PROTOCOL

Respiratory Syn**c**ytial Virus (RSV) **V**accin**e** and Monoclonal Antibody T**re**atment in Canadian Pregnant In**d**ividuals and their Infants (**RECOVERED**): An Evaluation of Acceptability, Safety, and Efficacy

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SUMMARY

Title	Respiratory Syncytial Virus (RSV) Vaccine and Monoclonal Antibody Treatment in Canadian Pregnant Individuals and their Infants (RECOVERED): An Evaluation of Acceptability, Safety, and Efficacy
Goal	Provide data on pregnant to assess the acceptability, safety, and efficacy of infant RSV prevention interventions, including maternal RSV vaccination and infant monoclonal antibody, in this population
Objectives	1. To examine attitudes towards RSV vaccination and infant monoclonal antibody treatment for prevention of severe RSV disease in infants among pregnant individuals 2. To assess the safety of RSV vaccines and infant monoclonal antibody treatments in pregnant individuals and their infants 3. To describe the effectiveness of RSV vaccines in pregnant individuals in preventing severe infant RSV disease 4. To describe the effectiveness of infant RSV monoclonal antibody in preventing severe RSV disease in infants
Timeline	September 2024-September 2025
Project design	Prospective Cohort
Inclusion criteria	(1) At least 19 years of age (2) Became pregnant in 2024 or later (3) Currently residing in Canada
Data collection and time points	• Baseline survey administered at start of enrollment • Follow-up surveys sent every 3 months until delivery (indicated by the completion of the Pregnancy Outcomes survey) • Infant Outcomes survey sent 6 months after delivery • Reminders to complete follow up surveys will be sent out periodically throughout study duration

1.0 BACKGROUND

1.1 Epidemiology of RSV

Globally, respiratory syncytial virus (RSV) is the largest contributor to infant lower respiratory tract infections, which in turn lead to a high burden of infant hospitalization and mortality. (1) From birth until 24 months of age, most infants will be infected with RSV at some point, and around 2% of these infants will be hospitalized due to RSV. (2) In Canada, this percentage of RSV-related hospitalizations represents an annual rate of over 3000 hospitalizations per year, making RSV a prominent health concern. (2) Hospitalization risk is especially high for premature infants, those less than six months of age, and those with other significant comorbidities. (3)

To address RSV infection and the burden of care associated with these hospitalizations, two main solutions have been developed to provide protection to infants against severe RSV infections: a maternal vaccine and an infant monoclonal antibody (mAb). The maternal vaccine (RSVpreF) has been found to be effective in reducing infant severe lower respiratory tract infections within the first 90 days after birth that require medical attention/intervention by 57.1% as well as having no major safety concerns. (4) The infant monoclonal antibody treatment (nirsevimab) is also successful in reducing severe lowering respiratory tract infections requiring medical attention, with a reduction of 74.5% observed during the first 150 days of life in treated infants. (5) Both of these treatments were approved for use by Health Canada in 2023, with it being suggested that the use of infant monoclonal antibody treatment (nirsevimab) is preferable over the use of maternal vaccination (RSVpreF). (6)

1.2 Study Rationale

Current preferences and acceptability of the two approved forms of infant RSV immunization in the Canadian pregnant population is largely unknown. Previous studies have been completed on the preference between maternal RSV vaccination and infant monoclonal antibody treatment in pregnant women and people with varying results. (7-9) Studies conducted in the USA and Italy saw greater preference for infant monoclonal antibody treatment over maternal vaccination in their study populations, but a British study found the opposite trend. However, some of these studies were conducted prior to the approval of RSVpreF by major governmental health agencies (Health Canada, the U.S. Food and Drug Administration, European Medicine Agency) which may have had an impact on the perceptions that were reported. Preliminary data on attitudes towards RSV immunization interventions in Canadian pregnant women was collected as part of the COVERED project and indicates high acceptability and preference of maternal RSV vaccine in this population (unpublished), although the RSV questions included in the COVERED survey were limited.

