STUDY PROTOCOL

Study Title:	**P**regnant and **LA**ctating Individuals & **N**ewborns COVID-19 **V**accination (PLAN-V) Prospective Cohort Study
Study Design	Multi-centre prospective cohort study
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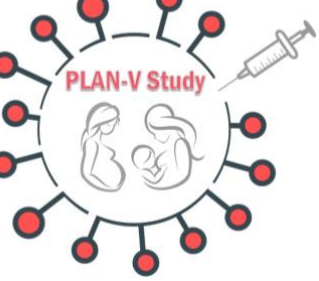

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LAY SUMMARY

There is an urgent need for research initiatives to provide evidence regarding the safety of COVID-19 vaccines in pregnant women/individuals, the immune response they generate, and the extent of protection they provide to mothers and their newborns. The PLAN-V Study will build on the successes of the COVID-19 Ontario Pregnancy Event (COPE) Network - a collaboration of 13 obstetrical hospitals in 6 of Ontario's' largest cities - to launch an in-depth study of pregnant women/individuals and their newborns.

We will recruit participants who receive the COVID-19 vaccine in pregnancy for close clinical follow-up, detailed data collection and biological sample analysis in pregnancy, at delivery and across the postpartum period. We will evaluate maternal immune responses to vaccination and examine evidence for transfer of protective antibodies to the newborn.

We have a successful track-record of research on COVID-19 infection, vaccination in pregnancy and multi-site birth cohorts. Our team includes obstetricians; maternity and newborn care specialists; virologists; infectious disease specialists; and vaccine and public health experts. This work will address key questions about COVID-19 vaccines during pregnancy that are important to Canadian families and their care providers. The PLAN-V Study is designed to fill critical knowledge gaps, and in doing so, will help inform public health recommendations, guide vaccine awareness efforts for pregnant women/individuals, and support patient counselling and informed decision-making by Canadians.

1. BACKGROUND AND RATIONALE

1.1. Background

Pregnant women/individuals are considered a high-risk population for COVID-19 infection, with higher disease severity, higher rates of hospitalization, intensive care unit admission, and death compared to non-pregnant individuals. Information related to COVID-19 vaccines in development are rapidly evolving. Pregnant women/individuals were excluded from the Phase II and Phase III vaccine trials completed to date. Therefore, there are no data on the safety of COVID-19 vaccines in this population or the effects of these vaccines in pregnancy, on the breastfed infant or on milk production.

In March 2021, the Society for Obstetricians and Gynaecologists of Canada (SOGC) re-affirmed their position that "*Women who are pregnant or breastfeeding should be offered vaccination at any time during pregnancy if they are eligible and no contraindications exist*".[1] In April 2021, amid reports of alarming numbers of pregnant women in intensive care units and calls to action by maternity care providers, the Ontario Ministry of Health declared pregnant women as a high priority population for vaccination, removing previous requirements for proof of physician counselling. However, the lack of data in this population still makes it challenging for pregnant women/individuals to make informed decisions about COVID-19 vaccination during pregnancy, and for their health care providers to provide evidence-based counselling. There remains an urgent need to monitor vaccine immunogenicity and safety in this population to address critical questions about the risks and benefits for vaccination on maternal, pregnancy and longer-term child health.

1.2. Our Approach

We will build on existing resources and expertise available through the COVID-19 Ontario Pregnancy Event (COPE) Network - a collaboration of 13 obstetrical hospitals in 6 of Ontario's largest cities - **to establish a prospective, longitudinal cohort study of pregnant women/individuals and their infants.** COPE Network sites collectively handle ~75% of in-hospital Ontario births. To-date, of the current COPE Network sites, 10 have been designated to run COVID-19 vaccine clinics and the other 3 are within proximity to a designated clinic.

We will launch an in-depth investigation of the immunogenicity of COVID-19 vaccines in pregnant women/individuals, and the role of maternal vaccination for the protection of their newborns. The study will include extensive Ontario-wide maternal and newborn bio-sampling in the prenatal, delivery and postpartum periods to address critical questions including: **(1)** ***What is the immunogenicity of COVID-19 vaccines in this population, (2) What is the fetal/newborn immune response to maternal vaccination (3) Does timing of maternal vaccination in pregnancy affect fetal/newborn antibody transfer? (4) How durable are maternal and newborn immune responses? and (5) How do newborn immune responses differ between natural maternal COVID-19 infection in pregnancy versus maternal vaccination in pregnancy?*** Our design will enable us to compile detailed longitudinal maternal-newborn clinical and immune response profiles beyond what can be accomplished from larger surveillance projects.

The framework for collaboration, participant recruitment and sample collection exist through the COPE Network infrastructure and we can rapidly operationalize this study. Since May 2020, the COPE Network has been collecting maternal and infant samples to generate complete infection and antibody profiles [CIHR-funded VR4-172760].[3] To date, more than 150 SARS-CoV-2 infected participants have delivered at a COPE site, or are enrolled and pending delivery. The PLAN-V study is the natural progression of this work and will leverage existing study infrastructure to address key questions about immunogenicity of COVID-19 vaccinations in the pregnant population and the fetal/newborn immune response.

2. GOAL & OBJECTIVES

There is a pressing need for research to answer critical questions about the role of maternal vaccination for protection of the mother-infant dyad, inform public health recommendations and support evidence-based decision-making by Canadian families and their care providers.

Our goal is to generate rapid, reliable evidence specific to immunogenicity and safety of COVID-19 vaccines in the pregnant population. The specific PLAN-V Study objectives are:

1. To evaluate immunogenicity of COVID-19 vaccines in pregnant women/individuals and the fetal/newborn immune response to maternal vaccination.
2. To evaluate safety of COVID-19 vaccination in pregnant women/individuals based on obstetrical, fetal and newborn health outcomes.
3. To compare immune responses to COVID-19 vaccination and natural COVID-19 disease among pregnant women/individuals and their infants exposed *in utero*
4. To compare the immune responses to COVID-19 vaccination between pregnant and non-pregnant women/individuals.

