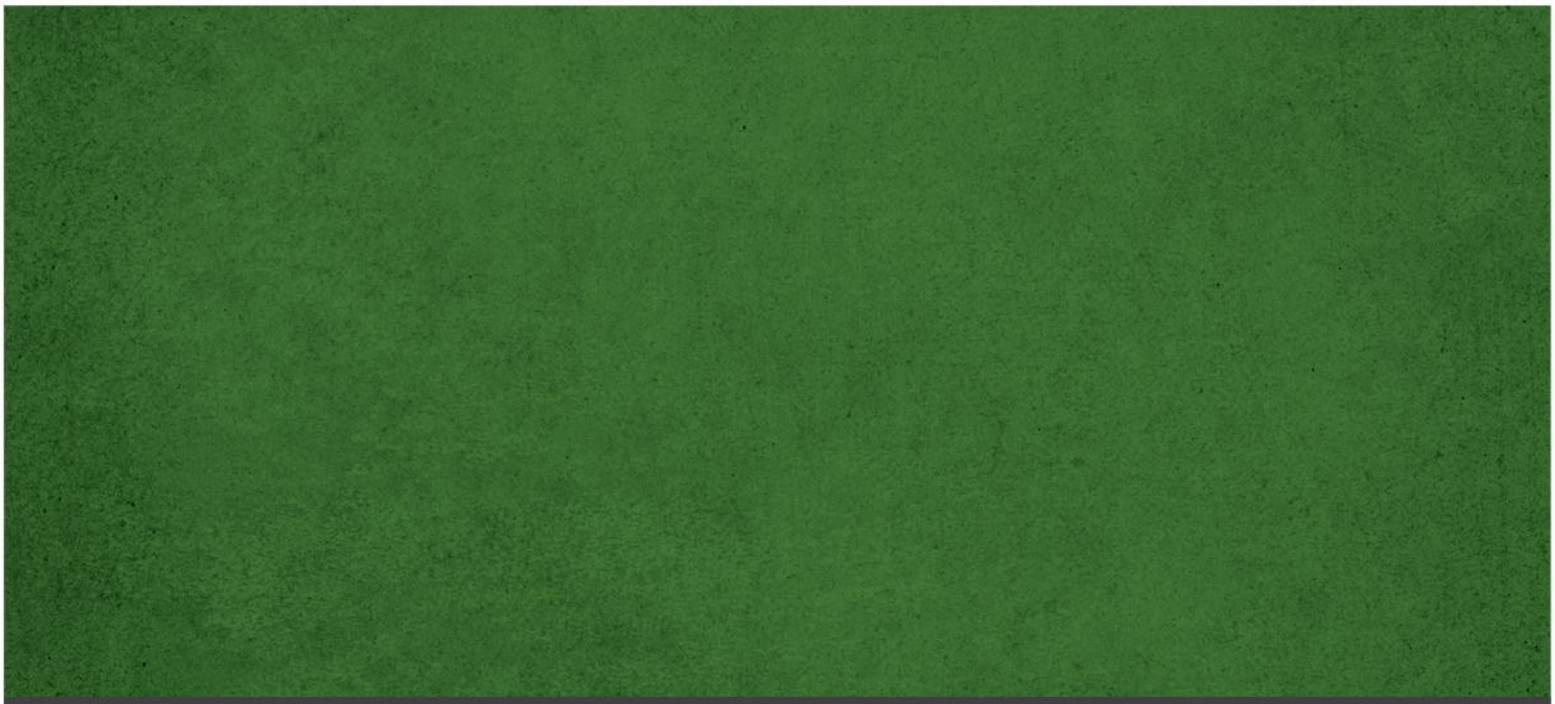
An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Updated guidance to protect infants and children from respiratory syncytial virus (RSV) disease: use of monoclonal antibodies (nirsevimab and clesrovimab) and the RSVpreF vaccine



PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

Public Health Agency of Canada
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TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

—Public Health Agency of Canada

Également disponible en français sous le titre :

Recommandations mises à jour pour protéger les nourrissons et les enfants contre la maladie causée par le virus respiratoire syncytial (VRS) : utilisation d'anticorps monoclonaux (nirsévimab et clesrovimab) et du vaccin RSVpreF.

