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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

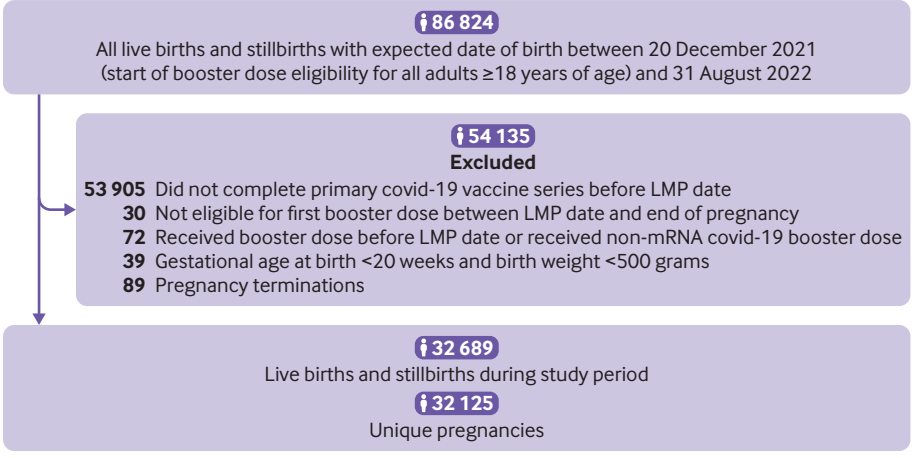

Figure 1 | Study flow diagram. Number of individuals who received a non-mRNA covid-19 vaccine as their third dose during pregnancy could not be shown separately as the number was <6. LMP=last menstrual period; mRNA=messenger RNA

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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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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

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Supplementary Table 1. Description of data sources

BORN Information System	Details about the BORN Information System (BIS) are available elsewhere.[1] Briefly, the BIS captures information on all Ontario births ≥20 weeks' gestation or ≥500 grams (all hospital births and the ~2.8% of home births with a midwife [2]) from over 250 hospitals, birth centres, midwifery practice groups, and prenatal screening labs. Prenatal and maternity care are publicly funded in the province. Records for pregnant individuals who undergo prenatal screening (about 70% in Ontario [3]) are uploaded weekly to the BIS from hospital- and community-based labs and ultrasound clinics. Thus, screened pregnancies are identifiable in the BIS as early as 10 weeks' gestation; 97% of prenatal screening records are linked with other health care encounters pertaining to birth. Unscreened pregnancies typically become identifiable in the BIS only at the time of the birth. When a pregnant individual presents to care around the time of birth, the birthing site generates a "Labour and birth encounter" in the BIS that captures information about labour and birth through to the first hour postpartum, regardless of birth setting (hospital, home, or birth centre). A separate "Birth-child encounter" documents information about each newborn (live births and stillbirths) through to the first hour postpartum. Postpartum encounters then capture clinical information about the mother and newborn(s) from the immediate postpartum period until discharge from hospital/birth centre. Unique identifiers (mother and newborn), assigned upon first record entry into the BIS, are used by the system to deterministically link all encounters through a robust automated algorithm. A system-generated signal indicates when each encounter record is complete. The BIS has a comprehensive data quality framework. Submitting sites are required to perform monthly automated data validation checks that flag records with missing encounters or data errors so that corrections can be made; every month, each site must report that it has reviewed and resolved flagged errors.[1] A formal validation study has been conducted, in which the accuracy of 29 core variables in the BORN registry was assessed by comparing data entered into the registry with original clinical data extracted from patient health records in a sample of hospitals. The study found good agreement between the two sources, with 76% of the variables (22 of 29) having greater than 90% agreement, and 12 of the categorical elements having almost perfect (kappa 0.81–0.99) or substantial (kappa 0.61–0.80) agreement.[4]
Canadian Census	To obtain information on rural/urban residence and dissemination-area based neighbourhood income quintile, we linked the study population to Statistics Canada's 2016 Census, based on postal code of maternal residence using Statistics Canada's Postal Code Conversion File Plus (PCCF+).
Ontario Marginalization Index	The Ontario Marginalization Index, which is derived from data from Statistics Canada's Census, quantifies the level of marginalization across the province. [5] The Index consists of four dimensions: residential instability, material deprivation, dependency, and ethnic concentration. Area-based quintile scores are available for each dimension, with quintile one representing the least marginalized areas, and quintile five representing the most marginalized. The Ontario Marginalization Index is linked with the BIS using postal code of maternal residence.

COVaxON	COVaxON, Ontario's COVID-19 immunization database, contains records for all COVID-19 vaccines administered in the province. Data are reported into COVaxON at the time of immunization, regardless of type of provider or delivery location (mass immunization clinic, pharmacy, etc.). Information includes vaccine product, dose number, and date(s) of vaccination. On a monthly basis, an extract of all immunization events in females aged 15-45 years is transferred to BORN Ontario, where they are deterministically linked using health card number to the BIS to identify individuals who received COVID-19 vaccination during pregnancy.
CCM	Ontario's Case and Contact Management System (CCM) is a centralized repository for COVID-19 case and contact management.[6] Each public health unit in the province collects information on COVID-19-positive cases and reports it to the Ministry of Health. On a monthly basis, an extract of all PCR-confirmed positive cases in females aged 15-45 years is transferred to BORN Ontario, where they are deterministically linked using health card number with the BIS to identify individuals who had laboratory-confirmed COVID-19 during pregnancy. A rapid increase in COVID-19 cases, due to the highly transmissible Omicron variant, starting in December 2021 led to changes in COVID-19 testing policies in the province (e.g., high-risk individuals, and individuals who work in high-risk settings were prioritized for testing) and delays in data entry. Consequently, COVID-19 case counts may be greatly underestimated since late 2021.

Supplementary Table 2. Description of study variables

Variable	Description
Exposure	
Third COVID-19 vaccine dose during pregnancy	Individuals who received a third dose any time between the LMP date up to one day before delivery (or before the end of the outcome-specific follow-up window for preterm birth outcomes) were considered 'exposed'. Those 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'. [NOTE: this study only included individuals who had already received their primary COVID-19 vaccine series prior to their LMP date, and became eligible to receive a third dose any time between their LMP date and the end of pregnancy, defined as 6 months after dose 2 (i.e., dose 2 date + 168 days)]
Pregnancy outcomes	
Hypertensive disorders of pregnancy	Gestational hypertension is hypertension that develops for the first time at ≥20 weeks of gestation without evidence of preeclampsia. Hypertension is defined as an office (or in-hospital) systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, based on the average of at least 2 measurements, taken after 5 minutes' rest, at least 15 minutes apart, using the same arm. Pre-eclampsia is gestational hypertension with new-onset proteinuria or one/more adverse conditions (defined as a maternal end-organ complication or evidence of uteroplacental dysfunction). Eclampsia is a severe complication of preeclampsia. It is a rare but serious condition where high blood pressure results in seizures during pregnancy. HELLP is an acronym for another severe condition associated with hypertensive disorders in pregnancy. It stands for Hemolysis, Elevated Liver Enzymes and Low Platelets.
Placental abruption	Defined as the early separation of the placenta from the lining of the uterus before the completion of the second stage of labour.
Chorioamnionitis	Acute inflammation of the chorion and membranes of the placenta due to bacterial infection.
Postpartum haemorrhage	Postpartum haemorrhage is defined as excessive bleeding that occurs within the first 24 hours after delivery. It is usually defined as >500 ml of blood loss for a vaginal delivery and >1000 ml for an abdominal delivery. Now, any blood loss that produces hemodynamic instability should be called postpartum haemorrhage and this will vary with the pre-existing condition of the woman.
Cesarean delivery	Delivery by cesarean section, including those for non-emergent indications (e.g., maternal request; elective; planned due to previous cesarean section) and emergent indications (see below).
Emergency cesarean delivery	Emergency cesarean is a subset of all cesarean births. Indication for emergent cesarean delivery: VBAC - Failed attempt; Uterine rupture; Placental abruption; Hypertensive disorders of pregnancy – Eclampsia; Hypertensive disorders of pregnancy – HELLP; Failed Induction; Failed forceps / vacuum; Prelabour Rupture of Membranes (PROM) in women with planned C-Section; Preterm prelabour rupture of membranes (PPROM) in women with planned C-Section; Nonprogressive second stage of labour; Nonprogressive labour/descent/dystocia; Suspected Chorioamnionitis; Other Obstetrical Complication; Nonprogressive first stage of labour; Hypertensive disorders of pregnancy – Preeclampsia; Placenta Previa