3. METHODOLOGY

3.1. Study design and setting

PLAN-V is an Ontario-based prospective, longitudinal study that will consist of extensive biosampling and detailed data collection from pregnant women/individuals and their infants across the prenatal, delivery and postpartum periods. With this approach, we will generate detailed participant profiles that will enable us to explore vaccine reactogenicity;[4] vaccine-associated adverse events;[5,6] frequency of obstetrical and fetal/newborn outcomes; and measures of infant health and well-being. We will build on existing resources and expertise available through the **COVID-19 Ontario Pregnancy Event (COPE) Network** to establish a prospective, longitudinal cohort study of pregnant women/individuals, and their infants.

3.2. Study population

The PLAN-V Study will consist of **pregnant women/individuals** who are planning to receive a COVID-19 vaccine(s) at any stage in pregnancy.

3.2.1. Inclusion criteria

Participants must meet all of the following inclusion criteria at the time of enrollment to be eligible:

- Women/Individuals ≥ 16 years of age who are ≥7 $^{0/7}$ weeks' gestation on the day of enrollment
- Capacity to provide informed consent and to comprehend and comply with the study requirements
- Planning to deliver at a participating site hospital
- Planning to receive or have previously received one-dose of a Health Canada approved COVID-19 vaccine (any product, any number of doses) during the current pregnancy

Gestational age will be calculated based on the date of the first day of the self-reported last menstrual period (LMP) and corroborated by ultrasound. Early pregnancy prior to first ultrasound will be confirmed by urine pregnancy test, collected by study team at time of enrollment. Documented viable pregnancy is required prior to first vaccine, to continue in the study.

3.2.2. Exclusion criteria

Women/Individuals meeting any of the following criteria will not be eligible for participation in this study

- Cases with known major fetal concerns (e.g., major congenital malformations, chromosomal abnormalities) at the time of enrollment
- Women/Individuals who are fully vaccinated against COVID-19
- Women/Individuals who are pregnant due to surrogacy, or planning to give their child up for adoption
- Women/Individuals with a non-viable pregnancy (e.g., ectopic)

COVID-19 infection
• Women/Individuals previously infected with COVID-19 will be eligible for this study • Women/Individuals who become infected with COVID-19 during the study period will be eligible to continue with the study protocol. COVID-19 infection (test-positive date, variant information) and symptomology for both mother and infant (if applicable) will be documented.

3.3. Study Exposure

The exposure of interest is COVID-19 vaccination in pregnancy. Participants will be those who receive a Health Canada approved COVID-19 vaccine (any product, any number of doses) during pregnancy.

Participants will be recruited *before* they are fully vaccinated and are pregnant with a viable fetus.

3.4. Study Outcomes

3.4.1. Primary Outcomes

The primary outcome of interest will be immunogenicity of COVID-19 vaccines. We will measure:

- Seroconversion rates in vaccinated mothers
- SARS-CoV-2 antibody titres and their persistence in mothers after vaccination in pregnancy
- Transfer of antibodies to breastmilk/chestmilk
- Transfer and persistence of SARS-CoV-2 antibodies to the neonate/infant over the study period.
- Other immune response markers in mothers and infants
- Comparing infection-acquired and vaccine-acquired immunity against COVID-19 in mothers and newborns (Objective 3: COPE Substudy)
- Comparing immune responses to COVID-19 vaccination in pregnant and non-pregnant women/individuals (Objective 4: SSO Substudy)

3.4.2. Secondary Outcomes

Secondary outcomes will be those related to vaccine safety for maternal, pregnancy and newborn health.

- Secondary perinatal outcomes will include: maternal (death, non-delivery hospitalization, any infection, preterm labour, hypertensive disorders of pregnancy, placental abruption, postpartum hemorrhage), and newborn (preterm birth [<37 weeks], small-for-gestational-age [<10th percentile for gestational age and sex-specific birth weight],[7] fetal loss/stillbirth, term low birthweight [<2500g], 5-minute Apgar score ≤5, cord blood pH <7.0, length of hospital stay for the birth admission, admission to neonatal ICU for >12 hours; and a composite neonatal adverse outcome indicator [NAOI], which includes congenital anomalies).[8,9]
- Secondary postpartum outcomes will include: infant growth, frequency of infection (e.g., influenza, pneumonia, sepsis, acute respiratory infections, gastrointestinal), rates of re-hospitalization and emergency department visits during the follow-up period, and a composite indicator for pediatric complex chronic conditions namely:[10] neurologic and neuromuscular; cardiovascular; respiratory; renal and urologic; gastrointestinal; hematologic or immunologic; metabolic; other congenital or genetic defect; and malignancy. Finally, we will note infant deaths at any time during the study.

3.5. Study Procedures

3.5.1. Participant Recruitment

Self-Identification

Women/Individuals will have the opportunity to self-identify to participate in the study.

- Recruitment posters and brochures will be distributed throughout the clinical care areas of participating hospital sites.
- Recruitment posters and brochures will be posted at COVID-19 vaccine clinics.
- Recruitment posters and brochures will be distributed to the offices of obstetricians and family physicians, midwifery clinics and birth centres, private clinics and other establishments within the study catchment area in order to increase awareness and profile of the birth cohort.
- We will also advertise the study more widely, online and through the professional and personal social media accounts of participating investigators and institutions.

Active recruitment from antenatal clinics

Participants will also be actively recruited from participating perinatal care settings where possible.

3.5.2. Participant Screening

Self-Identification Participant Screening

Potential participants may self-refer via the PLAN-V website and be screened for eligibility by a member of the research team at the SCC. Screening logic is summarized in **Figure 1.** After eligibility is confirmed, the SCC will inform the Site Investigator/Delegate at the participating hospital site geographically closest to the participant. Site Investigator/Delegates will then take on the responsibility of contacting the participant for consent, enrollment and follow-up for data and sample collection.