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Preamble

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Not all NACI statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

Table of contents

Statement overview

Respiratory syncytial virus (RSV) is one of the most common respiratory pathogens in infancy and a leading cause of acute lower respiratory tract infection, hospitalization, and intensive care use in Canada. Almost all children are infected by two years of age, with the most severe outcomes occurring in the first months of life. While certain medical conditions increase the risk of complications, the majority of infants hospitalized each year are otherwise healthy.

The authorization of clesrovimab for infants entering their first RSV season, together with the rapid accumulation of effectiveness, safety, and economic data for nirsevimab and RSVpreF vaccination during pregnancy, prompted the National Advisory Committee on Immunization (NACI) to re-examine the overall evidence base and program options for Canada. NACI reviewed randomized trials, real-world studies, and modelling analyses. Monoclonal antibodies and vaccination during pregnancy consistently reduce medically attended RSV infection and hospitalization for infants, with high effectiveness observed against ICU admission.

For clesrovimab, trial data show strong protection against hospitalization and little to no difference in serious adverse events compared with placebo. For most infants not at increased risk of RSV disease, an effective RSVpreF program is expected to provide sufficient protection when vaccination occurs at least two weeks prior to birth.

Overall, NACI strongly recommends that provinces and territories implement universal seasonal RSV immunization programs for infants. In weighing programmatic choices, NACI considered clinical benefit alongside ethics, equity, feasibility, acceptability, and cost-effectiveness. Economic analyses indicate that at current product list prices, strategies that incorporate RSVpreF vaccination during pregnancy for infants born during the RSV season and more selective use of monoclonal antibodies are more economically favourable than broader universal monoclonal antibody use. Broader monoclonal antibody approaches become more attractive as prices fall or in higher-burden settings.

Jurisdictions should adopt either an infant monoclonal antibody program for infants in their first season, or an approach that includes RSVpreF vaccination during pregnancy for infants born during the RSV season, with monoclonal antibodies reserved for infants who: 1) are at increased risk of RSV disease; or 2) are born to a woman or person who was not vaccinated in pregnancy.

I. Introduction

The need for updated NACI guidance on the pediatric respiratory syncytial virus (RSV) immunization program arose from the authorization of a new monoclonal antibody with a pediatric indication, as well as an evolving evidence base pertaining to the RSVpreF vaccine during pregnancy. On February 2, 2026, Health Canada authorized the use of clesrovimab (Enflonsia, Merck), a novel monoclonal antibody for passive immunization of infants in their first RSV season. This is the fourth product available to passively protect infants from RSV, in addition to palivizumab (Synagis, AstraZeneca), nirsevimab (Beyfortus, Sanofi) and RSVpreF (Abrysvo, Pfizer).

In June 2022, NACI published a statement on updated recommendations for the use of palivizumab. In May 2024, NACI published a Statement on the prevention of respiratory syncytial virus disease in infants which included guidance on nirsevimab and RSVpreF.

Guidance Objective:

The primary objectives of this statement are to:

- review the updated evidence on the potential benefits (efficacy and effectiveness), and safety of RSV immunization products to protect infants and children in Canada
- describe the ethics, equity, feasibility, and acceptability considerations for RSV immunization programs
- review the evidence on the cost-effectiveness of RSV immunization programs to protect infants from RSV disease
- provide updated recommendations for the use of immunizing products in Canada, including identifying groups that may be at increased risk of severe RSV disease and therefore would benefit the most from these products.