	(emergent if indication not known until time of delivery or uterine bleeding is present); Placenta Increta/Accreta/Percreta (emergent if indication not known until time of delivery or uterine bleeding is present); Cord prolapse; Cord prolapse \ Other; Atypical or Abnormal Fetal Surveillance; Malposition/Malpresentation; Intrauterine Growth Restriction (emergent if indication not known until time of delivery or fetal/atypical or abnormal surveillance observed); Congenital Anomalies (emergent if not planned C-section).
Fetal/neonatal outcomes	
Stillbirth	BORN Ontario uses the Ontario Vital Statistics Act's definition of stillbirth: "…..the complete expulsion or extraction from a person of a product of conception either after the 20th week of pregnancy or after the product of conception has attained a birth weight of 500g or more and shows no signs of life at birth." (**https://www.ontario.ca/laws/statute/90v04).** Stillbirth includes an antepartum or intrapartum fetal death at ≥20 weeks or ≥500 grams, with the gestational timing of the event based on the date of birth (information on the timing of fetal demise was not available).
Preterm birth	Live birth or stillbirth before 37 completed weeks of gestation.
Spontaneous preterm birth	Preterm birth was considered spontaneous if it occurred after spontaneous onset of labour or preterm premature rupture of membranes.
Clinician-initiated preterm birth	Preterm birth was considered spontaneous if it occurred after spontaneous onset of labour or preterm premature rupture of membranes, and considered clinician-initiated otherwise.
Very preterm birth	Live birth or stillbirth before 32 completed weeks of gestation.
NICU admission	Admission to neonatal intensive care unit (NICU) is related to prematurity, congenital anomalies requiring higher level of care (e.g., babies who are ill following birth). In the BIS, there is a flag on the file of any baby admitted to an NICU (Level 2 or Level 3).
5-minute Apgar score <7	The Apgar scoring system is a standardized method to assess the status of newborns immediately after birth (1, and 5 minutes). It comprises five components: 1) skin color, 2) heart rate, 3) reflexes, 4) muscle tone, and 5) respiration, each of which is given a score of 0, 1, or 2 (the highest score is 10).
Small for gestational age (SGA) at birth	Calculated field in the birth registry based on infant sex, gestational age, and birth weight. SGA at birth is defined as a singleton live birth below the 10th percentile of the sex-specific birth weight for gestational age distribution, based on a Canadian reference standard.[7]
Baseline variables included in propensity score model	
Maternal age	Calculated field indicating maternal age at time of live birth or stillbirth.
Estimated date of last menstrual period	Estimated date of last menstrual period was calculated from gestational age at birth. Gestational age in days is recorded in the birth registry and most pregnancy dating in Ontario is based on early ultrasound assessment.
Parity	The number of previous live births and stillbirths (term + preterm). This is automatically calculated by the birth registry at the time of data upload/entry.
Multiple birth	Number of fetuses in the current pregnancy.
Pre-existing medical condition	Maternal health conditions and/or complications including those pre-existing, diagnosed during pregnancy or active during pregnancy. Variable was derived as a composite of the following conditions: thyroid disease, asthma, diabetes, chronic hypertension, and heart disease.
Self-reported smoking during pregnancy	Self-reported amount of smoking per day closest to time of labour/admission or at time of first prenatal visit. Smoking status includes any self-reported cigarettes that were smoked at any time during the pregnancy. This does not include marijuana or vaping.

Self-reported substance use during pregnancy	Maternal self-reported drug and substance use during pregnancy. This refers to the use of street drugs and the inappropriate use of prescription and non-prescription drugs and includes cocaine, gas/glue, hallucinogens, opioids, and cannabis. Measure of substance use included maternal self-reported cannabis exposure (i.e., smoking, vaping, consumption of edibles and cannabis products, and topical application) at any point during this pregnancy as documented in the medical record.
Pre-pregnancy maternal BMI (kg/m^2)	Derived using maternal weight (kg) and height (cm). Maternal weight is reported as mother's self-reported weight closest to conception and no later than 12 weeks of gestation (metric or imperial units) and maternal height is reported in imperial or metric units.
Rural/urban residence	Rural or urban residence based on postal code of maternal residence.
Neighbourhood income quintile	Dissemination-area based neighbourhood income quintile.
Ontario Marginalization Index [5] – Residential instability	Residential instability identifies areas with high rates of family or housing instability. The Census indicators used to derive residential instability are: 1) percentage of population living alone; 2) percentage of population who are not youth aged 5-15 years; 3) average number of persons per dwelling; 4) percentage of dwellings that are in apartment buildings; 5) percentage of population who are single/divorced/widowed; 6) percentage of dwellings that are not owned; and 7) percentage of population who moved during the past five years.
Ontario Marginalization Index [5] – Material deprivation	Material deprivation, which is closely connected to poverty, identifies individuals and communities unable to access and attain basic material needs. The Census indicators used to derive material deprivation are: 1) percentage of population ≥20 years without a secondary diploma; 2) percentage of lone-parent families; 3) percentage of total income received from government transfer payments for population aged ≥15 years; 4) percentage of population aged ≥15 years who are unemployed; 5) percentage of population considered low-income; and 6) percentage of household dwellings in need of major repair.
Ontario Marginalization Index [5] – Dependency	Dependency identifies areas with high concentrations of residents who do not receive employment income. The Census indicators used to derive dependency are: 1) percentage of population who are aged ≥65 years; 2) dependency ratio (total population aged 0-14 years and ≥65 years / total population aged 15 to 64 years); and 3) percentage of population aged ≥15 years not participating in labour force.
Ontario Marginalization Index [5] – Ethnic concentration	Ethnic concentration identifies areas with high concentrations of recent immigrants and/or "visible minorities" (defined by Statistics Canada as "persons, other than Aboriginal peoples, who are non-Caucasian in race or non-white in colour"). Ethnic concentration is derived from two Census variables: 1) percentage of population who are recent immigrants (arrived in past five years); and 2) percentage of population who self-identify as a visible minority (Census respondents can indicate more than one race/ethnicity from a list, or can specify a group not listed on the Census questionnaire).
Public health unit region of residence	South West, Central West, Central East, Greater Toronto Area, Eastern, North West, North East
First prenatal visit during first trimester	Indication that mother had a prenatal care visit with a regulated health care provider during the first trimester (<14 weeks of gestation).

Supplementary Appendix 1. Multiple imputation and propensity score methods

Multiple imputation was used to address missing covariate values (16.6% of records had missing information for one or more covariates included in the propensity score models). Ten multiple imputation datasets were generated using a fully conditional specification ('MI' procedure in SAS Version 9.4, SAS Institute Inc, Cary, NC).

We used logistic regression to generate propensity scores (using each of the 10 imputed datasets) representing the predicted probability of receiving a third dose of COVID-19 vaccine during pregnancy (compared with not receiving a third dose of COVID-19 vaccine during pregnancy), conditional on the baseline variables listed in Supplementary table 2.