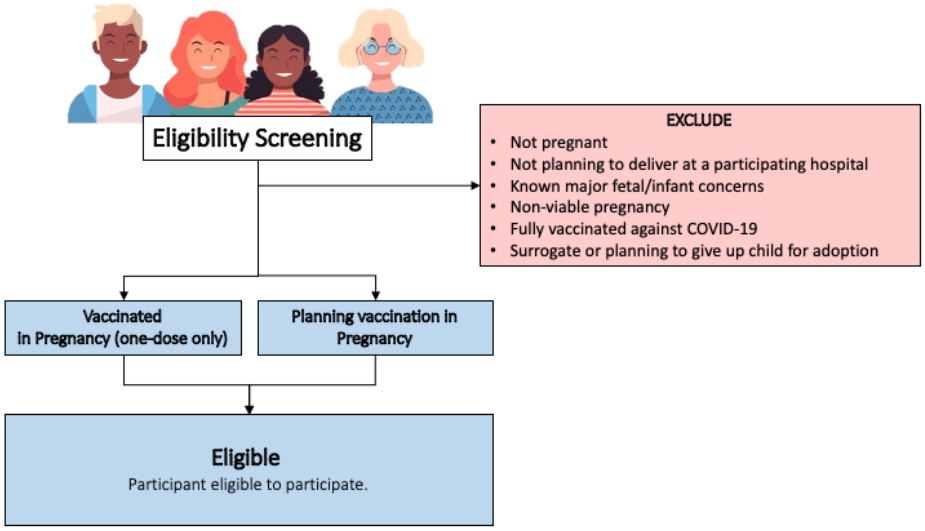

Figure 1. Screening logic applied to women/individuals interested in participating in the study.

Antenatal Clinics Participant Screening

There is more than one option for participant screening within the perinatal care setting.

1. A member of the potential participant's circle of care (healthcare provider (HCP)) identifies an individual as eligible for participation in the study, based on the inclusion/exclusion criteria, and approaches the individual to see if they would be interested in learning more about the study from the study team. If

the individual is interested, the HCP informs the study team that the potential participant would like to learn more, the potentially eligible participant contacts the study team based on locally approved methods.

2. A study team member screens the local institutional electronic medical record (EMR) and/or medical charts for participant eligibility. Potential participants identified are contacted by study team as per local institutionally approved methods.

3.5.3. Participant Consent and Enrollment

Written informed consent (via wet ink signature, verbal consent with deferred wet ink signature, scanned/photo copy of wet ink signature or electronic signature where permitted by the participating hospital site research ethics board) will be obtained from the participant prior to performing any protocol-specific procedures. Participants will provide consent for themselves and on behalf of their infants.

The Site Investigator/Delegate will discuss with each participant the nature of the study and the study requirements and restrictions. Consent form review will be conducted in-person, over the phone, or via video conference using a locally-approved, licensed institutional video conferencing platform. The participant will be informed of their right to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. The participant will be allowed as much time as required to consider the information. They will have the opportunity to question the Site Investigator/Delegate and consult with their primary care provider or other independent parties (e.g., their partner).

We will employ a consent model, in which participants consent to the current study as well as secondary use of collected data and samples. Our consent will cover consent to obtain data from participant medical charts, enable linkage of participant records with birth registry and health administrative data for more in-depth and longer-term follow-up, use samples and data in future research, and ask for permission to contact participants for future research opportunities.

The consent form will be signed and dated by both the participant and the Site Investigator/Delegate, and a copy will be given to the participant, and one copy will be retained at the study site.

3.5.4. Study Contacts/Follow-up Schedule

Study contacts will be made at baseline, post-vaccination, delivery and across the postpartum period. The extent of data and sample collection will vary by time-point (**See Figure 2).**

- Visit 1 (V1) will occur prior to 1st dose (if applicable)
- Visit 2 (V2) will occur ≥ 14 days after 1st dose and prior to 2nd dose
- Visit 3 (V3) will occur ≥ 14 days after 2nd dose and prior to Visit 4
- Visit 4 (V4) will occur 90 days ± 14 days after last dose
- Visit 5 (V5) will occur 180 days ± 14 days after last dose
- **Baseline** questionnaire will occur at the time of enrollment prior to or during V2, following participant consent.
- **General follow-up** questionnaires may be completed during the study visit or completed prior to the following study visit
- **Reactogenecity questionnaire 1 (RQ1)** must be completed prior to 2nd dose
- **Reactogenecity questionnaire 2 (RQ2)** must be completed within 30 days after last dose (for single vaccine or second dose)
- **Delivery follow-up** will include secondary data collection (to reduce burden on participants during the hospital delivery admission), and sample collection.

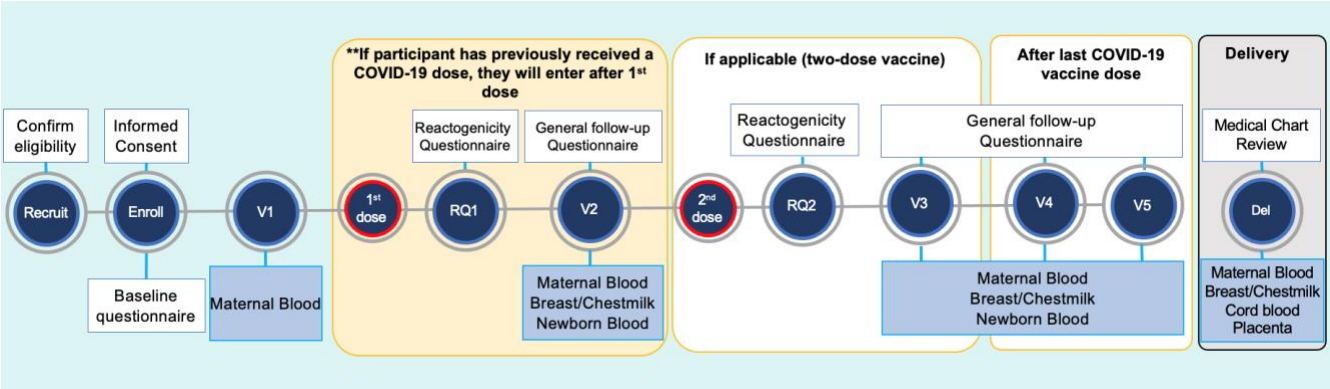

Figure 2. Study contacts/follow-up schedule.