The National Advisory Committee for Immunization (NACI), a panel of experts which makes vaccine recommendations to the Government of Canada, has suggested that the infant monoclonal antibody is preferable for use over RSVpreF and recommends provinces/territories move to universal delivery of nirsevimab to infants, which has resulted in varying financial coverage for these interventions by provincial health plans across Canada. (6, 10-12) Nirsevimab is covered for high-risk infants or all infants in some provinces/territories, but RSVpreF is not covered by any provincial/territorial government at this time. (6, 10-12) This recommendation by NACI and subsequent coverage by provincial health care plans was made without large-scale data on the preference and acceptability of the two immunization options among Canadian pregnant women and people. Previous research has shown that positive perception of vaccines during the COVID-19

pandemic in the Canadian pregnant population was a strong indicator for vaccine uptake, so acceptability and preference data on RSV immunization in Canadian pregnant women could help to ensure maximal uptake of RSV immunization and greatest reduction in severe RSV-related disease in infants. (13)

During the COVID-19 pandemic, our team created the COVERED Vaccine Registry, to similarly determine the safety, efficacy, and acceptability of COVID-19 vaccination in pregnant individuals by administering online surveys to assess vaccine, pregnancy, and infant outcomes and vaccine attitudes. We successfully recruited 8,000 pregnant and lactating individuals into COVERED and have demonstrated COVID-19 vaccine safety and effectiveness using this method. (14) Preliminary data on attitudes towards RSV immunization interventions in Canadian pregnant women was collected as part of the COVERED project and indicates high acceptability and preference of maternal RSV vaccine in this population (unpublished), although the RSV questions included in the COVERED survey were limited. We have modeled the present study off of the COVERED protocol, due the similar purpose and the success of the project.

This national study on the acceptability and perception of the RSV immunization strategies in Canadian women in the current context following approval of both immunization strategies and the limited current financial coverage in Canadian provinces is highly novel. We expect that this data will provide Canadian public health knowledge users, including the Public Health Agency of Canada (PHAC), the National Advisory Committee on Immunization (NACI), and provincial vaccine funding programs, with relevant data on the acceptability and interest in the RSV immunization strategies in the Canadian pregnant population to guide future recommendations for RSV vaccination in pregnancy and/or infant treatment.

2.0 OBJECTIVES

Primary objectives:

1. To examine attitudes towards RSV vaccination and infant monoclonal antibody treatment for prevention of severe RSV disease in infants among pregnant individuals
2. To assess the safety of RSV vaccines and infant monoclonal antibody treatments in pregnant individuals and their infants
3. To describe the effectiveness of RSV vaccination in pregnant individuals in preventing severe infant RSV disease
4. To describe the effectiveness of infant RSV monoclonal antibody treatment in preventing severe infant RSV disease

3.0 STUDY DESIGN

3.1 Study Design

Objectives will be addressed using a prospective cohort design. A public campaign will be launched to invite pregnant women and individuals across Canada to participate in online surveys with self-reported outcomes. This methodology has been modeled after that of the COVERED project, which saw great success in enrollment and participation.
This project will leverage the established national COVERED network and existing collaborations with public health partners.

3.2 Inclusion Criteria

(1) At least 19 years of age
(2) Became pregnant in 2024 or later
(3) Currently residing in Canada

4.0 PROTOCOL

4.1 Recruitment

Pregnant women and individuals will be invited to participate in a voluntary web-based surveillance. They will be followed prospectively as a cohort to collect data on attitudes and outcomes associated with vaccination and infant monoclonal antibody treatment for RSV. Recruitment will be targeted based on the inclusion criteria, regardless of vaccination/antibody treatment status or intention. Recruitment will occur through a social media and traditional media campaign and through dissemination of recruitment materials by health care providers. The study will have a UBC supported website that will contain study information as well as a link to the study e-consent. We plan to engage with physicians, midwives, The Society of Obstetricians & Gynaecologists of Canada, Black Physicians of Canada, Indigenous Physicians Association of Canada, and La Leche League to reach a diverse study population. We plan to recruit from local maternity, family medicine, and midwifery clinics, like Pomegranate and the Vancouver Family Practice Centre, as well as on the REACH BC website. We will also engage with the Oak Tree Clinic and the Maternal Fetal Medicine Clinic at BC Women's Hospital. We plan to implement a poster campaign with QR codes as well as utilize social media posts to share the study website using Instagram, Facebook and X (Twitter). As demographic data are collected from participants in the baseline survey, our team will be able to rapidly adjust the media campaign to target areas of the country or populations with lower enrollment, to ensure that a sample as diverse and representative as possible is included.