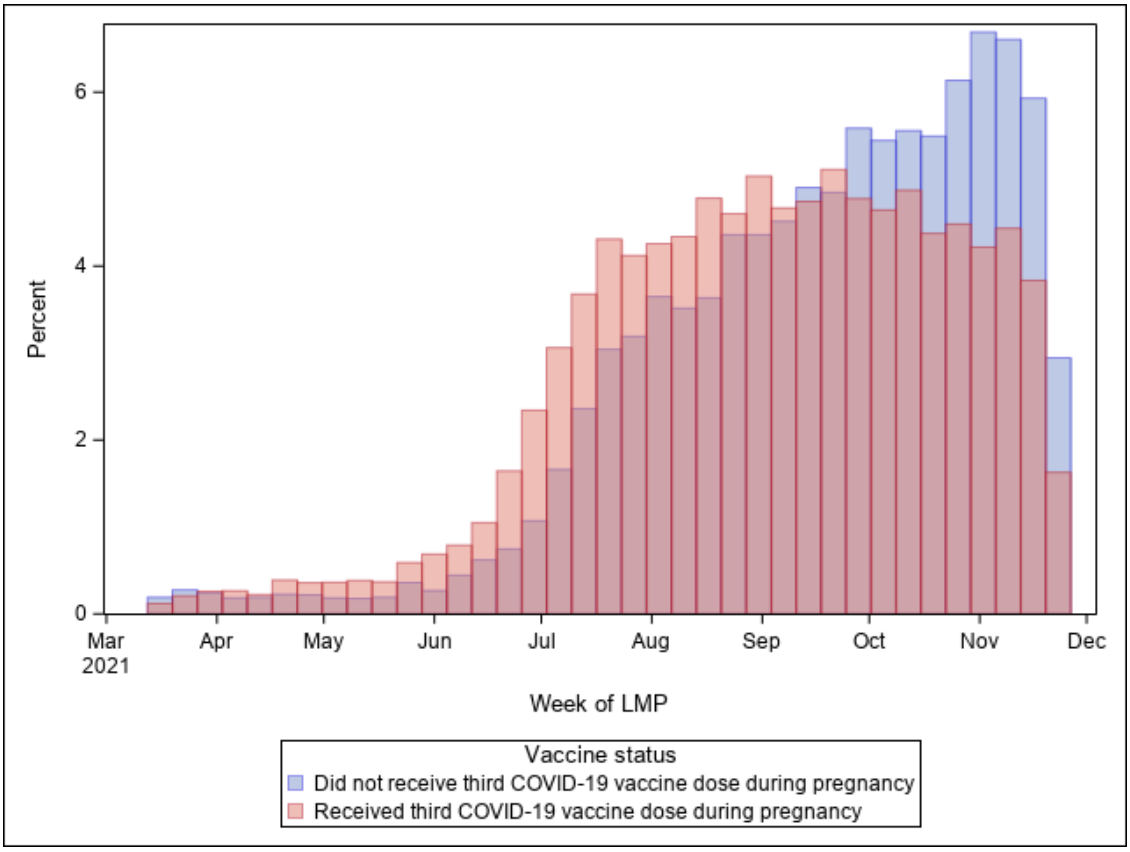
The propensity scores were then used to generate 10 sets of inverse probability of treatment weights using each of the 10 multiply-imputed datasets. Weight were computed as the inverse of the propensity score for exposed individuals and the inverse of 1 minus the propensity score for the comparison group.[8] We stabilized the weights by multiplying by the marginal propensity score [9,10] and applied trimming by reassigning any weights with a value below the 1st percentile or above the 99th percentile to the values at the 1st or 99th percentiles, respectively, to account for any large weights that could potentially influence the results and inflate variance.[11] We re-assessed the distribution of baseline variables by exposure group after applying propensity score weights (table 2 and Supplementary table 3).

Regression models incorporating stabilized weights from each of the 10 imputed datasets were used to generate adjusted coefficients and standard errors, which were combined using the 'MIANALYZE' procedure (SAS Version 9.4, SAS Institute Inc, Cary, NC) to produce adjusted estimates and 95% confidence intervals (CI).

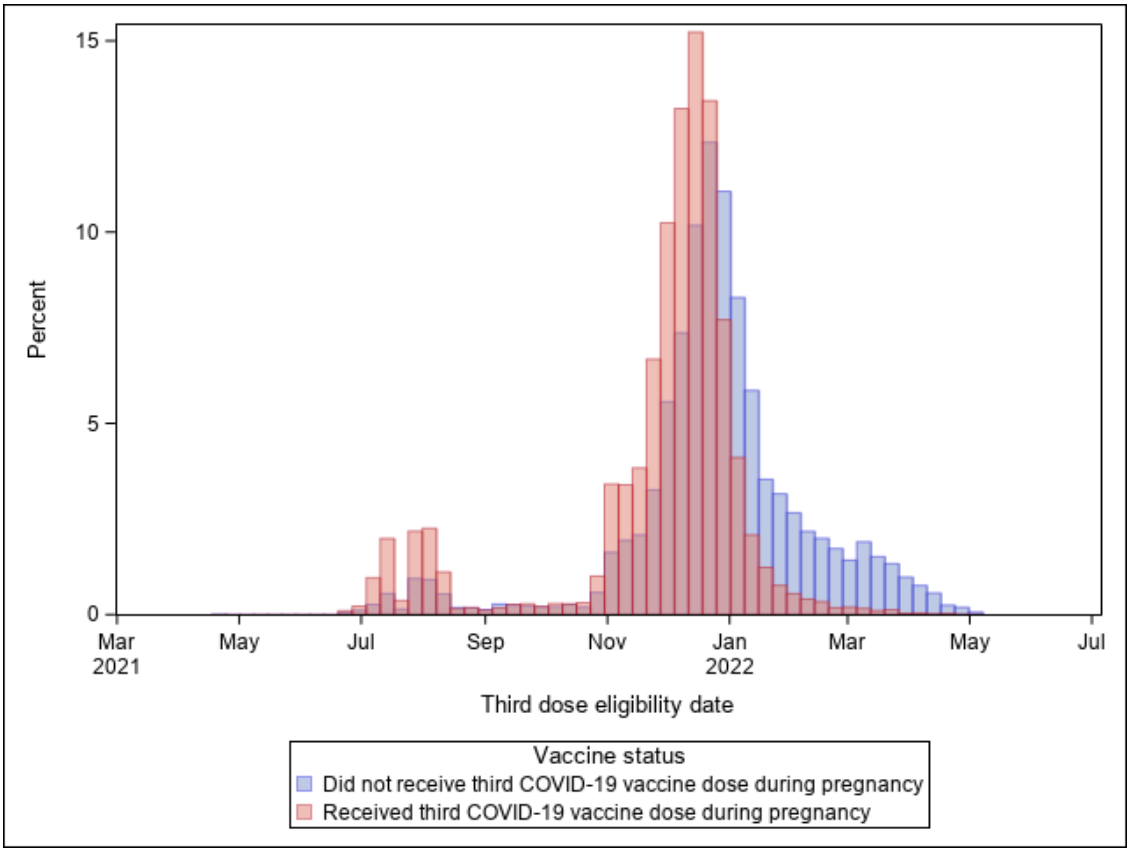
Supplementary Figure 1. Timing of COVID-19 primary series, relative to index pregnancy, among 53,905 individuals excluded from study