3.5.5. Communication with participants for follow-ups visits and/or reminders for questionnaires

We will collect the preferred contact information (i.e., telephone number and/or email address) of participants at the time of consent to facilitate follow-up visits and/or reminders. Participants agreeing to email communication will be informed that communication via email is not absolutely secure. The study team will contact the participant for the purposes of booking and reminding participants of follow-up appointments and completion of study questionnaires. No sensitive personal information will be shared via any text-based communication (e.g., email, SMS text, post).

3.5.6. Participant Compensation

Participants will be compensated for parking or bus fare for all in-person visits scheduled outside of their regularly scheduled obstetrical clinic visit to the study site, to offset the costs of participation. In addition, participants will be provided with a $5 gift card to a coffee shop at each in-person study visit to acknowledge their time participating in the study. A $5 gift card to a coffee shop will also be given to participants who complete all study questionnaires.

3.5.7. Premature Withdrawal/Discontinuation

Reasons for participant withdrawal from the study will be documented. If a participant no longer wants their samples to be used in this research, they can request to have their samples destroyed. However, samples will not be destroyed if they have been used in their entirety, or if they have been shared with a 3rd party. Collected data and test results from samples already collected for the study will be retained such that withdrawal will only affect future data or sample collection. Participants who withdraw from the study will no longer be contacted.

If a participant does not complete a study questionnaire, or does not contribute one or more study samples (by choice, or due to other factors) they are free to do so. Incomplete data or bio-sample collection will not exclude participants from the study.

An individual's participation may also be terminated prematurely at the request of the Site Investigator/Delegate, or the Study Coordinating Centre.

3.6. Data Collection

This study will involve a combination of primary and secondary data collection.

Sex and Gender-based Analysis Plus (SGBA+) considerations

All pregnant participants will be biological females, however through our primary data collection tools we will be able to gather information on gender and gender-related factors that shape the pregnancy and postpartum experience including self-reported ethnicity, age, income, education, and geography. In addition to maternal sex, we will collect information on current gender identity, sexual orientation and partnership status. All documents will be written with gender-inclusive language to improve engagement with members from the LGBTQ+ community. Infant biological sex assigned at birth will be used to detect effects within sex strata and potential biological differences influenced by infant hormones levels circulating in the blood at time of sampling.

3.6.1. Primary Data Collection

Primary data collection forms will be made available electronically (as fillable PDF documents or online forms), but may also be provided/completed in hard copy to suit the unique needs of each participating research site and participant visit. Where necessary, participants will have the option to have data collection forms mailed to them with pre-paid return envelopes to the research site or SCC. Thus, questionnaires can be completed at-home by participants, in-person during a scheduled study visit, or over the telephone with the Investigator/Delegate, as needed.

The primary data collection schedule is summarized in Table 1.

Table 1. Primary Data collection schedule for vaccinated participants

	Enrollment	Post-vaccination Follow-up[1]				
		RQ1 and RQ2	V2	V3	V4	V5
Baseline Questionnaire	X					
Reactogenicity Questionnaire		X				
General Follow-up Questionnaire			X	X	X	X

[1]Post-vaccination follow-up may occur or extend into the postpartum period depending on when participants enroll into the study.

- If participant is getting a 2-dose vaccine, and dose 2 scheduling is delayed (for any reason – federal/provincial/local recommendations, participant reasons), data and sample collection will be done every 3 months until dose 2 is administered.
- Baseline questionnaire must be completed prior to or at V2.
- General questionnaires must be completed prior to or at following study visit.
- RQ1 must be completed prior to 2nd dose.
- RQ2 must be completed within 30 days after last dose (for single vaccine or second dose)*
- If participant is getting a 2-dose vaccine, and dose 2 scheduling is delayed (for any reason – federal/provincial/local recommendations, participant reasons), data and sample collection will be done every 3 months until dose 2 is administered.

Baseline questionnaire

A baseline questionnaire will be administered **at enrollment** to document participant characteristics. We will collect socio-demographic information (e.g., maternal age, ethnicity, occupation, education, household income), medical and obstetrical histories (e.g., parity, pre-existing conditions), receipt of blood products or other vaccines in pregnancy, other lifestyle risks (e.g., tobacco, alcohol and other substance use), and previous SARS-CoV-2 infection history. Key factors influencing participant decision-making to receive the COVID-19 vaccine (decision needs, information access, family and societal pressures) will be documented.

Reactogenicity questionnaires

After each COVID-19 vaccine dose we will collect priority variables for studying COVID-19 vaccination in the maternal-newborn population[11]:

- **COVID-19 vaccine data**: vaccine product (e.g., Moderna, Pfizer-BioNTech, Janssen (Johnson & Johnson), Oxford-AstraZeneca, etc.), dose number (one or two) and date received (to calculate timing of exposure in pregnancy or postpartum relative to delivery, and length of time between doses, if applicable). Scheduled dates of second COVID-19 vaccine doses (if applicable) will also be collected.
- **Reactogenicity:** injection site (e.g., bruising, swelling, pain) and systemic (e.g., fever, headache, muscle ache, fatigue) reactogenicity since the participant received the most recent vaccine dose.

General follow-up questionnaires
At each subsequent follow-up timepoint:

- **If the participant is still pregnant:** We will ask about significant changes in maternal and fetal health (e.g., new medical diagnoses or illnesses), maternal receipt of any blood products or other vaccinations, and any new maternal COVID-19 diagnoses (including variant information if known) since the last study visit.
- **If the participant is postpartum:** We will ask about significant changes in maternal and infant health (e.g., new medical diagnoses or illnesses), receipt of any blood products or other vaccinations (mother or infant), infant feeding method (e.g., mother's own breastmilk/chestmilk, donor milk, formula, other, combination) and infant growth (e.g., weight, length). We will also ask about any new maternal or infant COVID-19 diagnoses (including variant information if known) since the last study visit.

