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Pregnancy, fetal, and neonatal outcomes after a first booster dose of covid-19 vaccine during pregnancy in Ontario, Canada: population based, retrospective cohort study

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ABSTRACT

OBJECTIVE To assess risk of adverse pregnancy, fetal, and neonatal outcomes after a third dose (first booster dose) of covid-19 vaccine during pregnancy among individuals who had completed both doses of primary covid-19 vaccine series before pregnancy.

DESIGN Population based, retrospective cohort study.

SETTING Ontario, Canada, from 20 December 2021 to 31 August 2022.

PARTICIPANTS Individuals were included if they were pregnant with an expected date of delivery from 20 December 2021 (start date of third dose eligibility for everyone ≥18 years) to 31 August 2022, who had completed the two doses of primary covid-19 messenger RNA vaccine series before pregnancy, and became eligible for a third dose (≥six months since dose two) before the end of pregnancy.

MAIN OUTCOME MEASURES Pregnancy outcomes included hypertensive disorders of pregnancy, placental abruption, caesarean delivery, chorioamnionitis, and postpartum hemorrhage. Fetal and neonatal outcomes included stillbirth, preterm birth, admission to neonatal intensive care unit for >24 h, newborn 5 min Apgar score <7, and small-for-gestational age infant (<10th percentile). We estimated hazard ratios and 95% confidence intervals for study outcomes, treating dose three as a time varying exposure and adjusting for confounding using inverse probability weighting.

RESULTS Among 32 689 births, 18 491 (56.6%) were born to individuals who received a third covid-19 dose during pregnancy. Compared with eligible individuals who did not receive a third dose during pregnancy, no increased risks were associated with receiving a third covid-19 vaccine dose during pregnancy for placental abruption (adjusted hazard ratio 0.84 (95% confidence interval 0.70 to 1.02)), chorioamnionitis (0.67 (0.49 to 0.90)), postpartum haemorrhage (1.01 (0.89 to 1.16)), caesarean delivery (0.90 (0.87 to 0.94)), stillbirth (0.56 (0.39 to 0.81)), preterm birth (0.91 (0.84 to 0.99)), neonatal intensive care unit admission (0.96 (0.90 to 1.03)), 5 min Apgar score<7 (0.96 (0.82 to 1.14)), or small-for-gestational age infant (0.86 (0.79 to 0.93)).

CONCLUSION Receipt of a third covid-19 vaccine dose during pregnancy was not associated with an increased risk of adverse pregnancy, fetal, or neonatal outcomes. These findings can help to inform evidence based decision making about the risks and benefits of covid-19 booster doses during pregnancy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Covid-19 illness during pregnancy is associated with an increased risk of adverse maternal and birth outcomes
⇒ Receiving the primary covid-19 vaccine series during pregnancy reduces the risk of covid-19 illness in pregnant individuals and their newborn infants
⇒ No adverse pregnancy or neonatal outcomes have been identified following the primary messenger RNA covid-19 vaccine series administered during pregnancy

WHAT THIS STUDY ADDS

⇒ Among people who had completed their primary covid-19 vaccine series before pregnancy, receiving a third dose during pregnancy did not increase risk of adverse pregnancy, fetal, and neonatal outcomes compared with no booster dose during pregnancy

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Given evidence of waning immunity and known risks of covid-19 illness during pregnancy, the results can help to inform evidence based decision making about the risks and benefits of covid-19 booster doses during pregnancy

Introduction

Covid-19 illness during pregnancy is associated with an increased risk of hospital and intensive care unit admission, mechanical ventilation, and even death of pregnant individuals.[1 2] Higher risks of preterm birth, stillbirth, small-for-gestational age at birth, and other pregnancy complications as a result of covid-19 during pregnancy have also been documented.[3–5] Receiving the primary covid-19 vaccine series during pregnancy reduces the risk of covid-19 illness in pregnant individuals[6] and their newborn infants.[7–9] Covid-19 vaccination during pregnancy has not been associated with any increased risk of clinically serious acute adverse events in pregnant

people[10] nor with any elevated risks of adverse pregnancy or neonatal outcomes.[11–16] Despite widespread recommendations for covid-19 vaccination during pregnancy globally,[17] lower coverage among pregnant individuals has been noted in several settings, including in Ontario, Canada.[18]

Due to waning effectiveness of the primary covid-19 vaccine series against symptomatic infection and severe outcomes (ie, admission to hospital or death) in the general population,[19] along with the emergence of the omicron variant of concern, a third dose (ie, first booster dose) of covid-19 vaccine was recommended in Ontario in mid-December 2021 for all individuals aged 18 years or older.[20] Initial recommendations from the National Advisory Committee on Immunization in December 2021[21] (reaffirmed in September 2022[22]) advised pregnant individuals, in any trimester of pregnancy, to receive a booster dose of an authorised messenger RNA (mRNA) covid-19 vaccine six months (168 days) after completion of a primary covid-19 vaccine series. Evidence has been shown that receiving a booster dose improves effectiveness against severe covid-19 outcomes during pregnancy.[9]

Although no adverse pregnancy or neonatal outcomes have been identified following the primary mRNA covid-19 vaccine series administered during pregnancy,[11–16] only a small number of studies to date have evaluated pregnancy and birth outcomes following receipt of the third dose in pregnancy.[23–26] These studies have, similarly, not identified any safety concerns; however, they have predominantly been small in size and not population based. Evidence from large populations could help to inform ongoing risk-benefit considerations for covid-19 booster doses among pregnant people who had already completed their primary covid-19 vaccine series prior to pregnancy. The objective of this population based study was, therefore, to assess whether there was any association between receiving a third mRNA covid-19 vaccine dose (ie, first booster dose) during pregnancy, compared with not receiving a third dose during pregnancy with risk of adverse pregnancy, fetal, or neonatal outcomes. This study was limited to individuals who had already completed their primary covid-19 vaccine series before pregnancy.