N=53,905 individuals who were excluded because they were not eligible, based on timing of primary series		BEFORE PREGNANCY			DURING PREGNANCY			AFTER PREGNANCY			Number
		Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3	
Never vaccinated	Excluded										21,530
Initiated vaccine series on or after date of delivery - received 1 dose	Excluded										585
Initiated vaccine series on or after date of delivery - received 2 doses	Excluded										1,325
Initiated vaccine series on or after date of delivery - received 3 doses	Excluded										56
Dose 1 before pregnancy, no further doses	Excluded										736
Dose 1 before pregnancy, dose 2 during pregnancy, no further doses	Excluded										5,475
Dose 1 before pregnancy, dose 2 after pregnancy, no further doses	Excluded										145
Dose 1 before pregnancy, dose 2 + 3 during pregnancy	Excluded										5,619
Dose 1 before pregnancy, dose 2 during pregnancy, dose 3 after pregnancy	Excluded										710
Dose 1 before pregnancy, dose 2 + 3 after pregnancy	Excluded										7
Dose 1 during pregnancy, no further doses	Excluded										1,290
Dose 1 + 2 during pregnancy, no further doses	Excluded										9,380
Dose 1 during pregnancy, dose 2 after pregnancy, no further doses	Excluded										540
Dose 1 + 2 + 3 during pregnancy	Excluded										3,669
Dose 1 + 2 during pregnancy, dose 3 after pregnancy	Excluded										2,811
Dose 1 during pregnancy, dose 2 + 3 after pregnancy	Excluded										27

Supplementary Figure 2. Distribution of last menstrual period (LMP) date among those who received a third COVID-19 dose during pregnancy (exposed) and those who did not (unexposed)

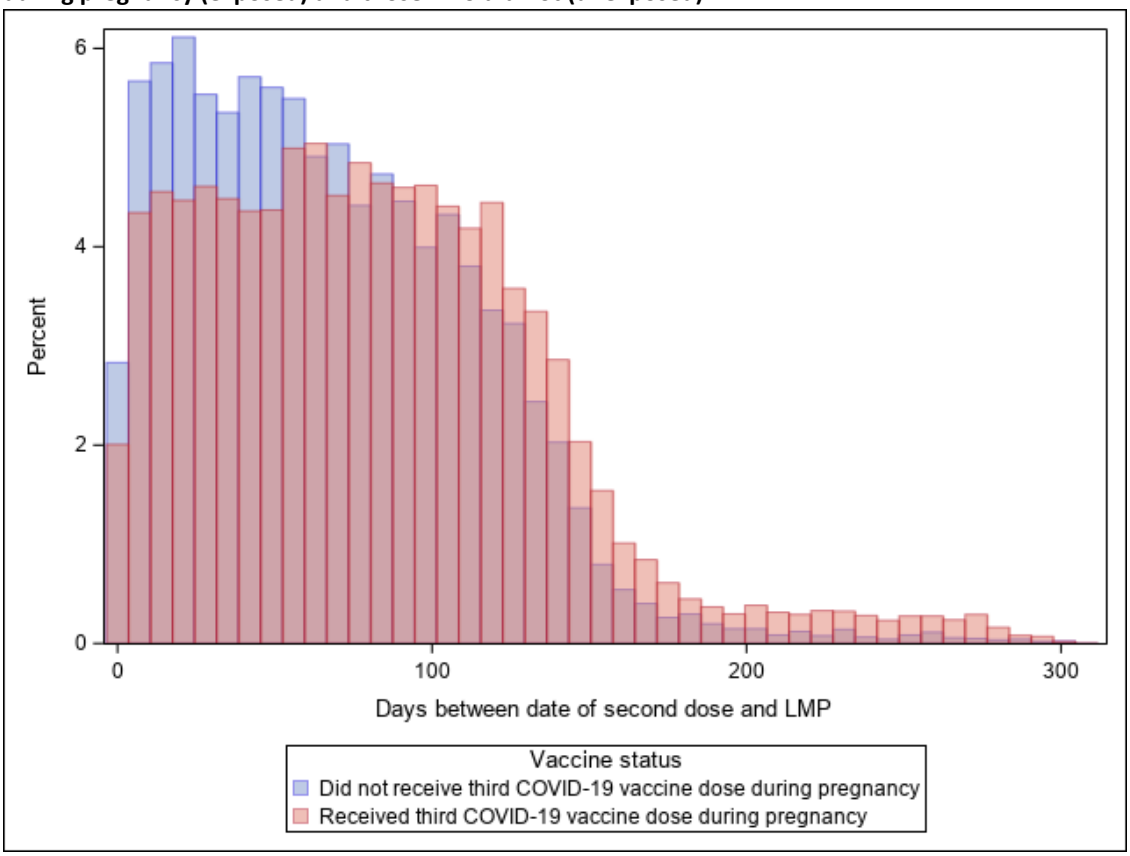


Supplementary Figure 3. Third dose eligibility date among those who received a third COVID-19 dose during pregnancy (exposed) and those who did not (unexposed) [a]

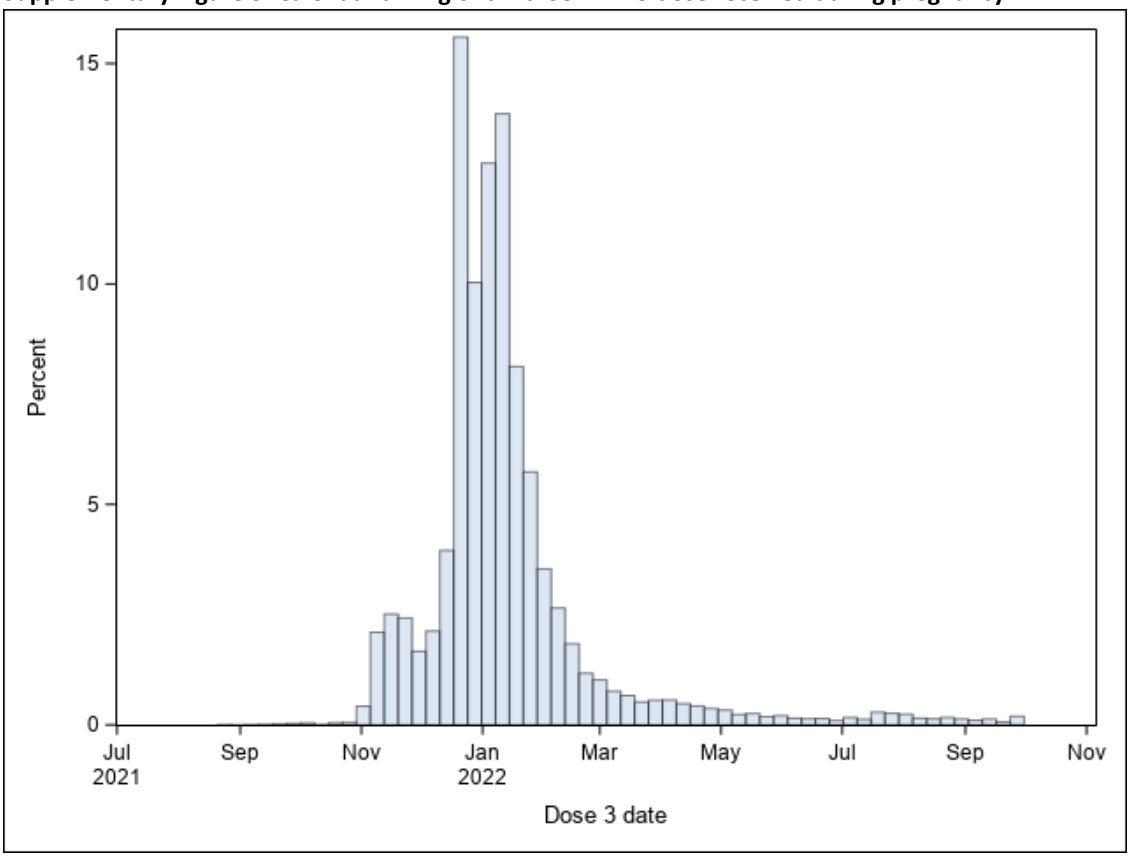


[a] Third dose eligibility date was calculated as 168 days (24 weeks) after the date of the second dose.