3.6.2. Secondary Data collection

Obstetrical, delivery and neonatal outcome data will be extracted from patient medical charts and will include information on pregnancy complications (e.g., hypertensive disorders of pregnancy, diabetes in pregnancy), delivery (e.g., type and mode of delivery, type of labour, live/stillbirth outcome) and newborn outcomes (e.g., gestational age at birth, birthweight, Apgar scores, NICU admission, need for resuscitation, IV antibiotics and other medications, feeding method from birth to hospital discharge).

Chart reviews will also be conducted if additional information is required to complete/verify the maternal and infant(s) data collection, and/or new information is revealed through participant correspondence. Participants who have an unanticipated delivery at a non-participating hospital site or hospital site without research coordinator support will be asked to sign an 'authorization for release of information' form to allow the research team access to their medical records for data extraction.

3.7. Sample Collection, Shipping and Analysis

3.7.1. Sample collection

Participants will be asked to contribute biological samples. We will allow participants to choose the scope of sample collection at each time-point. Samples will include maternal blood; breastmilk/chestmilk (postpartum collection only); and newborn blood (including cord blood at delivery). (Table 2)

Sampling will be coordinated alongside routine clinical collections where possible to minimize burden to participants. If participating hospital sites have sufficient capacity and resources, participants will be given the option to (1) return to the hospital or affiliated community clinic for sample collection/drop-off; (2) schedule a home visit with a research nurse/coordinator for sample collection/pick-up; (3) mail-in samples, if dried blood spot is preferred by the participant.

For the protection of all parties, both the Site Investigator/Delegate conducting the appointment and the participant will be directed to answer a series of self-assessment questions to assess likelihood or risk of COVID-19 infection before attending in-person visits.

Table 2. Sample collection schedule for vaccinated participants

	Visit 1	Post-vaccination Follow-up[3]				Delivery
		Visit 2	Visit 3	Visit 4	Visit 5	
Maternal blood[1]	X	X	X	X	X	X
Baby(ies) blood[1,2]		X	X	X	X	
Breast/Chest milk[2]		X	X	X	X	X
Cord blood						X
Placenta						X

[1]Blood samples will be taken as peripheral blood draws, or as dried blood spot samples, as per participant preferences.
[2]Baby(ies) and milk samples will only be collected after delivery.
[3]Post-vaccination follow-up schedule will be the same for all vaccine doses (dose 1 or dose 2, if applicable).

- Visit 2 will be scheduled for ≥ 14 days after 1st dose and prior to 2nd dose
- Visit 3 will be scheduled for ≥ 14 days after 2nd dose and prior to visit 4
- Visit 4 will be scheduled for 90 days ± 14 days after last dose
- Visit 5 will be scheduled for 180 days ± 14 days after last dose
- If participant is getting a 2-dose vaccine, 1-month follow-up for data collection for dose 1 will occur before dose 2 administration.
- If participant is getting a 2-dose vaccine, and dose 2 scheduling is delayed (for any reason – federal/provincial/local recommendations, participant reasons), data and sample collection will be done approximately every 3 months (~120 days) until dose 2 is administered

Blood samples

To enhance feasibility, maternal and infant blood samples will be collected as either peripheral whole blood or as dried blood spot samples, as per participant preferences.

Peripheral blood will be drawn via venipuncture. Cord blood will be collected immediately after delivery. Serum will be isolated from blood samples. Where possible, serum aliquots will be frozen at ≤-20°C until shipment.

For participants who prefer dried blood spot sampling, blood will be drawn by finger- (maternal), or heel-prick (newborn) using a sterile lancet. Blood drops will be collected on to protein saver cards, dried and stored protected from light in a climate-controlled setting until shipment.

Breastmilk/Chestmilk

To assess the potential for antibody transfer to breastmilk/chestmilk, breastmilk/chestmilk will be collected at the delivery visit, and each subsequent postpartum visit, if the participant chooses to breastfeed/chestfeed their newborn.
Breastmilk/chestmilk will be collected by hand expression or by pump into a sterile container. Where possible, samples will be divided into smaller aliquots. Samples will be frozen at ≤-20°C until shipment.

Placental biopsies

Placental biopsies will be taken from the umbilical side of the placenta, evenly spaced around the cord insertion site. Samples will be flash frozen in liquid nitrogen or on dry ice and stored at ≤-20°C until shipment.

3.7.2. Sample shipping/return to the Study Coordinating Centre

Samples will be labelled with a unique study ID upon collection. Study ID and corresponding participant information will be retained in site-specific master logs and securely stored on hospital/institutional approved servers. Samples will be shipped to the SCC for processing.

Participants submitting dried blood spot samples will have the option to mail-in these samples. In these cases, participants will be provided with a sample collection kit either in-person at a previous study visit or mailed-out

(sterile swabs, alcohol wipes, lancets, Protein Saver Card labelled with the participant's unique study ID, and detailed instructions) along with a pre-paid return envelope addressed to SCC.
De-identified samples will be distributed to collaborating laboratories for analysis. Unused samples will be retained at the SCC. Sample handling, transportation and packaging will adhere to regulations specified for potentially infectious materials.

3.7.3. Sample Analysis

Data derived from sample analysis will be linkable to the data file generated from primary and secondary data collection.

Antibody Response to Vaccination

Blood and breastmilk/chestmilk samples will be evaluated for antibodies to SARS CoV-2 and neutralizing antibodies to assess maternal and newborn immune responses to maternal vaccination in pregnancy. All samples will be analyzed using a high-throughput enzyme-linked immunosorbent assay based on previously published methods.[12,13] The assay probes for IgA, IgM and IgG anti-SARS-CoV-2 antibodies and also maintains sensitivity in the detection of antibodies raised against variants of concern: P1, B1.1.7 and B.1.351. The serological assay detects antibodies against the nucleoprotein (N), the receptor binding domain (RBD) and the full trimeric spike (S). Test sensitivity is 100% at 10 days post-symptoms and specificity is 99.2% as tested against pre-pandemic samples (manuscript in preparation). Such a strategy can distinguish infection-acquired immunity (against N+S+RBD) vs vaccine-induced immunity (S+RBD only). We will also run Neutralization assays (snELISA) on the full spike protein, based on previously published methods.[14] A positive cut-off will be established, equal to the mean of the optical density (OD) values of the negative control samples on the respective plate plus 2x the standard deviation of the OD value distribution from pre-COVID-19 plasma/serum. Background-corrected OD values will be divided by the cut-off to generate signal-to-cutoff (S/CO) ratios. Samples with S/CO values greater than 1.0 will be considered positive. Relative antibody levels measured against a standard curve will also be reported.