Methods

Study design, setting, and population

We followed the RECORD guidance for reporting observational studies[27] and methodological guidance for conducting studies of covid-19 vaccination during pregnancy[28 29] and influenza vaccination during pregnancy.[30]

The design was a retrospective population based cohort study, conducted in Ontario, Canada's most populous province, with approximately 14.7 million residents and 140 000 births annually. All Ontario residents are eligible to receive publicly funded healthcare, including services for prenatal and obstetrical care. We based the inclusion criteria for selecting the study population on recommendations for emulating a target trial.[29] Pregnant individuals were eligible for inclusion in the study if: (1) they had an expected date of delivery between 20 December 2021 (ie, when Ontario's booster campaign expanded to everyone 18 years and older[20]) and 31 August 2022; (2) had completed the two doses of their primary covid-19 vaccine series before the date of their last menstrual period; and (3) became eligible to receive a third dose any time between their last menstrual period and the end of their pregnancy, defined as six months after dose two (ie, dose two date+168 days[31]). Individuals who had already received a third dose of covid-19 vaccine before their last menstrual period were excluded, as were individuals whose third dose was a non-mRNA covid-19 vaccine, owing to small numbers. Additionally, records of individuals who gave birth at less than 20 weeks' gestational age and with a birth weight of less than 500 g, or who had a pregnancy termination, were also excluded as these events are not systematically collected in the birth registry.[32]

Data sources

We used the provincial birth registry (Better Outcomes Registry & Network (BORN) Ontario[32]) to identify the study population and obtain information on all outcomes, as well as maternal demographic and pregnancy characteristics, pre-existing health issues, and health behaviours. The registry receives integrated maternal-newborn records for all live birth and stillbirth events at 20 weeks' gestation or more or birth weight of 500 g or more from hospitals, birth centers, and midwifery practice groups (including home births) across Ontario.[32] Registry data are collected from health records, clinical forms, and patient interviews during clinical encounters and have been found to be of high quality in a validation study.[33] We deterministically linked the study population to the provincial database that captures all covid-19 immunisation events (known as COVaxON), regardless of setting where administered, to obtain information about covid-19 vaccine product, dose number, and date of vaccination. The maternal residential postal code was used to link the study population to the Statistics Canada's 2016 Census to determine rural or urban residence and dissemination area based household income fifth, and to the Ontario Marginalization Index, which provides area based measures of social and economic marginalisation.[34] Finally, we deterministically linked the study population to the Public Health Case and Contact Management Solution[35] to identify laboratory confirmed SARS-CoV-2 infections before or during pregnancy. Details on all data sources are provided in online supplemental table 1.

Outcome measures

Third covid-19 vaccine dose during pregnancy

A summary of the recommendations, timing, and coverage of primary covid-19 series vaccination in the pregnant population in Ontario can be found elsewhere.[15 16 18] Implementation of third doses in Ontario (ie, first booster doses) occurred in August 2021 and was initially limited to residents of high risk congregate settings for seniors, such as long term care homes. Over the course of the fall of 2021, eligibility expanded to include older adults, healthcare workers, and eventually, to all individuals aged 18 years and older (including pregnant and breastfeeding individuals) by mid-December 2021.[20–22] Canada's National Advisory Committee on Immunization recommended a 168 day (six month) interval between the second and third dose, but after the emergence of the omicron variant, the Ontario government reduced the minimum interval to 84 days (three months) on 15 December 2021.[20]

We obtained information on receipt of a third covid-19 vaccine dose during pregnancy from the COVaxON database. By virtue of the study inclusion criteria, all pregnant individuals included in this study were eligible to receive a third dose during their pregnancy. People who received a third dose any time between the last menstrual period date up to one day before delivery (or before the end of the outcome specific follow-up window for preterm birth outcomes (36 weeks+6 days for preterm birth; 31 weeks+6 days for very preterm birth)) were considered exposed. Whereas, people who did not receive a third covid-19 vaccine dose before the end of pregnancy (or before the end of the outcome specific follow-up window for preterm birth outcomes) were considered unexposed. We classified the gestational timing of the third dose as first trimester (pregnancy day 1 to 13 weeks+6 days), second trimester (14 weeks+0 days to 27 weeks+6 days), or third trimester (28 weeks+0 days to end of follow-up); gestational age in days is recorded in the birth registry and most dating of pregnancies in Ontario is on the basis of early ultrasound assessment.

Pregnancy, fetal, and neonatal outcomes

We studied the following pregnancy outcomes: hypertensive disorders of pregnancy, placental abruption, caesarean delivery, emergency caesarean delivery, chorioamnionitis, and postpartum hemorrhage. Fetal and neonatal outcomes included stillbirth, preterm birth, very preterm birth, spontaneous or clinician-initiated preterm birth, admission to neonatal intensive care unit for more than 24 h, newborn 5 min Apgar score of less than 7, and small-for-gestational age birth (<10th percentile). Detailed definitions of all study outcomes can be found in online supplemental table 2.