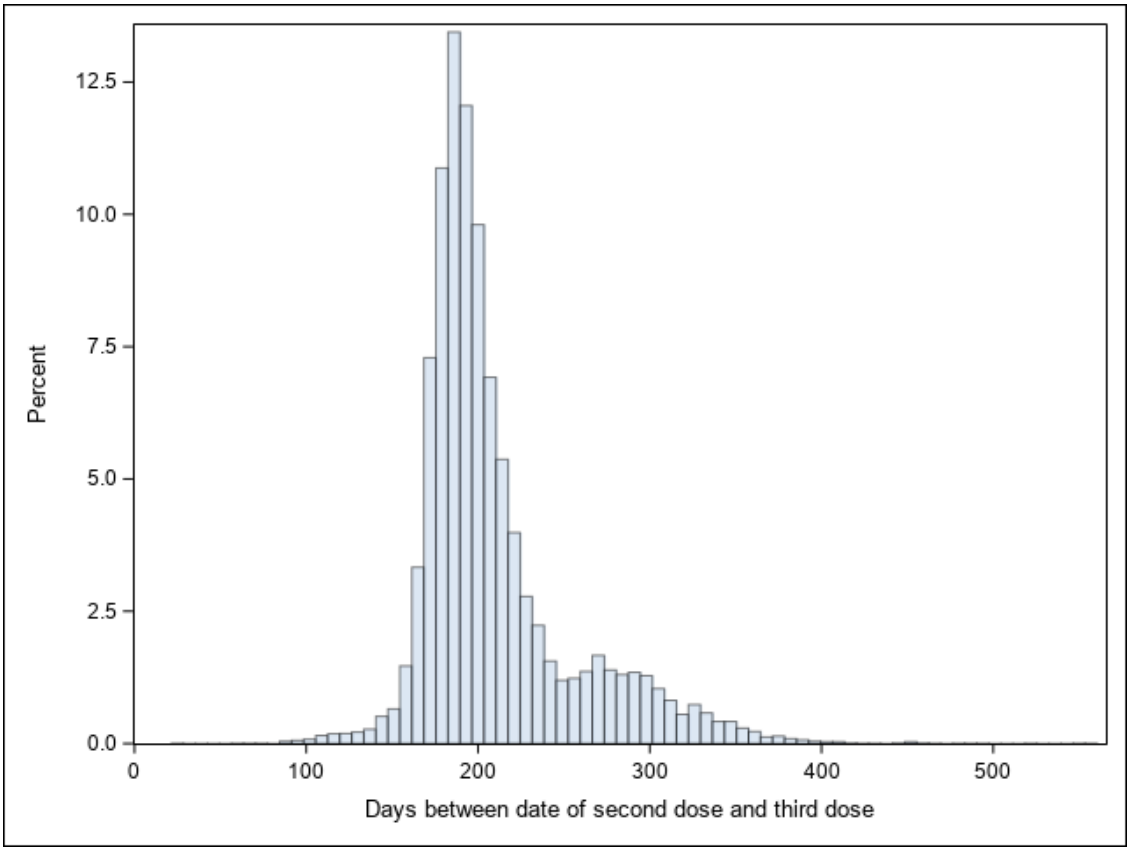
Supplementary Figure 4. Distribution of number of days between date that the second dose was received and the last menstrual period (LMP) date among those who received a third COVID-19 dose during pregnancy (exposed) and those who did not (unexposed)



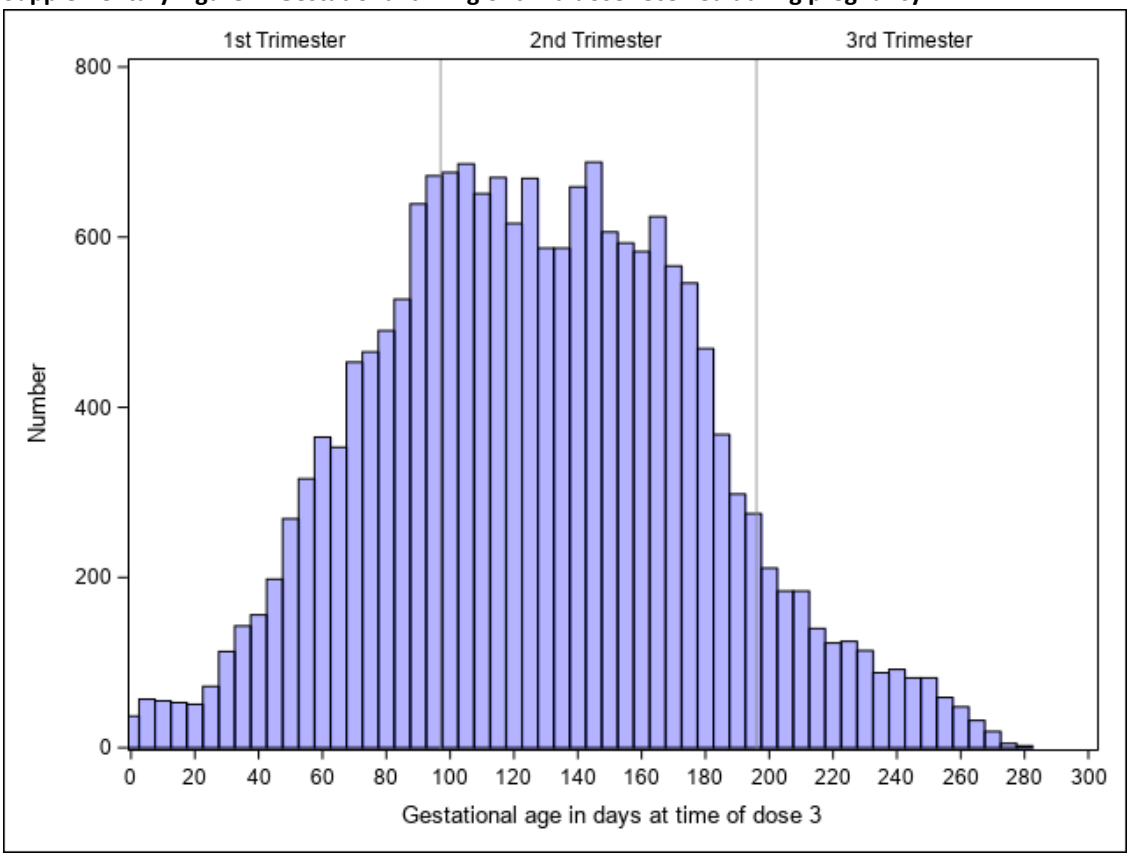
Supplementary Figure 5. Calendar timing of third COVID-19 dose received during pregnancy



Supplementary Figure 6. Distribution of number of days between the second and third COVID-19 dose, among those who received the third COVID-19 dose during pregnancy



Supplementary Figure 7. Gestational timing of third dose received during pregnancy



Supplementary Table 3. Additional characteristics of study population overall and by status of third COVID-19 vaccine dose received during pregnancy

Characteristics	Unweighted							Stabilized inverse probability of treatment weighted [a]		
	All live births and stillbirths (n =32,689)		Received third COVID-19 vaccine dose during pregnancy (n =18,491)		Did not receive third COVID-19 vaccine dose during pregnancy (n =14,198)		Standardized difference [b]	Received third COVID-19 vaccine dose during pregnancy	Did not receive third COVID-19 vaccine dose during pregnancy	Standardized difference [b]
	n	% [c]	n	% [c]	n	% [c]		% [c]	% [c]	
Last menstrual period date										
Before August 2021	7,087	21.7	4,757	25.7	2,330	16.4	0.23	21.7	21.9	0.00
August - September 2021	12,970	39.7	7,582	41.0	5,388	37.9	0.06	40.3	39.1	0.03
October - November 2021	12,632	38.6	6,152	33.3	6,480	45.6	0.26	37.9	39.0	0.02
Multiple birth										
No	31,565	96.6	17,876	96.7	13,689	96.4	0.01	96.6	96.5	0.01
Yes	1,124	3.4	615	3.3	509	3.6	0.01	3.4	3.5	0.01
Asthma										
No	31,375	96.0	17,674	95.6	13,701	96.5	0.05	95.8	96.3	0.02
Yes	1,314	4.0	817	4.4	497	3.5	0.05	4.2	3.7	0.02
Chronic hypertension										