NACI separately publishes recommendations for the use of vaccines to prevent severe RSV disease in adults at high risk.[1]

II. Methods

This NACI advisory committee statement was prepared through the following activities:

1. Analysis of the burden of disease caused by RSV in infants and pregnant women and pregnant people
2. Retrieval, synthesis, quality assessment, and summarization of individual studies on RSV immunizations to protect infants, including quantification of the magnitude of effects when appropriate, by the NACI Secretariat
3. Application of a published, peer-reviewed framework and evidence-informed tools to ensure that issues related to ethics, equity, feasibility, and acceptability (EEFA) are systematically assessed and integrated into the guidance (Ismail SJ et al. Vaccine 2020)
4. Use of an environmental scan and model-based economic evaluation of RSVpreF and/or monoclonal antibodies (nirsevimab or clesrovimab) for prevention of RSV-related outcomes in Canadian infants to generate economic evidence
5. Review of immunization guidance from international and domestic guidance issuing bodies through an environmental scan consideration of vaccine and immunization principles
6. Translation of evidence into recommendations

For details on when and how NACI incorporates economic evidence for vaccine recommendations, please refer to the NACI process for incorporating economic evidence into federal vaccine recommendations.

Further information on NACI's evidence-based methods is available elsewhere.[2] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess the certainty of the clinical evidence.

For this advisory committee statement, NACI reviewed the key questions for the literature review as proposed by the RSV Working Group (WG) and considered the available evidence on the burden of illness; immunization safety, immunogenicity, efficacy, and effectiveness; administration schedules; and other aspects of the overall immunization strategy. Knowledge synthesis was performed by NACI Secretariat and supervised by the RSV WG.[2] Following critical appraisal of individual studies, clinical evidence was synthesized leveraging GRADE methodologies to inform recommendations for vaccine and immunization use. NACI secretariat consulted with the Public Health Ethics Consultative Group (PHECG) on October 28, 2025, and provided key ethical considerations from the PHECG to the RSV WG for discussion. A summary of PHECG deliberations was also considered by NACI prior to issuing guidance recommendations.

The Working Group chair and NACI Secretariat presented the evidence and proposed recommendations to NACI. Following thorough review of the evidence and consultation at the NACI meetings of September 25, 2025 and December 9, 2025, the committee voted on specific recommendation.

A note on language

NACI recognizes that not all people giving birth or breastfeeding will identify as women or mothers. The writing in this statement uses a gender additive approach where the term “woman” is used alongside gender neutral language. This is intended to demonstrate a commitment to redress the historic exclusion of trans and non-binary people, whilst avoiding the risk of marginalizing or erasing the experience of women within the health care environment.

In addition, much of the research available currently uses gendered language (e.g., “women”) or gender neutral language (e.g., pregnant people) when discussing pregnancy. When citing research, NACI considers the language used in the study. In some cases, “woman” refers to someone who was assigned female at birth. For the purposes of this statement, the terms “woman,” and “women,” should be considered to also apply to those individuals who do not specifically identify as female gender but are the parent gestating the fetus or breastfeeding or chestfeeding the infant. However, in line with best practice, it is recognized that when discussing or caring for individuals in a one-on-one capacity language and documentation should reflect the gender identity of the individual.

Finally, NACI acknowledges the dynamic nature of language. It is likely that language deemed to be suitable or affirming in one context may not translate across others, and over the coming years will likely change and evolve with respect to appropriate representations.

III. Epidemiology

III.1 Burden of disease in infants and young children

RSV is a common respiratory pathogen that infects almost all children by age 2 years old.[3] Primary infection does not confer sterilizing or complete immunity, and recurrent infection tends to occur throughout a person's lifetime although more severe and symptomatic infection generally occurs in the first year of life.[4] The most common clinical presentations of RSV in young children requiring hospitalization are bronchiolitis (an acute lower respiratory tract infection associated with tachypnea, cough, and wheezing), and pneumonia. Pre-pandemic, RSV seasonality in Canada was typically November to April with peak incidence of cases in January and/or February; however, in the three most recent seasons (2022-23 to 2024-25), RSV activity has started earlier with peak incidence of cases occurring in late-December.[5-8] Seasonality can also vary by jurisdiction.[9-11]