Covariates

We used propensity score methods to adjust for a range of variables potentially associated with receiving a third dose of covid-19 vaccine during pregnancy or for study outcomes, or both. The following variables were included in the propensity score models: maternal age at delivery (<25 years, 25-29 years, 30-34 years, 35-39 years, ≥40 years); prepregnancy body mass index of 30 or higher (*v* <30); self-reported smoking status (yes or no) or substance use (ie, cannabis, opioid, or alcohol use) during pregnancy (yes or no); public health unit region (seven regions); pre-existing maternal health conditions (composite of: asthma, chronic hypertension, diabetes, heart disease, thyroid disease; yes or no); parity (nulliparous *v* multiparous); multifetal pregnancy (yes or no); rural or urban residence; neighbourhood income grouping (fifths); neighbourhood marginalisation (four dimensions: residential instability, material deprivation, dependency, and ethnic group concentration); calendar week of last menstrual period (continuous); and first prenatal care visit in the first trimester (yes or no). Additional details on covariate definitions are provided in online supplemental table 2. The percentage of missing data for any individual covariate included in the propensity scores was less than 5% (range 0.5-4.2%), with the exception of body mass index, which had 11.8% missing.

Statistical analysis

We described the distribution of baseline characteristics in the study population overall and according to exposure group (ie, received a third dose during pregnancy *v* did not receive a third dose during pregnancy). We compared unweighted and inverse probability of treatment weighted distributions using absolute standardised differences, where a value of less than 0.1 was considered indicative of a balanced distribution across the two groups.[36] Inverse probability weights were computed using a logistic regression model to derive a propensity score. This score represented the predicted probability of receiving a third dose of covid-19 vaccine during pregnancy, conditional on the covariates described previously (additional details about inverse probability of treatment weight derivation are provided in the online supplemental appendix 1).

We used extended Cox proportional hazards regression models to estimate hazard ratios with 95% confidence intervals. Gestational age in days was used as the underlying time scale, with follow-up starting at 20 weeks, which is the lower gestational age limit for defining all study outcomes in the birth registry.[29 30] Receipt of the third covid-19 vaccine dose was treated as a time varying exposure after the start of follow-up. Pregnant individuals who received the third dose after the start of follow-up contributed both unexposed and exposed time. Those who received the third dose during pregnancy but prior to 20 weeks contributed only exposed time. Those who did not receive a third dose during pregnancy contributed

only unexposed time. Follow-up continued until the end of pregnancy for all outcomes except preterm birth, for which the end of follow-up was 36 weeks+6 days of gestation (pregnancy day 258) and very preterm birth, for which follow-up ended at 31 weeks+6 days (pregnancy day 223). We used the stabilised inverse probability of treatment weights in the Cox models to generate adjusted hazard ratios.[36] All outcome models were fitted using each of the 10 probability weights from the 10 imputed datasets, and the results were combined using the MIANALYZE procedure in SAS. Robust sandwich variance estimation was used to account for statistical dependence across repeated observations due to the time varying exposure variable.

For the assessment of hypertensive disorders of pregnancy, we limited the exposed group to those who had received their third covid-19 dose before 20 weeks. We used this restriction to ensure the correct temporal order of the exposure to outcome relation because gestational hypertensive disorders are diagnosed after 20 weeks of gestation, but we did not have the exact date of diagnosis.[37] For assessment of preterm birth subtypes, we fit separate models for spontaneous and clinician initiated preterm birth, and censored the other subtype at birth. For the analysis of small-for-gestational age birth, we lagged the date that the third dose was received by 14 days because any potential adverse effect of vaccination on fetal growth would take time to become apparent.[13]

We performed subgroup analyses to evaluate trimester specific and product specific estimates for the third mRNA covid-19 dose (ie, BNT162b2 (Comirnaty, Pfizer-BioNTech) and mRNA-1273 (Spikevax, Moderna)). During this study, all booster doses were original formulations (not bivalent) because bivalent mRNA products were not authorised by Health Canada until after 31 August 2022. In sensitivity analyses, we reassessed study outcomes after excluding individuals who had a laboratory confirmed covid-19 illness before or during their pregnancy.

Patient and public involvement

This research was done without direct patient involvement, however, our study team included four obstetricians (MCW, DE-C, JB, NO) who were involved from the outset of planning the study and brought forward their experiences from patient interactions related to covid-19 vaccination during pregnancy. These experiences were taken into consideration when planning this research, and its wide dissemination, to ensure the findings were relevant, accessible, and more likely to be useful for a broad group of knowledge users, including pregnant individuals.

Results

Overall, 86 824 live births and stillbirths occurred in Ontario during the study period; of these, 53 905 were excluded because both doses of the primary covid-19 vaccine series had not been received before the last menstrual period date (online supplemental figure 1). After additional exclusions, 32 689 live births and stillbirths, corresponding to 32 125 unique pregnancies, met all eligibility criteria and were included in the study (figure 1). People who received a third covid-19 vaccine dose during pregnancy had 18 491 (56.6%) live births and stillbirths. The temporal distribution of last menstrual period dates by exposure group was generally similar (online supplemental figure 2), as was the distribution of third dose eligibility dates (online supplemental figure 3). The time interval between the date of the second dose and the last menstrual period date was longer among individuals who received a third dose during pregnancy (median 11.0 weeks) than among those who did not receive a third dose in pregnancy (median 8.9 weeks; table 1). Overall, exposed pregnancies tended to occur slightly earlier in calendar time