No	32,346	99.0	18,279	98.9	14,067	99.1	0.02	98.9	98.9	0.00
Yes	343	1.0	212	1.1	131	0.9	0.02	1.1	1.1	0.00
Diabetes										
No	32,274	98.7	18,242	98.7	14,032	98.8	0.02	98.7	98.7	0.00
Yes	415	1.3	249	1.3	166	1.2	0.02	1.3	1.3	0.00
Heart disease										
No	32,644	99.9	18,465	99.9	14,179	99.9	0.00	99.9	99.8	0.00
Yes	45	0.1	26	0.1	19	0.1	0.00	0.1	0.2	0.00
Thyroid disease										
No	30,466	93.2	17,178	92.9	13,288	93.6	0.03	93.4	92.8	0.02
Yes	2,223	6.8	1,313	7.1	910	6.4	0.03	6.6	7.2	0.02
Substance use during pregnancy [d]										
No	30,610	93.6	17,328	93.7	13,282	93.5	0.01	97.1	97.2	0.00
Yes	816	2.5	336	1.8	480	3.4	0.10	2.9	2.8	0.00
Missing	1,263	3.9	827	4.5	436	3.1	0.07			
PHU region of residence										
South West	3,501	10.7	1,900	10.3	1,601	11.3	0.03	10.9	10.9	0.00
Central West	6,217	19.0	3,567	19.3	2,650	18.7	0.02	19.0	19.1	0.00
Central East	9,702	29.7	4,812	26.0	4,890	34.4	0.18	29.8	29.8	0.00
Greater Toronto Region	6,914	21.2	4,396	23.8	2,518	17.7	0.15	21.2	21.2	0.00

Eastern	4,482	13.7	2,853	15.4	1,629	11.5	0.12	13.7	13.7	0.00
North West	666	2.0	346	1.9	320	2.3	0.03	2.2	2.1	0.00
North East	1,045	3.2	538	2.9	507	3.6	0.04	3.2	3.2	0.00
Missing	162	0.5	79	0.4	83	0.6	0.02			
Material deprivation quintile										
Quintile 1 - least deprived	8,377	25.6	5,407	29.2	2,970	20.9	0.19	25.8	26.0	0.00
Quintile 2	7,014	21.5	4,258	23.0	2,756	19.4	0.09	21.7	21.7	0.00
Quintile 3	6,163	18.9	3,382	18.3	2,781	19.6	0.03	19.0	18.8	0.00
Quintile 4	5,557	17.0	2,866	15.5	2,691	19.0	0.09	17.2	17.2	0.00
Quintile 5 - most deprived	5,076	15.5	2,340	12.7	2,736	19.3	0.18	16.4	16.3	0.00
Missing	502	1.5	238	1.3	264	1.9	0.05			
Residential instability quintile										
Quintile 1 – least unstable	6,603	20.2	3,532	19.1	3,071	21.6	0.06	20.3	20.3	0.00
Quintile 2	6,134	18.8	3,522	19.0	2,612	18.4	0.02	18.9	19.0	0.00
Quintile 3	5,982	18.3	3,422	18.5	2,560	18.0	0.01	18.6	18.5	0.00
Quintile 4	5,771	17.7	3,346	18.1	2,425	17.1	0.03	17.9	17.9	0.00
Quintile 5 – most unstable	7,697	23.5	4,431	24.0	3,266	23.0	0.02	24.2	24.3	0.00
Missing	502	1.5	238	1.3	264	1.9	0.05			

Dependency quintile										
Quintile 1 – least dependent	11,065	33.8	6,162	33.3	4,903	34.5	0.03	34.1	34.2	0.00
Quintile 2	6,791	20.8	3,875	21.0	2,916	20.5	0.01	21.0	21.0	0.00
Quintile 3	5,333	16.3	3,063	16.6	2,270	16.0	0.02	16.6	16.6	0.00
Quintile 4	4,767	14.6	2,754	14.9	2,013	14.2	0.02	14.9	14.9	0.00
Quintile 5 – most dependent	4,231	12.9	2,399	13.0	1,832	12.9	0.00	13.4	13.3	0.00
Missing	502	1.5	238	1.3	264	1.9	0.05			
Ethnic concentration quintile										
Quintile 1 – least concentration	4,282	13.1	2,484	13.4	1,798	12.7	0.02	13.9	13.9	0.00
Quintile 2	5,091	15.6	3,057	16.5	2,034	14.3	0.06	16.0	15.9	0.00
Quintile 3	6,011	18.4	3,735	20.2	2,276	16.0	0.11	18.6	18.5	0.00
Quintile 4	7,302	22.3	4,396	23.8	2,906	20.5	0.08	22.5	22.7	0.00
Quintile 5 – most concentration	9,501	29.1	4,581	24.8	4,920	34.7	0.22	29.1	29.0	0.00
Missing	502	1.5	238	1.3	264	1.9	0.05			
Birth location										
Home	510	1.6	312	1.7	198	1.4	0.02	1.7	1.4	0.02

Hospital	32,001	97.9	18,056	97.6	13,945	98.2	0.04	97.7	98.2	0.03
Birth centre, midwifery clinic, other Ontario location	178	0.5	123	0.7	55	0.4	0.04	0.6	0.4	0.03
Health care provider										
Midwives	3,449	10.6	2,116	11.4	1,333	9.4	0.07	11.5	9.4	0.07
CNS/NP, Registered nurse	179	0.5	98	0.5	81	0.6	0.01	0.6	0.5	0.01
Family physician	1,792	5.5	1,051	5.7	741	5.2	0.02	6.0	5.2	0.04
Obstetrician	24,063	73.6	13,288	71.9	10,775	75.9	0.09	72.7	75.9	0.07
Other Healthcare Provider, Resident, Surgeon	2,900	8.9	1,724	9.3	1,176	8.3	0.04	9.0	8.8	0.01
Unattended	58	0.2	31	0.2	27	0.2	0.01	0.2	0.2	0.00
Missing	248	0.8	183	1.0	65	0.5	0.06			

Abbreviations: PHU, Public Health Unit; CNS/NP, Clinical Nurse Specialist/Nurse Practitioner.

[a] Column percentages and weights for the weighted study population were based on imputation dataset 1.

[b] Absolute standardized difference comparing those who received a third dose of COVID-19 vaccine during pregnancy and those who did not; standardized difference >0.10 indicates an imbalance in the distribution of the baseline characteristic between these two exposure groups.

[c] Column percentages.

[d] Self-reported cannabis, opioid or alcohol use during pregnancy.