Risk of serious clinical outcomes in children include hospitalization, intensive care unit (ICU) admission, and death; these risks increase with presence of comorbidities such as prematurity, chronic lung disease, congenital heart disease, congenital airway disorders, Down syndrome and immunocompromise.[12-17] The range of annual hospitalizations for RSV-associated respiratory infections varies between seasons and studies, but rates consistently decrease with increasing chronologic age with the exception of extreme prematurity.[18] The range of annual hospitalization rates for RSV-associated acute respiratory infections has varied in studies of term infants with no comorbidities and young children from 5 to 28 per 1,000 in infants less than 6 months, 3 to 13 per 1,000 in infants 6 to 11 months, and 2.5 to 5 per 1,000 in children 1 to 5 years of age.[18,19] Recent Canadian data suggests a higher burden of RSV-associated hospitalization than previously reported.[5] Approximately 5-10% of infants hospitalized with RSV require ICU admission although in newer studies this proportion can be higher.[10,11,18,20-23] While risk is higher with comorbidities, the majority of hospitalizations and deaths associated with RSV occur in healthy term infants.[18] In some pediatric studies RSV can be associated with more severe outcomes than influenza. Recent studies show a high risk in infants and young children of serious outcomes from RSV associated with a number of conditions including Down Syndrome and extreme prematurity in the second RSV seasons.[13-17]

III.2 Burden of disease in pregnant women and pregnant people

There are limited data on the impact of RSV during pregnancy. RSV has historically rarely been tested for in pregnancy, which contributes to lesser availability of RSV data. Despite limited available data, RSV is generally not more severe in pregnancy, though it may be more severe in those with underlying health conditions.[18]

In one systematic review on burden of RSV during pregnancy, the proportion of pregnant people with acute respiratory infection that tested positive for RSV ranged from 0.9% to 10.7% (meta-estimate: 3.4%). The pooled incidence was 26.0 per 1,000 person-years. RSV hospitalization rates in pregnancy in two studies were 2.4 and 3.0 per 1,000 person-years. In this systematic

review, no deaths associated with RSV were reported in pregnant individuals.[24] There is limited evidence that burden may be higher in pregnancy with the presence of some underlying conditions, including human immunodeficiency virus (HIV).[25] In studies comparing RSV-positive to RSV-negative pregnant individuals, no differences were noted in the risk of miscarriage, stillbirth, low birth weight or small size for gestational age. While there was a significant difference in the odds of preterm birth between RSV-positive and RSV-negative pregnant individuals, this was based on one study and as a result there are not yet enough data to inform this outcome.[24]

IV. Vaccines and immunizing agents

IV.1 Preparation(s) authorized for use in Canada

Characteristics of the RSV immunization products currently authorized for use in Canada for the protection of infants are summarized in Table 1.

Table 1. Comparison of RSV immunizing agents authorized for use in Canada for the protection of infants

	SYNAGIS® (palivizumab)[26]	**BEYFORTUS® (nirsevimab)[27]**	**ENFLONSIA (clesrovimab)[28]**	**ABRYSVO™ (RSVpreF)[29]**
Manufacturer	AstraZeneca	Sanofi	Merck	Pfizer
Date of authorization in Canada	May 15, 2002	April 19, 2023	February 2, 2026	December 21, 2023
Type of Immunizing Agent	Monoclonal antibody	Monoclonal antibody	Monoclonal antibody	Stabilized subunit vaccine with no adjuvant
Composition	Palivizumab (100 mg/mL), chloride, glycine, histidine, and water for injection	Nirsevimab (100mg/mL), L-arginine hydrochloride, L-histidine, L-histidine hydrochloride, polysorbate 80, sucrose, water for injection	Clesrovimab (150 mg/mL), L-arginine hydrochloride, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose, and water for injection	Lyophilized powder containing 120 mcg of RSV stabilized prefusion F protein (60 mcg each of subgroup A and subgroup B antigens), 22.5 mg mannitol, 0.08 mg polysorbate 80, 1.1 mg sodium chloride, 11.3 mg sucrose, 0.11 mg tromethamine, 1.04 mg trometamol hydrochloride reconstituted with sterile water (diluent)
Schedule and Dose	A series of 4 doses. Each dose of 15 mg/kg of body weight are administered	For the first RSV season, nirsevimab is given as a single dose. Those weighing less	For the first RSV season, a single dose of 105 mg/0.7 mL	A 1 dose schedule of 0.5 mL is administered during pregnancy between 32