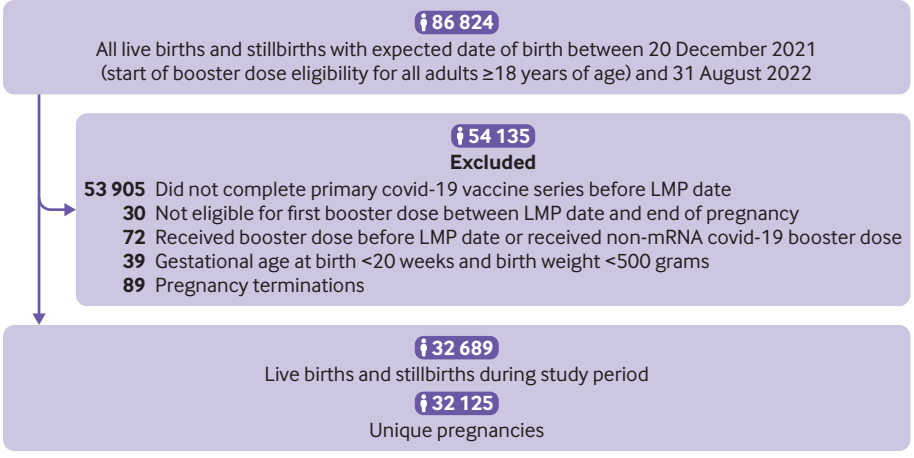

Figure 1 | Study flow diagram. Number of individuals who received a non-mRNA covid-19 vaccine as their third dose during pregnancy could not be shown separately as the number was <6. LMP=last menstrual period; mRNA=messenger RNA

Table 1 | Vaccination characteristics of study participants

	Received third covid-19 vaccine dose during pregnancy (n=18 491)	Did not receive third covid-19 vaccine dose during pregnancy (n=14 198)
Time in days, (weeks) between second dose and LMP:		
<56 days (<8 weeks)	6544 (35.4)	6380 (44.9)
56 to <84 days (8 to <12 weeks)	3555 (19.2)	2764 (19.5)
84 to <112 days (12 to <16 weeks)	3350 (18.1)	2466 (17.4)
112 to <140 days (16 to <20 weeks)	2770 (15.0)	1715 (12.1)
140 to <168 days (20 to <24 weeks)	1215 (6.6)	552 (3.9)
≥168 days (≥24 weeks)	1057 (5.7)	321 (2.3)
Median days	77 (40-115)	62 (30-100)
Median weeks	11.0 (5.7-16.4)	8.9 (4.3-14.3)
Vaccine products received for primary covid-19 series:		
BNT162b2+BNT162b2*	11 438 (61.9)	9188 (64.7)
mRNA-1273+mRNA-1273*	3407 (18.4)	3009 (21.2)
BNT162b2+mRNA-1273 or mRNA-1273+BNT162b2†	3361 (18.2)	1877 (13.2)
Other‡	285 (1.5)	124 (0.9)
Time in days, weeks, between second dose and third dose:		
<168 days (<24 weeks)	1132 (6.1)	—
168 to <196 days (24 to <28 weeks)	7945 (43.0)	—
196 to <224 days (28 to <32 weeks)	5030 (27.2)	—
≥224 days (≥32 weeks)	4384 (23.7)	—
Median days	196 (182-221)	—
Median weeks	28.0 (26.0-31.6)	—
Trimester when third covid-19 dose received:		
First	5484 (29.7)	—
Second	11 332 (61.3)	—
Third	1675 (9.1)	—
Median gestational age in days	126 (91-163)	—
Median gestational age in weeks	18.0 (13.0-23.3)	—
mRNA vaccine received for third dose:		
BNT162b2 (Comirnaty, Pfizer-BioNTech)	11 281 (61.0)	—
mRNA-1273 (Spikevax, Moderna)	7210 (39.0)	—

Data are number (percentage) or median (interquartile range). LMP=last menstrual period; mRNA=messenger RNA.
*Same type of mRNA vaccine for dose one and dose two (homologous mRNA series).
†Different type of mRNA vaccine for dose one and dose two (heterologous mRNA series).
‡AstraZeneca/Oxford's covishield Novavax's nuvaxovid covid-19 vaccine; unspecified.

(online supplemental figure 4). Most individuals in both groups (>80%) received a homologous primary mRNA covid-19 vaccine series (table 1).

Most individuals who received dose three during pregnancy were vaccinated between 1 November 2021 and 28 February 2022 (online supplemental figure 5) and received dose three at a median of 196 days (28 weeks) after dose two (table 1; online supplemental figure 6). The median gestational age when dose three was received was 126 days (18 weeks); 29.7% were vaccinated in the first trimester, 61.3% in the second trimester, and 9.1% in the third trimester (table 1; online supplemental figure 7). Baseline characteristics before and after inverse probability weighting are provided in table 2, with additional variables presented in online supplemental table 3. Compared with individuals who did not receive a third dose of covid-19 vaccine during pregnancy, people who did were more likely to be 30 years or older and live in neighbourhoods with the highest median household income and lowest material deprivation. Individuals who received the third dose during pregnancy were also less likely to report smoking or substance use (ie, cannabis, opioid, or alcohol use). Following inverse probability weighting, absolute standardised differences for all variables other than the highest category of maternal age were less than 0.1, indicating that baseline characteristics were well balanced across the two exposure groups.