Biomarker evaluation

To add understanding to the immunological microenvironment driving the quality and quantity of maternal and newborn antibody responses to maternal COVID-19 vaccination, serum samples will be analyzed for relevant biomarker expression (e.g., serum cytokines). Multiplex immunobead-based assays (BioRad) will be used to quantify serum cytokines.

3.7.4. Sample Retention

Placental biopsies and unused blood and breastmilk/chestmilk samples will be stored at the SCC for future research (e.g., placenta immunohistochemistry, metabolomic analyses). Banked samples, when paired with the detailed PLAN-V dataset will be an important resource for future research.

Objective 3 - COPE Sub-study
Comparing immune responses to COVID-19 vaccination and natural COVID-19 disease among pregnant women/individuals and their infants exposed in utero

Study design: A cross sectional analysis of maternal and infant samples at the time of delivery.

Study Population: We will use samples collected at the time of delivery from mother-infant dyads who were enrolled in the current PLAN-V study and the PI's CIHR-funded COPE Network study (CTO ID 2168).[3]

- PLAN-V study participants: Mother-infant dyads in which mothers received at least one dose of the COVID-19 vaccine in pregnancy (any type). Eligible dyads will be those where mothers had no COVID-19 infection history and from whom maternal blood and infant cord blood samples were collected at delivery (i.e., vaccinated mother-infant dyads from the pregnancy group).
- COPE Network study participants: The COPE Network Study is an ongoing pregnancy and birth cohort study of mothers with documented COVID-19 infection during pregnancy.[3] COPE Network study participants contributed both maternal blood and infant cord blood samples at delivery. Samples from more than 100 dyads have been collected to date.

Exposures: The exposure of interest is maternal COVID-19 vaccination (PLAN-V Study) or infection (COPE Network Study) in pregnancy.

Outcome Measures: The primary outcomes are: seroconversion rates and antibody titres in pregnant women/individuals after COVID-19 vaccination and COVID-19 disease in pregnancy; trans-placental transfer of antibodies to neonates with *in utero* exposure to COVID-19 vaccination compared to COVID-19 disease; and differences in antibody transfer to breast/chest milk where samples are available. (Breastmilk/chestmilk samples are available from 50% of COPE Network participants). Secondary outcomes will be the nature and frequency of pregnancy and newborn outcomes at delivery.

Sample analysis. Maternal and newborn cord blood serum samples collected at the time of delivery will be evaluated for SARS CoV-2 specific IgG and neutralizing antibody titres and IgG subclass distribution. Samples will be analyzed using the methods described in Section 3.7.3.

Data Sources: Immunogenicity data (including seroconversion rates and antibody titres), and data on participant characteristics (including sociodemographic information and pregnancy, delivery and newborn outcomes), will be obtained from the PLAN-V and COPE Network study datasets. The PLAN-V dataset has been purposefully aligned with that of the COPE Network Study thereby facilitating robust comparison of antibody and health outcome data. The COPE Network Study dataset includes comprehensive information on SARS-CoV-2 infection (date and gestational age of diagnosis, virus titres, symptomology, maternal and newborn case management) derived from the Ontario provincial birth registry, BORN Ontario, which has province-wide data collection on COVID-19 infection in pregnancy. The PLAN-V study data will be transferred to BORN for analysis.

Objective 4: SSO Sub-study
Comparing immune responses to COVID-19 vaccination between pregnant and non-pregnant women/individuals

Study design: A retrospective analysis of immunological data generated from two research studies

Study Population: We will use samples collected from mothers who were enrolled in the current PLAN-V study and the *Stop the Spread Ottawa (SSO)* study (OHSN: 20200481-01H; uOttawa: H-09-20-6135).[3]

- **PLAN-V study participants:** Women/Individuals who received at least one COVID-19 vaccine dose in pregnancy (any type). We will limit this analysis to women/individuals without known history of SARS-CoV-2 infection, and for whom maternal blood samples were collected.
- **Stop the Spread Ottawa (SSO) participants:** Non-pregnant females of reproductive age without known history of SARS-CoV-2 infection who received at least one COVID-19 vaccine dose. SSO is an ongoing Ottawa-based, 1000-person prospective cohort study designed to investigate the SARS-CoV-2-specific immune response on COVID-19 convalescent and COVID-19 vaccinated individuals. A total of 126 non-pregnant individuals of reproductive age who have received a COVID-19 vaccine have been enrolled to date. Participants provide monthly blood samples post-vaccination using the same protocols described for the PLAN-V study protocol and are followed for 10 months, allowing for comparison across the PLAN-V time points.

Exposures: The exposure of interest is maternal COVID-19 vaccination in pregnancy (PLAN-V Study) or while not pregnant (SSO Study)

Outcome Measures: The primary immunological outcome measure will be antibody titres acquired from COVID-19 vaccination in pregnant women/individuals will be compared to those of non-pregnant women/individuals. Secondary outcomes will include vaccine reactogenicity, as well as nature and frequency of vaccine-related adverse events.

Sample analysis. Blood serum samples will be evaluated for SARS CoV-2 specific antibodies and neutralizing antibody titres, as well as antibody subclass distributions where appropriate. Samples will be analyzed using the methods described in Section 3.7.3.