Supplementary Table 4. Third dose coverage of COVID-19 vaccine during pregnancy by baseline characteristics of the study population

	All		Received third COVID-19 vaccine dose during pregnancy		Unadjusted risk ratio (95% CI)
	n	% [a]	n	% [b]	
Overall	32,689		18,491		---
Maternal age at delivery (years)					
<25	1,441	4.4	453	31.4	0.53 (0.49 to 0.57)
25-29	6,932	21.2	3,130	45.2	0.76 (0.74 to 0.79)
30-34	14,107	43.2	8,351	59.2	1.00
35-39	8,333	25.5	5,414	65.0	1.10 (1.07 to 1.12)
≥40	1,876	5.7	1,143	60.9	1.03 (0.99 to 1.07)
Last menstrual period date					
Before August 2021	7,087	21.7	4,757	67.1	1.38 (1.35 to 1.41)
August – September 2021	12,970	39.7	7,582	58.5	1.20 (1.17 to 1.23)
October – November 2021	12,632	38.6	6,152	48.7	1.00
Parity					
0 (nulliparous)	15,519	47.5	9,047	58.3	1.00
≥1 (multiparous)	17,170	52.5	9,444	55.0	0.94 (0.93 to 0.96)
Multiple birth					
No	31,565	96.6	17,876	56.6	1.00
Yes	1,124	3.4	615	54.7	0.97 (0.92 to 1.02)
Pre-existing medical condition [c]					
No	28,615	87.5	16,041	56.1	1.00
Yes	4,074	12.5	2,450	60.1	1.07 (1.04 to 1.10)
Asthma					
No	31,375	96.0	17,674	56.3	1.00
Yes	1,314	4.0	817	62.2	1.10 (1.06 to 1.15)
Chronic hypertension					

No	32,346	99.0	18,279	56.5	1.00
Yes	343	1.0	212	61.8	1.09 (1.01 to 1.19)
Diabetes					
No	32,274	98.7	18,242	56.5	1.00
Yes	415	1.3	249	60.0	1.06 (0.98 to 1.15)
Heart disease					
No	32,644	99.9	18,465	56.6	1.00
Yes	45	0.1	26	57.8	1.02 (0.80 to 1.31)
Thyroid disease					
No	30,466	93.2	17,178	56.4	1.00
Yes	2,223	6.8	1,313	59.1	1.05 (1.01 to 1.09)
Smoked during pregnancy					
No	31,674	96.9	18,133	57.2	1.00
Yes	1,015	3.1	358	35.3	0.62 (0.57 to 0.67)
Substance use during pregnancy [d]					
No	31,768	97.2	18,113	57.0	1.00
Yes	921	2.8	378	41.0	0.72 (0.67 to 0.78)
Maternal BMI (kg/m2)					
<30.0	25,845	79.1	14,713	56.9	1.00
≥30.0	6,844	20.9	3,778	55.2	0.97 (0.95 to 0.99)
First prenatal care visit in the first trimester					
Yes	31,267	95.6	17,791	56.9	1.00
No	1,422	4.4	700	49.2	0.86 (0.81 to 0.91)
Birth location					
Home	510	1.6	312	61.2	1.08 (1.01 to 1.16)
Hospital	32,001	97.9	18,056	56.4	1.00
Birth centre, midwifery clinic, other Ontario location	178	0.5	123	69.1	1.22 (1.11 to 1.35)

Health care provider					
Midwives	3,478	10.6	2,142	61.6	1.11 (1.08 to 1.14)
CNS/NP, Registered nurse	179	0.5	98	54.7	1.00 (0.88 to 1.14)
Family physician	1,821	5.6	1,071	58.8	1.07 (1.02 to 1.11)
Obstetrician	24,242	74.2	13,418	55.4	1.00
Other Healthcare Provider, Resident, Surgeon	2,911	8.9	1,731	59.5	1.07 (1.04 to 1.11)
Unattended	58	0.2	31	53.4	0.97 (0.76 to 1.23)
Neighbourhood median family income quintiles					
Quintile 1 – lowest	5,808	17.8	2,792	48.1	0.74 (0.72 to 0.76)
Quintile 2	6,373	19.5	3,404	53.4	0.82 (0.80 to 0.85)
Quintile 3	7,238	22.1	4,067	56.2	0.86 (0.84 to 0.89)
Quintile 4	7,287	22.3	4,338	59.5	0.92 (0.89 to 0.94)
Quintile 5 – highest	5,983	18.3	3,890	65.0	1.00
Rural residence					
No	28,672	87.7	16,228	56.6	1.00
Yes	4,017	12.3	2,263	56.3	1.00 (0.97 to 1.02)
PHU region of residence					
South West	3,522	10.8	1,911	54.3	0.85 (0.83 to 0.89)
Central West	6,249	19.1	3,579	57.3	0.90 (0.88 to 0.93)
Central East	9,751	29.8	4,841	49.6	0.78 (0.76 to 0.80)
Greater Toronto Region	6,942	21.2	4,406	63.5	1.00
Eastern	4,507	13.8	2,866	63.6	1.00 (0.97 to 1.03)
North West	671	2.1	349	52.0	0.82 (0.76 to 0.88)
North East	1,047	3.2	539	51.5	0.81 (0.76 to 0.86)
Residential instability quintile					

Quintile 1 – least unstable	6,681	20.4	3,572	53.5	1.00
Quintile 2	6,188	18.9	3,550	57.4	1.07 (1.04 to 1.11)
Quintile 3	6,064	18.6	3,459	57.0	1.07 (1.03 to 1.10)
Quintile 4	5,859	17.9	3,383	57.7	1.08 (1.05 to 1.11)
Quintile 5 – most unstable	7,897	24.2	4,527	57.3	1.07 (1.04 to 1.10)
Material deprivation quintile					
Quintile 1 – least deprived	8,442	25.8	5,441	64.5	1.00
Quintile 2	7,086	21.7	4,296	60.6	0.94 (0.92 to 0.96)
Quintile 3	6,226	19.0	3,416	54.9	0.85 (0.83 to 0.88)
Quintile 4	5,633	17.2	2,901	51.5	0.80 (0.78 to 0.82)
Quintile 5 – most deprived	5,302	16.2	2,437	46.0	0.71 (0.69 to 0.74)
Dependency quintile					
Quintile 1 – least dependent	11,159	34.1	6,204	55.6	1.00
Quintile 2	6,876	21.0	3,919	57.0	1.03 (1.00 to 1.05)
Quintile 3	5,420	16.6	3,095	57.1	1.03 (1.00 to 1.06)
Quintile 4	4,869	14.9	2,808	57.7	1.04 (1.01 to 1.07)
Quintile 5 – most dependent	4,365	13.4	2,465	56.5	1.02 (0.98 to 1.05)
Ethnic concentration quintile					
Quintile 1 – least concentration	4,489	13.7	2,585	57.6	1.00
Quintile 2	5,180	15.8	3,107	60.0	1.04 (1.01 to 1.08)
Quintile 3	6,096	18.6	3,772	61.9	1.07 (1.04 to 1.11)
Quintile 4	7,362	22.5	4,421	60.1	1.04 (1.01 to 1.08)
Quintile 5 – most concentration	9,562	29.3	4,606	48.2	0.84 (0.81 to 0.86)
Time in days between second dose and LMP					

<56 days (<8 weeks)	12,924	39.5	6,544	50.6	1.00
56-<84 days (8-<12 weeks)	6,319	19.3	3,555	56.3	1.11 (1.08 to 1.14)
84-<112 days (12-<16 weeks)	5,816	17.8	3,350	57.6	1.14 (1.11 to 1.17)
112-<140 days (16-<20 weeks)	4,485	13.7	2,770	61.8	1.22 (1.19 to 1.26)
140-<168 days (20-<24 weeks)	1,767	5.4	1,215	68.8	1.36 (1.31 to 1.41)
≥168 days (≥24 weeks)	1,378	4.2	1,057	76.7	1.51 (1.46 to 1.57)

Abbreviations: CI, confidence interval; BMI, body mass index; PHU, Public Health Unit; CNS/NP, Clinical Nurse Specialist/Nurse Practitioner; LMP: last menstrual period date

[a] Column percentages. Percentages were based on imputation dataset 1.

[b] Row percentages. Percentages were based on imputation dataset 1.

[c] Composite of: asthma, chronic hypertension, diabetes, heart disease, thyroid disease. Sum of individual conditions does not equal the total number of individuals with any individual condition, as categories were not mutually exclusive.

[d] Self-reported cannabis, opioid or alcohol use during pregnancy.