The proportion of individuals who received a third dose of covid-19 vaccine during pregnancy was lower

Table 2 | Characteristics of study population overall and by status of third covid-19 vaccine dose received during pregnancy

Characteristics	Unweighted			Stabilised inverse probability of treatment weighted *		
	Received third covid-19 vaccine dose during pregnancy (n=18 491), n (%)	Did not receive third covid-19 vaccine dose during pregnancy (n=14 198), n (%)	Standardised difference †	Received third covid-19 vaccine dose during pregnancy, %	Did not receive third covid-19 vaccine dose during pregnancy, %	Standardised difference †
Maternal age at delivery (years):						
<25	453 (2.4)	988 (7.0)	0.21	3.9	4.8	0.05
25-29	3130 (16.9)	3802 (26.8)	0.24	20.2	22.2	0.05
30-34	8351 (45.2)	5756 (40.5)	0.09	45.1	40.1	0.10
35-39	5414 (29.3)	2919 (20.6)	0.20	25.8	24.9	0.02
≥40	1143 (6.2)	733 (5.2)	0.04	4.9	8.0	0.13
Mean (standard deviation)	33.5 (4.2)	32.0 (4.8)	0.34	32.9 (4.3)	32.9 (4.8)	0.02
Parity:						
0 (nulliparous)	8987 (48.6)	6447 (45.4)	0.06	47.5	47.6	0.00
≥1 (multiparous)	9403 (50.9)	7700 (54.2)	0.07	52.5	52.4	0.00
Missing	101 (0.5)	51 (0.4)	0.03			
Pre-existing medical condition‡:						
No	16 041 (86.8)	12 574 (88.6)	0.06	87.6	87.4	0.01
Yes	2450 (13.2)	1624 (11.4)	0.06	12.4	12.6	0.01
Smoked during pregnancy:						
No	17 576 (95.1)	13 314 (93.8)	0.06	96.8	96.9	0.00
Yes	327 (1.8)	609 (4.3)	0.15	3.2	3.1	0.00
Missing	588 (3.2)	275 (1.9)	0.08			
Maternal BMI:						
<30.0	13 001 (70.3)	9735 (68.6)	0.04	78.9	78.9	0.00
≥30.0	3383 (18.3)	2718 (19.1)	0.02	21.1	21.1	0.00
Missing	2107 (11.4)	1745 (12.3)	0.03			
First prenatal care visit in the first trimester:						
Yes	16 919 (91.5)	13 040 (91.8)	0.01	95.6	95.6	0.00
No	661 (3.6)	698 (4.9)	0.07	4.4	4.4	0.00
Unknown	911 (4.9)	460 (3.2)	0.09			
Neighbourhood median family income quintiles:						
Quintile 1 (lowest)	2782 (15.0)	2998 (21.1)	0.16	17.9	17.7	0.00
Quintile 2	3390 (18.3)	2949 (20.8)	0.06	19.4	19.5	0.00
Quintile 3	4041 (21.9)	3157 (22.2)	0.01	22.1	22.0	0.00
Quintile 4	4314 (23.3)	2930 (20.6)	0.07	22.3	22.4	0.00
Quintile 5 (highest)	3874 (21.0)	2079 (14.6)	0.17	18.3	18.4	0.00
Missing	90 (0.5)	85 (0.6)	0.02			
Rural residence:						
No	16 228 (87.8)	12 444 (87.6)	0.00	87.4	87.4	0.00
Yes	2263 (12.2)	1754 (12.4)	0.00	12.6	12.6	0.00
Missing	238 (1.3)	264 (1.9)	0.05			
Laboratory confirmed covid-19 test result before pregnancy§:						
No	18 473 (99.9)	14 191 (100.0)	0.02	99.9	100.0	0.02
Yes	18 (0.1)	7 (0.0)	0.02	0.1	0.0	0.02
Laboratory confirmed covid-19 diagnosis during pregnancy¶:						
No	16 185 (87.5)	12 175 (85.8)	0.05	87.5	85.4	0.06
Yes	2306 (12.5)	2023 (14.2)	0.05	12.5	14.6	0.06

BMI=body mass index; LMP=last menstrual period.

*No missing values are shown in the weighted distributions of baseline characteristics from inverse probability of treatment because multiple imputation was used to address missing values. Column percentages and weights for the weighted study population were based on imputation dataset one.

†Absolute standardised difference comparing people who received a third dose of covid-19 vaccine during pregnancy and those who did not; standardised difference >0.10 indicates an imbalance in the distribution of the baseline characteristic between these two exposure groups.

‡Composite of: asthma, chronic hypertension, diabetes, heart disease, and thyroid disease. Sum of individual conditions does not equal the total number of individuals with any individual condition, as categories were not mutually exclusive (individual conditions shown in online supplemental table 3).

§Laboratory confirmed covid-19 diagnosis before the last menstrual period date. Represents pre-omicron time period.

¶Laboratory confirmed covid-19 diagnosis between the last menstrual period date up to one day before the date of birth (the specimen collection date, which was a proxy for date of infection, was lagged by two days).

Table 3 | Association between receipt or no receipt of third covid-19 vaccine dose during pregnancy and adverse pregnancy outcomes

Outcome*	Received third covid-19 vaccine dose (n=18 182)	Did not receive third covid-19 vaccine dose (n=13 943)	Unadjusted hazard ratio†	Adjusted hazard ratio†‡
Hypertensive disorders of pregnancy§	1408 (7.7)	940 (6.7)	1.13 (1.03 to 1.24)	1.03 (0.94 to 1.14)
Placental abruption	263 (1.4)	222 (1.6)	0.91 (0.76 to 1.09)	0.84 (0.70 to 1.02)
Caesarean delivery	5952 (32.7)	4626 (33.2)	0.95 (0.92 to 0.99)	0.90 (0.87 to 0.94)
Emergency caesarean delivery	2405 (13.2)	1840 (13.2)	0.96 (0.90 to 1.02)	0.90 (0.85 to 0.96)
Chorioamnionitis	94 (0.5)	92 (0.7)	0.74 (0.56 to 0.99)	0.67 (0.49 to 0.90)
Postpartum hemorrhage	634 (3.5)	446 (3.2)	1.04 (0.92 to 1.18)	1.01 (0.89 to 1.16)

Data are number (percentage with outcome) or hazard ratio (95% confidence interval).