Data Sources: Immunogenicity data (including seroconversion rates and antibody titres), vaccine-related data (including product information, reactogenicity and adverse events), and participant characteristics (including sociodemographics, health behaviour risks and medical history) will come from the PLAN-V and the SSO study datasets. The PLAN-V and SSO datasets are both stored at the OHRI, and data elements are aligned thereby facilitating robust comparison of outcome measures.

4. STATISTICAL ANALYSIS

Descriptive summary statistics will be presented for the study sample, and will include sociodemographic information, obstetrical histories and delivery details. Data will be summarized using frequency distributions for categorical variables, means and medians for continuous variables. A sex and gender-based analysis plus (GBA+) framework will be applied throughout to investigate both sex and gendered related aspects of vaccination among pregnant and their infants including, social and geographic position, race, age, sexuality, sex and gender.

Relative antibody levels will be reported on all positive tests as geometric mean (GM) and their 2-sided 95% confidence intervals (CIs). The maternal response to vaccination will be determined by anti-SARS-CoV-2 antibody levels in maternal serum. Antibody GM with 95% CIs will be compared across time points and between study groups for each sample type. The contribution of IgG subclasses to the total SARS-CoV-2 antibody response will also be reported. Extent and duration of antibody transfer to breastmilk/chestmilk will be evaluated. Infant antibody titres will also be examined to investigate the extent and duration of passive immunity conferred through antibody transfer via the placenta or breastmilk/chestmilk, if any.

Cytokine data will be correlated to detected antibody isotype titres to identify integrated, multi-factorial maternal and newborn immune response signatures to COVID-19 vaccination.

We will account for timing of maternal vaccination in pregnancy/postpartum, vaccine product, number of vaccine doses, COVID-19 infection history, and receipt of other vaccines (mother/child) within the study follow-up period in all analyses.

5. SAMPLE SIZE

Study power is calculated using our primary outcome, seroconversion, defined as a four-fold increase in antibody titre over baseline. mRNA vaccines produce a robust immune response in over 90% of non-pregnant women/individuals.[15,16] We will recruit 150 individuals who received a COVID-19 vaccine during pregnancy; a feasible goal based on our prior recruitment successes in the COPE Network Study and other obstetrical prospective studies.[17,18] This will give 93% to 95% power to detect a difference in the seroconversion rate of SARS-CoV-2 neutralizing antibodies of 15% (i.e., 95% vs 80%) alpha=0.05, depending on the comparison group. The sample size will also be sufficient to detect a ratio of 1.19 in the GM of antibody titres against the SARS-CoV-2 viral spike protein.[19,20]

6. ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Participants, adopted by the General Assembly of the World Medical Association (2008). The study will also be conducted in accordance with the protocol, the ICH/GCP, and applicable local regulatory requirements and laws.

6.1. Research Ethics Approval

The study will be initiated by the SCC at OHRI upon the written approval of the Clinical Trials Ontario (CTO) Research Ethics Board.

- The SCC will complete the *Provincial Initial Application* and obtain ethics approval, and if applicable, ongoing renewals of the study protocol, protocol amendments, or amendments to any study documents that are required at the provincial level.
- Site Investigators/Delegates will complete the *Centre Initial Application* on CTO and obtain ethics approval, and if applicable, ongoing renewals of the study protocol, protocol amendments, informed

consent forms, and all other relevant documents (e.g., recruitment advertisements) specific to their local site. Copies of additional, local approvals, if applicable, will be forwarded to the SCC prior to the study initiation or continuation at the site.

6.2. Potential risks and benefits to participants

As an observational study, there is minimal risk to the participants and their infants. No interventions will be undertaken in connection with the project. We anticipate no adverse events associated with the study protocol. All data and samples will be collected for research purposes only.

Although there are no medical risks associated with participating in this study, participants may feel some discomfort associated with blood sample collection. Other participants may feel unease or inconvenienced with providing samples for analysis in the current or future studies, or may feel uncomfortable answering some of the survey questions. We will allow participants to choose the scope of data and sample collection at each time-point. Incomplete data or sample collection will not be an exclusion criterion for this study. To minimize burden to participants, sampling will be coordinated alongside routine clinical collections or via home-visits where possible.

There are no direct benefits to participants for taking part in this study.

6.3. Privacy and Confidentiality

All data and samples will be collected for research purposes only. Analyses will be conducted on de-identified datasets. Samples will be de-identified before being shipped to the SCC for to distribution for local laboratories for sample analysis.

Personal health information and matched unique study IDs will be kept stored on hospital/institutional approved secure networks and will be accessible only by authorized members of each participating site.

6.4. Data and Sample Management

Data and sample management will be coordinated by the SCC at the OHRI. Data and sample transfer (as well as funding and other resource transfer as needed) between the participating sites and the SCC will be governed by a contractual research agreement initiated by the SCC at the OHRI.

All data will be collected, managed and securely stored on hospital/institutional approved servers (electronic copies), or in locked offices (hard copies). The study data will be either directly captured from participants or entered by the Site Investigator/Delegate into an electronic data capture system – Research Electronic Data Capture (REDCap) – managed by the SCC at the OHRI and licensed to the Children's Hospital of Eastern Ontario Research Institute (CHEO RI; the data custodian).

REDCap uses 128-bit data encryption, and provides role-based security requiring a user ID and password for access, facilitated by the SCC. Participants will be issued secure, web-based access to study questionnaires at the appropriate study follow-up timepoints. Site Investigators/Delegates at each participating hospital site will have access to REDCap via a unique account and password made available for each site/site user. Each site will only be able to access their site's participant data. Data validation (range and logic checks for all variables) will be embedded where possible. Data queries will be generated and shared with study sites to ensure accuracy and completion of data. The SCC and the CHEO RI (the data custodian), will have access to all data entered in REDCap. An audit trail will be maintained for all data entry and modification. The online system (REDCap) will allow viewing the audit trail for all of the data collection forms.

Sample data will be managed separately in an encrypted file until it is merged into a single de-identified analytical file.

Research data and samples collected for this project will be archived for up to 25 years after study termination. At the end of the archival period, electronic data files will be securely deleted and any hard copies shredded. Samples will be destroyed as per institutional practices.