	throughout the RSV season. The second dose of palivizumab should follow at 21 to 28 days after the first and the interval between subsequent doses is 28 to 35 days. An additional dose should be given after cardiac bypass or extracorporeal membrane oxygenation. An additional dose may be considered in remote northern areas where RSV outbreaks may continue longer than is usual elsewhere.	than 5 kg should receive a 0.5 mL dose (50 mg/0.5 mL) and those weighing 5 kg or more should receive a 1 mL dose (100 mg/1 mL). For a second RSV season, nirsevimab is given as a single dose of 200 mg (2 x 100 mg/1 mL). Although not reflected in the product monograph, if the child weighs less than 10 kg, a single dose of 100 mg may be considered at clinical discretion. An additional dose should be given after cardiac bypass and can be considered at the conclusion of extracorporeal membrane oxygenation.	is administered regardless of weight. For a second RSV season, although not reflected in the product monograph, administration of clesrovimab 210 mg (2 x 105 mg/0.7 mL) as per the clinical trial may be considered at clinical discretion.	through 36 weeks gestation. Although not reflected in the product monograph, this product could be used off label as early as 28 weeks gestation.
Route of administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular injection
Indications	Authorized for the prevention of serious lower respiratory disease caused by RSV in pediatric patients up to 24 months at high risk of RSV disease, which includes infants with: • Bronchopulmonary dysplasia • Prematurity (35 weeks gestational age or less)	Authorized for the prevention of RSV lower respiratory tract disease in: • Neonates and infants entering or during their first RSV season • Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season, which may include	Authorized for the prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season	Authorized for active immunization of pregnant individuals from 32 through 36 weeks of gestation for the prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by RSV in infants from birth through 6 months of age. No data are available on either the efficacy or safety of additional doses of RSVpreF

	Hemodynamically significant congenital heart disease (CHD)	but is not limited to children with: • Chronic lung disease of prematurity (CLD) ○ Hemodynamically significant congenital heart disease (CHD) ○ Immunocompromised states ○ Down syndrome ○ Cystic fibrosis ○ Neuromuscular disease ○ Congenital airway anomalies		given during subsequent pregnancies. Although not reflected in the product monograph, this product could be used off label as early as 28 weeks gestation.
Contraindications	Infants with known hypersensitivity to palivizumab injection or to any of its excipients and in patients with known hypersensitivity to other humanized monoclonal antibodies.	Infants with a history of severe hypersensitivity reactions, including anaphylaxis, to this drug or to any ingredients in the formulation, including any non-medicinal ingredient, or component of the container.	Infants with a history of serious hypersensitivity reactions, including anaphylaxis, to any component of the product	Individuals who are hypersensitive to the active substance or to any component of the vaccine
Precautions	Not indicated for adult use.	Not indicated for adult use.	Not indicated for adults, pregnant or breastfeeding individuals. Use supported in infants up to 12 months of age but not yet established for other pediatric age groups. Risk of serious hypersensitivity reactions including anaphylaxis	Immunocompromised individuals (limited data; may have diminished immune response) Breastfeeding (limited data)

Storage Requirements	Single use vials. Store in a refrigerator between 2°C and 8°C in its original container. Do not freeze.	Single dose pre-filled syringe. Store in a refrigerator between 2°C and 8°C. Keep the pre-filled syringe in the outer carton to protect from the light. Do not freeze, shake, or expose to heat. May be kept at room temperature (20°C – 25°C) for a maximum of 8 hours after removal from the refrigerator.	Single dose prefilled syringe. Store at 2°C to 8°C in original carton, protected from light; can be kept at 20°C to 25°C for up to 48 hours; do not freeze or shake	Single dose vials and pre-filled syringe with diluent. Store the unreconstituted vaccine in a refrigerator between 2°C and 8°C. Do not freeze. After reconstitution, ABRYSVO should be administered immediately (within 4 hours). Reconstituted vaccine should be stored between 15°C and 30°C.

For complete prescribing information for palivizumab, nirsevimab, clesrovimab and RSVpreF consult the product leaflet or information contained within Health Canada's authorized product monographs available through the Drug Product Database.