*Among unique pregnancies (n=32 125).

†Hazard ratios were estimated using an extended Cox model with a time varying exposure variable for third dose of covid-19 vaccine received during pregnancy, after 20 weeks' gestation. Since vaccination status was treated as a time varying variable, individuals vaccinated after 20 weeks could have contributed both unexposed and exposed follow-up time. In all models, the reference category was unexposed follow-up time.

‡Model was performed on ten multiple imputation datasets and adjusted using stabilised inverse probability of treatment weights derived from a propensity score model including the variables listed in online supplemental table 2.

§To ensure the correct temporal order of the exposure-outcome association, the model included only individuals who received a third covid-19 vaccine dose before 20 weeks of gestation as gestational hypertensive disorders are diagnosed after 20 weeks of gestation. Individuals vaccinated on or after 20 weeks of gestation were excluded from the analysis.

in younger age groups (31.4% for <25 years *v* 59.2% for 30-34 years), among those with no pre-existing medical conditions (56.1% *v* 60.1% in people with pre-existing medical conditions), among those who smoked during pregnancy (35.3% *v* 57.2% in people who did not smoke during pregnancy), and who lived in neighbourhoods with lower household incomes (48.1% for quintile 1 *v* 65.0% for quintile 5) and higher material deprivation (46.0% for quintile 5 *v* 64.5% for quintile 1) (online supplemental table 4).

Pregnancy outcomes

Among 32 125 pregnant individuals, 7.7% of those who received a third dose of covid-19 vaccine any time during pregnancy were diagnosed with a gestational hypertensive disorder compared with 6.7% among individuals who did not receive a third dose during pregnancy. Following inverse probability weighting and limiting to covid-19 doses received before 20 weeks, the risk of developing a hypertensive disorder was not increased (adjusted hazard ratio 1.03 (95% confidence interval 0.94 to 1.14); table 3). Receipt of the third covid-19 vaccine dose during pregnancy was not associated with placental abruption (0.84 (0.70 to 1.02)) or postpartum hemorrhage (1.01 (0.89 to 1.16)). A slightly reduced risk was noted for caesarean delivery among individuals who received a third covid-19 vaccine dose during pregnancy, compared with those who did not receive a third dose, following inverse probability weighting (0.90 (0.87 to 0.94)). We additionally observed a lower risk of chorioamnionitis (0.67 (0.49 to 0.90); table 3). Results by trimester of vaccination and type of mRNA vaccine received as the third dose were consistent with the main findings (online supplemental tables 5 and 6). Following exclusion of individuals who had a laboratory confirmed covid-19 illness before or during pregnancy, the results did not change, except for the risk of chorioamnionitis, which was attenuated and no longer statistically significant (online supplemental table 7).

Fetal and neonatal outcomes

Crude cumulative incidence rates of adverse fetal and neonatal outcomes were either similar between the two exposure groups, or lower among those who received a third covid-19 vaccine dose during pregnancy. Following adjustment using inverse probability weights, either no association or an inverse association was noted between receiving a third covid-19 vaccine dose during pregnancy and risk of stillbirth (adjusted hazard ratio 0.56 (95% confidence interval 0.39 to 0.81)), preterm birth (0.91 (0.84 to 0.99)), very preterm birth (0.83 (0.68 to 1.03)), admission to neonatal intensive care unit (0.96 (0.90 to 1.03)), 5 min Apgar score <7 (0.96 (0.82 to 1.14)), or small-for-gestational age at birth (0.86 (0.79 to 0.93); table 4). Overall, associations were similar in subgroup analyses stratified by mRNA vaccine product and trimester of vaccination (online supplemental tables 5 and 6). Similarly, following exclusion of individuals who had confirmed covid-19 illness before or during pregnancy, the results were consistent with the main findings (online supplemental table 7).

Discussion

Principal findings

In this large, population based study of more than 32 000 individuals who had completed both doses of their primary covid-19 vaccine series prior to pregnancy and who were eligible for a third covid-19 dose (ie, first booster dose) during their pregnancy, more than 18 000 individuals (57%) received a covid-19 mRNA booster dose during pregnancy. We did not observe any increased risks of the pregnancy, fetal, and neonatal adverse outcomes that we assessed associated with receiving the third covid-19 dose

Table 4 | Association between third covid-19 vaccine dose received during pregnancy and adverse fetal and neonatal outcomes

Outcome*	Received third covid-19 vaccine dose during pregnancy	Did not receive third covid-19 vaccine dose during pregnancy	Unadjusted hazard ratio†	Adjusted hazard ratio†‡‡
All live births and stillbirths	18 491	14 198	—	—
Stillbirth	54 (0.29)	89 (0.63)	0.60 (0.43 to 0.85)	0.56 (0.39 to 0.81)
Preterm birth <37 weeks	1452 (7.9)	1276 (9.0)	0.93 (0.86 to 1.00)	0.91 (0.84 to 0.99)
Spontaneous preterm birth <37 weeks §	826 (4.5)	761 (5.4)	0.91 (0.82 to 1.00)	0.93 (0.83 to 1.03)
Clinician initiated preterm birth <37 weeks §	626 (3.4)	515 (3.6)	0.95 (0.85 to 1.07)	0.90 (0.79 to 1.02)
Very preterm birth <32 weeks	197 (1.1)	255 (1.8)	0.79 (0.65 to 0.95)	0.83 (0.68 to 1.03)
Live births	18 437	14 109	—	—
NICU admission >24 h ¶	2173 (11.8)	1773 (12.6)	0.94 (0.88 to 1.00)	0.96 (0.90 to 1.03)
5 min Apgar score <7 **	366 (2.0)	288 (2.1)	1.00 (0.86 to 1.17)	0.96 (0.82 to 1.14)
Singleton live births	17 614	13 406	—	—
Small-for-gestational age infant	1495 (8.5)	1326 (9.9)	0.82 (0.76 to 0.88)	0.86 (0.79 to 0.93)

Data are number, number (percentage with outcome), or hazard ratio (95% confidence interval). NICU=neonatal intensive care unit.