7. STUDY TIMELINE

We plan to conduct this research over a 2-year period. Participant recruitment, sample and data collection will begin immediately upon receipt of research ethics approval. Sample analysis will be conducted bi-weekly. Interim reports/data analysis will be completed throughout the study period.

The study timeline may be subject to changes due to duration of the pandemic, COVID-19 vaccine roll-out, and study funding.

8. KNOWLEDGE TRANSLATION

We will employ an integrated knowledge translation (iKT) strategy whereby Public Health and other Knowledge Translation partners will be involved at all project stages (design, implementation, interpretation, dissemination). The iKT plan will include strategic, traditional and patient-oriented methods of dissemination customized for patients, decision makers, clinicians and researchers.

Strategic dissemination will be achieved through regular reporting to our project partners and more broadly throughout our professional networks. The Society for Obstetricians and Gynaecologists of Canada (SOGC) produces clinical practice guidelines for public and medical education. SOGC has prioritized collating evidence-based information and recommendations on COVID-19 infection and vaccination in pregnancy. SOGC will review our research findings for integration into practice recommendations, and other patient and provider information tools and resources (Cook; Chief Scientific Officer). Public Health Ontario (PHO) works with the Ministry of Health, public health units and other health system partners to provide evidence and expertise that will support COVID-19 efforts. This includes providing scientific advice, resources and surveillance to support implementation of COVID-19 vaccine programs. PHO partners have committed their scientific expertise to the study (Buchan; infectious disease epidemiology, vaccine coverage and program evaluation) and will support timely integration of findings into evidence briefs (Carsley; Chair, Health Growth & Development Evidence Network). The BORN Ontario birth registry manages accurate and reliable reproductive data for population health surveillance and program/service planning to improve Ontario's maternal child health system[21]. BORN is coordinating province-wide data collection on COVID-19 infection in pregnancy and will be conducting provincial vaccine safety surveillance. BORN will provide their technical and scientific expertise toward the study design, and support knowledge dissemination. (Walker; Scientific Director). At the local level, the Champlain Maternal Newborn Regional Program (CMNRP) will help advertise the study to the public, and disseminate our findings by hosting webinars, and distributing educational materials.

Among our team, we also have direct access to vaccine and maternity care authorities including the National Advisory Committee on Immunization (NACI) (Fell, Pham-Huy) and the Ontario Provincial Council for Maternal and Child Health Maternal-Neonatal COVID-19 Task Force (Walker).

Traditional dissemination will occur in the form of peer-reviewed publications and scientific presentations targeted at clinicians and researchers. To ensure optimal impact we will apply open science best practices across

all aspects of the research program.[22–24] Where possible, anonymized data will be shared at the end of the program.

Public dissemination will be achieved through a combination of traditional and social media platforms. Public dissemination will be informed by **Patient Partners.** The COPE Network research hub in Ottawa runs a **Patient Partner Program** designed to integrate the experiences of pregnant women/individuals throughout the research process. We have found this to improve the quality of research, knowledge transfer, and advance patient care. All technical reports and scientific publications will be accompanied by **lay summaries** to ensure that our messaging is clear and easily understood. We will leverage **in-house communication/media support** to draft press-releases as the project achieves key milestones, so that these can be shared with the public.

A dedicated project website will document recruitment progress and host all technical reports, publications, presentations and lay summaries.

9. RESEARCH TEAM

We have assembled a highly qualified, interdisciplinary team to complete this work. Each individual has been chosen for their specific expertise – either clinical, technical or methodological, or for their capacity to support knowledge translation as decision makers or knowledge users. **Principal Investigator El-Chaâr** is the lead of the COPE Network, and NPA on a ~$800k CIHR operating grant for the ongoing COPE Network Study to characterize the impact of COVID-19 infection in pregnancy. She is engaged with existing national and international COVID-19 in pregnancy initiatives including, CANCOVID-Preg (a pan-Canadian surveillance project), and the WHO's Maternal newborn, child and adolescent health research networks. **Co-PI Langlois** is leading research on COVID-19 antibody neutralization efficiency and cellular immunity, with a combined $2.6M from CITF and CIHR. **Co-PI McGuinty** is an infectious disease clinician scientist leading work to provide insight into the body's response to COVID-19 infection and therapies.

The greater research team includes individuals with expertise across the following disciplines and specialties: maternal-fetal/obstetrical medicine/neonatal (**El-Chaâr, Walker, Lawrence, COPE Network site leads**), molecular virology and immunology (**Langlois, Crawley**), infectious disease medicine (**McGuinty, Cameron, Brophy, Pham-Huy, Brophy, Saginur**), pediatric and perinatal pathology (**El-Demellawy**); pediatric medicine (**Pham-Huy, Brophy, Lawrence**), perinatal epidemiology (**Fell, Walker, Wen, Corsi, Fakhraei**), infectious disease and vaccine epidemiology **(Fell, Brophy, Pham-Huy, Wilson, Fakhraei, Buchan**), sex and gender research (**Muldoon**), knowledge translation and dissemination (**Dunn, Murphy**), public health (**Carsley, Buchan**), perinatal registries (**Walker, Fell, Corsi**), evidence briefs and clinical guidelines for maternity and newborn care (**Cook, Carsley**). Each member has a history of collaboration with at least one other member of the team either through the COPE Network, or through other professional collaborations, further enhancing the feasibility of this project.

10. RELEVANCE AND IMPACT

This study will build on existing projects and infrastructure to provide insight into the impact on vaccine timing, dosing and type on immunogenicity and safety of COVID-19 vaccination in the maternal-newborn population, and placental antibody transfer to newborns. Our findings will be informative for knowledge-users and policy-makers on COVID-19 vaccination and support informed decision-making about COVID-19 vaccination for new and expectant Canadian families. Finally, this work will lay the foundation for longer-term follow-up studies of maternal and pediatric health outcomes after COVID-19 vaccination in pregnancy and the pivotal role of maternal vaccination for protection of newborns.

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