IV.2 Efficacy of clesrovimab in infants

Clesrovimab is a prophylactic monoclonal antibody, which was authorized in Canada on February 2, 2026.

Among infants entering their first RSV season, available evidence indicates that clesrovimab is efficacious at preventing hospitalizations due to RSV respiratory tract infection (RTI) and medically attended RSV RTI, and is also likely efficacious at preventing ICU admission due to RSV RTI.

Evidence on the efficacy of clesrovimab in infants is derived from two clinical trials.[30-32] The CLEVER trial is a phase IIb/III randomized, double-blind, placebo-controlled trial with active RSV surveillance through six months, designed to evaluate the efficacy and safety of clesrovimab in healthy preterm and full-term infants entering their first RSV season. Participants were randomized in a 2:1 ratio to either a single intramuscular dose of clesrovimab (n=2,411) or placebo (n=1,203). The primary efficacy endpoint was medically-attended lower respiratory tract infection (MALRI) with at least one indicator of lower respiratory tract infection or infection severity (indicators included wheezing, chest-wall in-drawing/retractions, rales or crackles, hypoxemia, tachypnea, or dehydration caused by respiratory symptoms) at month five. The secondary efficacy endpoints were RSV-associated hospitalization at month five and RSV-associated MALRI requiring at least one indicator of lower respiratory infection or diseases severity at month six. There were 1,518 infants and children enrolled and followed for 515 days post-dose, through their second RSV season. The trial enrolled a diverse population across race and ethnicity from 22 countries, across five continents.[32]

The SMART trial is a phase III, randomized, partially-blinded, palivizumab-controlled trial with active RSV surveillance during an infant's first two RSV seasons, designed to evaluate the safety, efficacy and pharmacokinetics of clesrovimab in infants at increased risk for severe RSV disease, including those with chronic lung disease, premature gestational age of 35 weeks or less, or congenital heart disease. Participants were randomized in a 1:1 ratio to either a single intramuscular dose of clesrovimab (105 mg, n=450) or doses of palivizumab (n=451). The primary endpoint was safety and tolerability. The secondary efficacy endpoints were RSV-associated MALRI with at least one indicator of lower respiratory tract infection or infection severity and hospitalization due to lower respiratory tract infection at month five. The trial enrolled a diverse population across race and ethnicity from 27 countries, across six continents. Approximately 300 enrolled participants received a second dose of clesrovimab, ahead of their second RSV season, however only limited data from season two are available. Efficacy outcomes were assessed in a subset of participants who received clesrovimab (210 mg) for their second RSV season, following clesrovimab (105 mg) or palivizumab received during their first season. Pharmacokinetic data indicate that drug exposures in infants entering their second RSV season were generally comparable to those observed in season 1.[33]

IV.2.1 Efficacy of clesrovimab against infant death due to RSV

There is limited evidence on the efficacy of clesrovimab for the prevention of death due to RSV infection among infants in their first RSV season. There were no deaths due to RSV in either of the clinical trials conducted to date; however neither of the studies were powered to detect differences in this outcome. The certainty of evidence for this outcome could therefore not be assessed (Table 4).

For season 2, mortality data were available from the SMART trial; there were no deaths due to RSV in either the clesrovimab group (n=89), or the palivizumab group (n=89).[33]

IV.2.2 Efficacy of clesrovimab against infant RSV respiratory tract infection with ICU admission

Available evidence indicates that, compared to placebo, clesrovimab is likely efficacious at preventing ICU admission due to RSV RTI in infants entering their first RSV season (moderate certainty of evidence, Table 4). In the CLEVER trial, there were four ICU admissions due to RSV RTI in the placebo group (n=1,201) and none in the clesrovimab group (n=2,398) through five months of follow-up, corresponding to an estimated vaccine efficacy (VE) of 100% (95% CI 24 to 100%).[32] There were no data on ICU admissions reported from the SMART trial.[33]

For season 2, no data on ICU admissions were reported in the SMART trial.