*End of follow-up: 36+6 weeks of gestation (pregnancy day 258) for preterm birth; 31+6 weeks of gestation (pregnancy day 223) for very preterm birth; and end of pregnancy for all other outcomes.

†Hazard ratios were estimated using an extended Cox model with a time varying exposure variable for third dose of covid-19 vaccine received during pregnancy, after 20 weeks' gestation. Since vaccination status was treated as a time varying variable, individuals vaccinated after 20 weeks could have contributed both unexposed and exposed follow-up time. In all models, the reference category was unexposed follow-up time.

‡Model was performed on ten multiple imputation datasets and adjusted using stabilised inverse probability of treatment weights derived from a propensity score model including the variables listed in online supplemental table 2.

§For spontaneous preterm birth, clinician initiated preterm births were censored at delivery. For clinician initiated preterm birth, spontaneous preterm births were censored at delivery.

¶Due to missing values for this outcome, the denominator for the exposed group was 18 427 live births and for the unexposed group was 14 095 live births.

**Due to missing values for this outcome, the denominator for the exposed group was 18 005 live births and for the unexposed group was 13 799 live births.

during pregnancy—most estimates were close to, or below, the null value. The results were robust to various subgroup and sensitivity analyses.

Comparison with other studies

An increasing number of studies have assessed the safety of receiving the primary covid-19 vaccine series during pregnancy, and none have identified any elevated risks of adverse maternal or neonatal outcomes,[11–16] including two earlier studies conducted in this Ontario based pregnant population.[15 16] Conversely, relatively few studies to date have evaluated pregnancy and birth outcomes following receipt of a covid-19 booster dose during pregnancy. In one multicenter cohort study conducted across seven US states from January 2021 to July 2022, outcomes from 7558 individuals who received a booster dose during pregnancy were compared with 9708 individuals who received two primary vaccine doses but did not receive a booster dose during pregnancy.[23] Following propensity score matching, individuals who received a booster had significantly lower rates of preterm birth compared with people who did not receive a booster dose during pregnancy (7.6% *v* 8.9%), as well as lower rates of stillbirth (0.2% *v* 0.5%), small-for-gestational age at birth (12.6% *v* 13.8%), and very low birth weight (0.8% *v* 1.2%).[23] A multicenter, retrospective cohort study of 2583 births in Israel between 1 August and 31 December 2021 evaluated receipt of BNT162b2 covid-19 booster doses during pregnancy, comparing 626 individuals who received a booster during pregnancy with 1094 who received two primary covid-19 vaccine doses during pregnancy, and with 863 unvaccinated pregnant individuals.[24] Compared with those who received two primary covid-19 vaccine doses during pregnancy, receiving a booster dose was not associated with risk of the composite maternal outcome (eg, chorioamnionitis, postpartum hemorrhage, and use of blood product transfusion; adjusted odds ratio 0.89 (95% confidence interval 0.65 to 1.22)) or the composite neonatal outcome (eg, intrauterine fetal death, 5 min Apgar score of ≤7, and neonatal intensive care unit admission; 0.74 (0.53 to 1.05)). Compared with individuals who were not vaccinated, no difference was also reported in risk of the composite maternal outcome (0.73 (0.52 to 1.08)), however, the risk of the composite neonatal outcome was significantly lower among infants born to mothers who received a booster dose (0.60 (0.42 to 0.86)).[24] Another study from a single tertiary medical center in Israel investigated obstetrical outcomes after a covid-19 booster dose during pregnancy between July and October 2021.[25] Of 6507 individuals included in the study, 294 received three doses of covid-19 vaccine during pregnancy, 2845 received two doses, and 3368 were unvaccinated. Comparing those who received three doses of covid-19 vaccine during pregnancy with unvaccinated individuals, no differences were reported in risk of preterm birth or small-for-gestational age at birth. However, an increase in risk of postpartum hemorrhage was recorded among people who received a booster dose compared with

people who received only two vaccine doses during pregnancy (adjusted odds ratio 3.34 (95% confidence interval 2.07 to 5.39)) and compared with unvaccinated women (3.88 (2.41 to 6.25)).[25] Finally, a summary of 323 spontaneous reports to the Vaccine Adverse Event Reporting System (known as VAERS) in the US for pregnant people who received an mRNA booster dose from 22 September 2021 to 24 March 2022 estimated a reporting rate for stillbirth (13.7 per 100 000 live births and fetal deaths) and preterm birth (5.5 per 100 000 live births), both of which were well below established background rates for these events in the US.[26]

