63.9 (63.4–64.4)	0.91 (0.86–0.97)	0.97 (0.91–1.04)
Non-immune-related morbidity outcomes						
Neoplasm[b]	14	0.44 (0.26–0.74)	658	0.31 (0.28–0.33)	1.51 (1.07–2.13)	1.36 (0.76–2.44)
Sensory disorders[b]	8	0.25 (0.13–0.50)	764	0.36 (0.33–0.38)	0.70 (0.35–1.41)	0.72 (0.34–1.52)
Nonspecific morbidity outcome						
Rates of urgent and inpatient health service utilization[c]	22 965	722.1 (703.6–741.5)	1 615 068	751.1 (748.3–753.9)	0.96 (0.94–0.99)	0.93 (0.91–0.96)
Negative-control outcome						
All-cause injuries[b]	2527	90.6 (87.2–94.1)	172 244	95.9 (95.4–96.3)	1.32 (1.27–1.38)	0.99 (0.95–1.03)

[a] Cohort for asthma is restricted to children with a minimum of 3 y of follow-up.

[b] 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.

[c] 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.

hospitalization in the first 6 months of life compared with control infants (adjusted odds ratio, 0.79 [95% CI, 0.67–0.94]). Given only 3% of infants hospitalized for respiratory causes had a pertussis-specific *International Classification of Diseases* code documented on their hospital record, the investigators posited that the observed association might be due to under-diagnosis and/or under-reporting of pertussis or possible residual confounding.[46] We also observed an inverse association between maternal Tdap vaccination during pregnancy and gastrointestinal infection. Although no other published research has investigated this outcome after Tdap vaccination during pregnancy, 2 studies of 2009 pandemic A/H1N1 vaccination during pregnancy and longer-term childhood morbidity outcomes by Hviid et al[48] and Walsh et al[24] also revealed inverse associations with gastrointestinal infections (adjusted rate ratio, 0.84 [95% CI, 0.74–0.94] and aIRR, 0.94 [95% CI, 0.91–0.98], respectively). One possible explanation is residual confounding due to a "healthy vaccinee effect," an increased likelihood of vaccinated mothers to engage in other behaviors that have health benefits, such as exclusive breastfeeding or ensuring rotavirus vaccination in their children. We were unable to account for these factors directly but attempted to address the latter through a sensitivity analysis in which we restricted the cohort to infants who had at least 2 well-baby or routine immunization visits during the first year to see if the association was present among infants more likely to have received their rotavirus vaccine. Following this restriction, the estimate of association remained statistically significant and was only slightly attenuated.

Strengths and Limitations

The main strength of this study was the availability of population-based databases that contained sociodemographic, clinical, and vaccination information in pregnant women linked with up to 6 years of follow-up information on health outcomes in their infants. Use of this large study population allowed for a large sample of mother–child pairs to be analyzed, despite the low percentage of pregnant women vaccinated with Tdap in Ontario during the study period. These data sets have low rates of loss to follow-up, and few subjects were excluded because of missing data.

Propensity score methods have been shown to effectively reduce bias in studies using large administrative databases[49,50]; we were able to demonstrate improved comparability of exposed and unexposed subjects following propensity score matching. Although it is reassuring that there was no association with the negative control outcome (all-cause injury rates), we cannot rule out the possibility that residual confounding biased our estimates. If unmeasured confounders associated with a higher risk of adverse outcomes were more prevalent in the unvaccinated group, or if those associated with a lower risk of adverse outcomes were more

prevalent in the Tdap-vaccinated group, our estimates would have been biased downward, potentially obscuring an increased risk. Other limitations include possible nondifferential exposure or outcome misclassification, which would have attenuated the magnitude of our estimates.[51] The impact of nondifferential misclassification of an uncommon exposure, such as Tdap in this study, is minimal when specificity is high,[51] and vaccine-specific fee codes in Ontario have high specificity (eg, 96% for influenza immunizations and 89%–92% for infant immunizations).[20,52] Finally, despite the large size of our study, we were still underpowered to rule out increased risks for the rarest outcomes, such as neoplasm, which had a low number of events in the Tdap-exposed group. Given the high uncertainty and elevated point estimate, this outcome should be assessed by future larger studies.

CONCLUSIONS

Exposure to Tdap during pregnancy was not associated with any increased risk of infection, asthma, neoplasm, sensory disorders, or urgent and inpatient health service use in children in their first 6 years of life, supporting the long-term safety of Tdap administration in pregnancy. Additional larger studies are needed to corroborate these findings, particularly for rare outcomes, and a core set of standardized long-term pediatric health outcomes for ongoing surveillance of maternal immunization worldwide would enhance comparability of future such studies.

ABBREVIATIONS

A/H1N1: influenza A virus subtype H1N1
aIRR: adjusted incidence rate ratio
CI: confidence interval
OHIP: Ontario Health Insurance Plan
Tdap: tetanus, diphtheria, and acellular pertussis vaccine

Ms Laverty contributed to the study concept and design, performed the statistical analyses, contributed to the interpretation of data, drafted the manuscript, and critically reviewed the manuscript for important intellectual content; Ms Sucha performed the statistical analyses, contributed to the interpretation of data, and critically reviewed the manuscript for important intellectual content; Ms Fakhraei and Drs Crowcroft, Bolotin, Hawken, Wilson, Amirthalingam, Biringer, Cook, Dubey, Halperin, Jamieson, Kwong, Sadarangani, and Walker contributed to the study concept and design, contributed to the interpretation of data, and critically reviewed the manuscript for important intellectual content; Dr Fell contributed to the study concept and design, contributed to the interpretation of data, drafted the manuscript, critically reviewed the manuscript for important intellectual content, obtained funding, and supervised the study; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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