4.2 Data Collection

Once consent has been obtained, the baseline survey will automatically be pushed to the participant. The baseline answers will determine if pregnancy and or vaccine outcome surveys are to be answered at the same time. A short follow-up questionnaire will be administered every three months until delivery (if they have not yet delivered at the time of the baseline survey), to capture changes in maternal vaccination status, pregnancy outcomes, significant health events, infant RSV monoclonal antibody treatment status, and infant RSV/respiratory infection status. The follow-up surveys will determine if/when outcome surveys need to be completed. If consent is withdrawn, the study will immediately cease for the participant. The survey modules are as follows:

1. Baseline survey: Pregnancy status, vaccination status, demographics, health history, & pregnancy history - Administered at enrollment starting Sept 1, 2024
2. Vaccine Attitudes: Knowledge and perception of RSV, feelings, opinions, and attitudes towards RSV vaccination and infant monoclonal antibody
3. Pregnancy Outcomes: Pregnancy & neonatal outcomes – Administered if pregnancy started in 2024 and are not currently pregnant
4. Vaccine Outcomes: Answered if a dose of a maternal RSV vaccine received during the current pregnancy
5. Monoclonal Antibody Outcomes: Answered if infant received monoclonal antibody in he first 6 months of life
5. Follow-up survey: Pregnancy status, vaccination status, health events – administered every three months until delivery with reminders sent out periodically throughout study duration
6. Health Event: Significant health events resulting in a visit to the emergency department or

hospitalization – Administered if triggered by Follow-up survey
7. Infant Outcomes: Infant respiratory infection symptoms, emergency department visits, hospitalizations, & RSV diagnosis – Administered 6 months after delivery

Data collected from individuals who do not receive RSV vaccines/monoclonal antibody treatment will act as an internal comparison group. We will also capture self-identified gender through our online demographics questionnaire and examine differences by gender. Adverse events as detailed in data collection forms, severity and duration of adverse event, resultant medical visits (including to emergency department) or hospitalization, and treatments administered.

Pregnancy and infant safety outcomes measured are key outcomes identified previously for the COVERED project. These major pregnancy complications/outcomes include but are not limited to gestational hypertension, gestational diabetes, placental abruption, infant birthweight, preterm birth, NICU admission, congenital anomalies, spontaneous abortion or termination, and stillbirth or neonatal death.

4.3 Data Management / Stewardship

Participants will enter survey data directly into a secure REDCap database housed at the national coordinating centre at the University of British Columbia (UBC). The REDCap software uses a web server designed to enable secure transfer of data between a client computer and the data centre, located in a highly-secured area at UBC. Support for data management will be provided by the Faculty of Medicine Digital Solutions Research Technology Unit.

4.4 Statistical Analysis and Metrics

Vaccine confidence and attitudes, including intention to receive the RSVpreF vaccine or infant monoclonal antibody treatment (nirsevimb) , will be assessed using a validated survey grounded in the Theory of Planned Behaviour (TPB) and part of the WHO Vaccine Hesitancy Scale (VHS). (15,16) The TPB is well established as a psychological model to predict and understand health-related behaviours. This theory defines the most significant predictors of a health behaviour as attitudes, social norms (direct, indirect), and perceived behavioural controls; measures of each of these predictors will be included in the survey. Prior evidence from Canada has shown that this model is able to accurately predict vaccine uptake (17,18). The factors included in the VHS are vaccine lack of confidence and vaccine risk. All items in the TPB and VHS are measured on a 5-point Likert scale. Vaccine attitudes will be reported overall and by vaccination status. Comparisons among subgroups (e.g. by age, region, cultural background, and gender) will be conducted using linear regressions. Importantly, comparisons among subgroups (e.g. by age, region, cultural background, and gender) will identify priority areas for vaccine education and outreach.

The presence of any adverse outcomes (vaccine and pregnancy-related) will be compared between vaccinated and unvaccinated (both through maternal RSV vaccine and infant antibody treatment) using time-varying Cox's proportional hazards models and including important confounders. Effectiveness will be assessed descriptively through participant reporting of infant RSV/respiratory infection diagnoses in vaccinated and unvaccinated participants (both through maternal RSV vaccine and infant antibody treatment). Clinical features of breakthrough cases will be described in those vaccinated. Exploratory analyses will investigate differences between vaccinated and unvaccinated people (both through maternal RSV vaccine and infant antibody treatment).

As gender does not exist in isolation from other socially-relevant contextual factors such as class,

immigrant status, rurality, race, and indigeneity which, in turn, also affect health outcomes. We will collect data on all these factors and our analysis will adopt a SGBA+ approach to compare vaccine attitudes between gender groups and how these interact with other intersectional variables.

4.5 Knowledge Translation

We will disseminate findings from this study to public health officials and a diverse range of the Canadian population through a variety of strategies, including directed reports to policy makers and accessible, infographics and posts on social media to the general public., We will leverage our partnerships with pan-Canadian university communications departments to expand the reach of our knowledge translation outputs. Finally, our team includes clinician and policy knowledge users who will be active in the interpretation and dissemination of results, including amongst professional organizations that influence vaccine recommendations (e.g. NACI, PHAC, SOGC).

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