With the exception of postpartum haemorrhage, for which we did not observe any increased risk (in contrast with findings from Dick et al[25]), our results are generally compatible with these published studies of covid-19 booster doses during pregnancy. However, direct comparison across studies is difficult owing to substantial differences in study design and analytical approaches. Our study followed methodological recommendations for conducting studies of vaccination during pregnancy to guide decisions about inclusion and exclusion criteria, comparison groups, time varying exposure definition, and outcome specific follow-up.[28–30] This is important because researchers face some unique methodological challenges for studies of vaccination during pregnancy (eg, attaining adequate control of confounding factors, accounting for cohort truncation or attrition, and considering complex temporal issues, such as immortal time and seasonality) that, if not appropriately addressed, can lead to bias.[28 30 38–40] Time dependent pregnancy outcomes, such as stillbirth and preterm birth, are particularly sensitive to these issues.[28] Similar to our previous study that evaluated stillbirth risk following receipt of the primary covid-19 vaccine series during pregnancy,[16] we also observed a reduced risk of stillbirth associated with receiving a covid-19 mRNA booster dose during pregnancy (adjusted hazard ratio 0.56 (95% confidence interval 0.39 to 0.81)), despite following methodological guidance for best practices for the design and analysis of this study.[28–30] SARS-CoV-2 infection and associated covid-19 illness during pregnancy have been associated with placental damage[41] and a higher stillbirth risk[5]; however, while some pathogen specific benefit is plausible and may be expected given the effectiveness of covid-19 vaccines against SARS-CoV-2 infection and related severe outcomes,[6] a risk reduction of such large extent is unlikely considering the multifactorial cause of stillbirth.[42] Indeed, in sensitivity analyses, no meaningful difference was noted in our findings for stillbirth after excluding individuals who had documented covid-19 before or during pregnancy. Alternative explanations for these findings could include unresolved methodological issues related to cohort truncation, temporal issues, and residual confounding.[28 30 38–40] Although non-specific (pathogen agnostic) benefits of vaccination during pregnancy have been hypothesised against adverse outcomes, such as stillbirth,[43] the biological mechanisms are yet not well elucidated.

Strengths and limitations

Strengths of this study include its large size and availability of population wide databases with detailed information on vaccination, pregnancy and birth outcomes, clinical, and sociodemographic variables. As we were able to deterministically link the centralised covid-19 vaccine database with the birth registry, exposure misclassification is unlikely. This study also has limitations. Although the birth registry information has been shown to have high validity,[33] heterogeneous diagnostic criteria (particularly for chorioamnionitis[44]) could have introduced some non-differential outcome misclassification. Pregnancies that ended prior to reaching 20 weeks' gestation were not included in this study, which could have introduced selection bias due to so-called depletion of susceptibles[38] if covid-19 vaccination in early pregnancy led to fetal losses before 20 weeks' gestation. However, population based case-control studies of covid-19 primary series vaccination have not found any association with miscarriage.[45 46] Despite attaining a good balance of baseline covariates following inverse probability weighting, we were limited to the variables available in the study databases; thus, we cannot rule out residual confounding of our results. This is particularly the case because we did not have information available on other healthcare seeking behaviours (such as receipt of influenza vaccination in recent seasons) or on attitudes toward vaccination during pregnancy. Generally, we observed similar patterns in uptake of the third dose during pregnancy as we observed in Ontario for the primary covid-19 vaccine series[18]—namely, that uptake of a booster dose was lower among pregnant individuals who were younger, smoked during pregnancy, and who lived in lower income neighbourhoods with higher material deprivation scores. These factors also tend to be associated with a higher risk of adverse pregnancy outcomes, therefore, residual confounding by these or other unmeasured characteristics and health behaviours can lead to a healthy vaccinee effect, in which risk estimates would be biased downward.[28 39] We may have had insufficient statistical power to rule out small differences in risk for some outcomes, and findings should be interpreted cautiously, particularly given the observational design. Moreover, we were only able to evaluate mRNA booster doses using original formulations because bivalent mRNA vaccines were not authorised in Canada until after 31 August 2022.

Conclusions

In this large, population based cohort study of more than 18 000 individuals who received a third covid-19

mRNA vaccine dose during pregnancy, we did not observe any increased risks of adverse pregnancy, fetal, or neonatal outcomes compared with individuals who had completed their primary covid-19 vaccine series prior to pregnancy, but did not receive a third dose in pregnancy. Given evidence of waning immunity with increased time since the primary covid-19 vaccine series, ongoing SARS-CoV-2 transmission, and known risks of covid-19 illness during pregnancy, the findings from this study can help to inform evidence based decision making about the risks and benefits of covid-19 booster doses during pregnancy.

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Contributors DBF, JSK, AS, DE-C, and SD conceived the original study idea. DBF, JSK, RWP, AKR, SEH, and CAG developed the study design and analytic approach, in consultation with other project team members. GDA, TD, SD-C, and DBF linked the data sources and SD-C performed the statistical analyses, which were supervised by DBF. The initial version of the manuscript was drafted by DBF; all authors contributed to the interpretation of the findings and reviewed and edited the manuscript for intellectual content. All authors approve the final version of the manuscript to be published and agreed to be accountable for all aspects of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. DBF is the guarantor. DBF (the guarantor) accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; KW is Chief Scientific Officer and a Director for CANImmunize Inc. He has served as a member of safety advisory boards for Medicago and Moderna.

Ethics approval Ethical approval for this study was obtained from the Children's Hospital of Eastern Ontario Research Ethics Board (CHEO REB protocol number 21/05PE). This study involved secondary use of databases housed at BORN Ontario; therefore, individual patient consent was not required. As a Prescribed Registry under the Personal Health Information Protection Act (PHIPA), BORN Ontario has the authority to collect, use, and disclose personal health information without patient consent for the purpose of facilitating and improving the provision of health care.

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