Supplementary Table 5. Trimester-specific estimates for the third mRNA COVID-19 dose received during pregnancy

Outcome	Adjusted hazard ratio (95% CI) [a]
Pregnancy outcomes	
Hypertensive disorder during pregnancy [b]	
Dose 3 received in 1st trimester	1.07 (0.94 to 1.21)
Dose 3 received in 2nd trimester	1.06 (0.94 to 1.19)
Dose 3 received in 3rd trimester	NA
Placental abruption	
Dose 3 received in 1st trimester	0.66 (0.50 to 0.88)
Dose 3 received in 2nd trimester	0.93 (0.75 to 1.15)
Dose 3 received in 3rd trimester	1.11 (0.71 to 1.73)
Cesarean delivery	
Dose 3 received in 1st trimester	0.87 (0.82 to 0.92)
Dose 3 received in 2nd trimester	0.91 (0.87 to 0.96)
Dose 3 received in 3rd trimester	1.03 (0.93 to 1.13)
Emergency cesarean delivery	
Dose 3 received in 1st trimester	0.82 (0.75 to 0.90)
Dose 3 received in 2nd trimester	0.94 (0.87 to 1.01)
Dose 3 received in 3rd trimester	1.11 (0.96 to 1.28)
Chorioamnionitis	
Dose 3 received in 1st trimester	0.42 (0.25 to 0.70)
Dose 3 received in 2nd trimester	0.75 (0.54 to 1.05)
Dose 3 received in 3rd trimester	1.16 (0.60 to 2.21)
Postpartum hemorrhage	
Dose 3 received in 1st trimester	0.87 (0.72 to 1.05)
Dose 3 received in 2nd trimester	1.06 (0.92 to 1.23)
Dose 3 received in 3rd trimester	1.15 (0.87 to 1.53)
Fetal and neonatal outcomes	
Stillbirth [c]	
Dose 3 received in 1st trimester	0.73 (0.45 to 1.19)
Dose 3 received in 2nd trimester	0.61 (0.39 to 0.94)
Dose 3 received in 3rd trimester	0.26 (0.04 to 1.95)
Preterm birth <37 weeks [c]	
Dose 3 received in 1st trimester	0.92 (0.81 to 1.04)
Dose 3 received in 2nd trimester	0.94 (0.86 to 1.04)
Dose 3 received in 3rd trimester	0.89 (0.71 to 1.11)
NICU transfer [d]	
Dose 3 received in 1st trimester	0.90 (0.82 to 0.99)

Dose 3 received in 2nd trimester	0.98 (0.91 to 1.05)
Dose 3 received in 3rd trimester	1.01 (0.86 to 1.19)
5-minute Apgar score <7 [d]	
Dose 3 received in 1st trimester	0.89 (0.71 to 1.13)
Dose 3 received in 2nd trimester	0.99 (0.83 to 1.19)
Dose 3 received in 3rd trimester	0.95 (0.62 to 1.45)
Small-for-gestational-age (SGA) infant [e]	
Dose 3 received in 1st trimester	0.86 (0.76 to 0.97)
Dose 3 received in 2nd trimester	0.86 (0.79 to 0.95)
Dose 3 received in 3rd trimester	0.94 (0.78 to 1.14)

Abbreviations: CI, confidence interval

[a] Multivariable models were performed on ten multiple imputation datasets and adjusted for week of last menstrual period, maternal age, nulliparity, multifetal pregnancy, pre-existing maternal medical condition (composite of: asthma, chronic hypertension, diabetes, heart disease, thyroid disease), first prenatal care visit in the first trimester, smoking during pregnancy, self-reported substance use during pregnancy, maternal body mass index ≥30 kg/m2, neighbourhood median family income fifths, rural residence, public health region of residence, and four marginalization indices (residential instability, material deprivation, dependency, ethnic concentration).

[b] To ensure the correct temporal order of the exposure-outcome relationship, 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.

[c] All live births and stillbirths.

[d] Live births.

[e] Singleton live births.

Supplementary Table 6. Product-specific estimates for the third mRNA COVID-19 dose received during pregnancy

Outcome	Adjusted hazard ratio (95% CI) [a]
Pregnancy outcomes	
Hypertensive disorder during pregnancy [b]	
Pfizer	1.14 (1.02 to 1.28)
Moderna (including bivalent)	0.95 (0.83 to 1.08)
Placental abruption	
Pfizer	0.88 (0.71 to 1.08)
Moderna (including bivalent)	0.80 (0.63 to 1.01)
Cesarean delivery	
Pfizer	0.92 (0.88 to 0.96)
Moderna (including bivalent)	0.88 (0.84 to 0.93)
Emergency cesarean delivery	
Pfizer	0.93 (0.87 to 1.00)
Moderna (including bivalent)	0.87 (0.80 to 0.95)
Chorioamnionitis	
Pfizer	0.62 (0.44 to 0.86)
Moderna (including bivalent)	0.71 (0.49 to 1.05)
Postpartum hemorrhage	
Pfizer	1.08 (0.94 to 1.24)
Moderna (including bivalent)	0.89 (0.75 to 1.05)
Fetal and neonatal outcomes	
Stillbirth [c]	
Pfizer	0.62 (0.41 to 0.94)
Moderna (including bivalent)	0.66 (0.41 to 1.06)
Preterm birth <37 weeks [c]	
Pfizer	1.00 (0.91 to 1.09)
Moderna (including bivalent)	0.84 (0.75 to 0.93)
NICU transfer [d]	
Pfizer	0.96 (0.89 to 1.04)
Moderna (including bivalent)	0.94 (0.86 to 1.02)
5-minute Apgar score <7 [d]	
Pfizer	0.94 (0.79 to 1.13)
Moderna (including bivalent)	0.97 (0.79 to 1.19)
Small-for-gestational-age (SGA) infant [e]	
Pfizer	0.87 (0.80 to 0.95)
Moderna (including bivalent)	0.86 (0.78 to 0.96)

Abbreviations: CI, confidence interval

[a] Multivariable models were performed on ten multiple imputation datasets and adjusted for week of last menstrual period, maternal age, nulliparity, multifetal pregnancy, pre-existing maternal medical condition (composite of: asthma, chronic hypertension, diabetes, heart disease, thyroid disease), first prenatal care visit in the first trimester, smoking during pregnancy, self-reported substance use during pregnancy, maternal body mass index ≥30 kg/m2, neighbourhood median family income fifths, rural residence, public health region of residence, and four marginalization indices (residential instability, material deprivation, dependency, ethnic concentration).
[b] To ensure the correct temporal order of the exposure-outcome relationship, 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.
[c] All live births and stillbirths.
[d] Live births.
[e] Singleton live births.

Supplementary Table 7. Association between third COVID-19 vaccine dose received during pregnancy and adverse pregnancy, fetal, and neonatal outcomes following exclusion of individuals who had confirmed COVID-19 illness before or during pregnancy.

Outcome	Adjusted hazard ratio (95% CI) [a]
Pregnancy outcomes	
Hypertensive disorder during pregnancy [b]	1.02 (0.92 to 1.14)
Placental abruption	0.88 (0.72 to 1.08)
Cesarean delivery	0.91 (0.87 to 0.95)
Emergency cesarean delivery	0.93 (0.87 to 1.00)
Chorioamnionitis	0.76 (0.55 to 1.06)
Postpartum hemorrhage	1.02 (0.89 to 1.18)
Fetal and neonatal outcomes	
Stillbirth [c]	0.51 (0.34 to 0.76)
Preterm birth <37 weeks [c]	0.91 (0.84 to 1.00)
NICU transfer [d]	0.97 (0.90 to 1.04)
5-minute Apgar score <7 [d]	0.95 (0.80 to 1.14)
Small-for-gestational-age (SGA) infant [e]	0.87 (0.80 to 0.95)

Abbreviations: CI, confidence interval

[a] Models were 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 Supplementary table 2.

[b] To ensure the correct temporal order of the exposure-outcome relationship, 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.

[c] All live births and stillbirths.

[d] Live births.

[e] Singleton live births.

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