IV.2.3 Efficacy of clesrovimab against infant RSV respiratory tract infection with hospitalization

Available evidence indicates that, compared to placebo, clesrovimab is efficacious at preventing hospitalizations associated with RSV RTI in infants entering their first RSV season (high certainty of evidence, Table 4).

In the CLEVER trial, through five months of follow-up, there were 37 total RSV-associated hospitalizations, nine in the clesrovimab group (n=2,398) and 28 in the placebo group (n=1,201), corresponding to a VE of 84.2% (95% CI 66.6 to 92.6%). In their second RSV season (days 365 to 515 post-dose), incidence rates (IR) of RSV-associated hospitalization were similar in children who did (IR 0.3%; 95% CI 0.1 to 0.9% [n=1,016]) and did not (IR 0.4%; 95% CI 0.0 to 1.4% [n=502]) receive clesrovimab prior to their first RSV season, indicating that there was no shift of disease burden in the second RSV season in infants and children who received clesrovimab prior to their first RSV season and that protection did not extend into the second season. In the SMART trial, there were 11 total hospitalizations due to RSV RTI, five in the clesrovimab group (n=443) and six in the palivizumab group (n=437), through five months of follow-up. The incidence rate of hospitalization due to RSV RTI was similar in the clesrovimab group (IR 1.3%; 95% CI 0.4 to 3.0%) and palivizumab group (IR 1.5%; 95% CI 0.6 to 3.3%).[33]

For season 2, no data on RSV-related hospitalizations were reported in the SMART trial.

IV.2.4 Efficacy of clesrovimab against medically attended RSV respiratory tract infection

Available evidence indicates that, compared to placebo, clesrovimab is efficacious at preventing medically attended RSV RTI in infants entering their first RSV season (high certainty of evidence, Table 4).

In the CLEVER trial, through five months of follow-up, there were 60 cases of medically attended RSV RTI in the clesrovimab group (n=2,398), compared to 74 in the placebo group (n=1,201), corresponding to a VE of 60.4% (95% CI 44.1 to 71.9%). In their second RSV season (days 365 to 515 post-dose), incidence rates of medically attended RSV RTI were similar in children who did (IR 5.5%; 95% CI 4.1 to 7.1% [n=1,016]) and did not (IR 5.4%; 95% CI 3.5 to 7.9% [n=502]) receive clesrovimab prior to their first RSV seasons, indicating that there was no shift of disease burden in the second RSV season in infants and children who received clesrovimab prior to their first RSV season and that protection did not extend into the second season.[32] In the SMART trial, there

were 26 total cases of medically attended RSV RTI, 14 in the clesrovimab group (n=446) and 12 in the palivizumab group (n=450), through five months of follow-up. The incidence rate of medically attended RSV RTI was similar in the clesrovimab group (IR 3.6%; 95% CI 2.0 to 6.0%) and the palivizumab group (IR 3.0%; 95% CI 1.6 to 5.3%).[33]

For season 2, no data on medically-attended RSV illness were reported in the SMART trial.

IV.3 Effectiveness of nirsevimab and RSVpreF in infants

This statement aims to summarize the newly available efficacy data for clesrovimab and effectiveness data for RSVpreF and nirsevimab. Currently, there are no data on the real-world effectiveness of clesrovimab. However, real-world effectiveness data for both nirsevimab and RSVpreF for the protection of infants from severe RSV disease have been accumulating. RSVpreF and nirsevimab have been available in Canada since 2024 and palivizumab since 2002. Previously available efficacy data for RSVpreF and nirsevimab are available in the previous NACI statement on the protection of infants from RSV disease.[19]

Real-world effectiveness (RWE) data from multiple international jurisdictions and surveillance networks, including recent Canadian evidence, are consistent with efficacy data from prelicensure clinical trials, demonstrating that both nirsevimab and maternal RSVpreF vaccination provide substantial protection against severe RSV outcomes in infants during their first RSV season. A recent meta-analysis of 32 real-world observational studies indicates that nirsevimab is highly effective at reducing RSV-related hospitalizations (VE 83%; 95% CI 77 to 88%), ICU admissions (VE 81%; 95% CI 71 to 88%) and medically attended RSV infections (VE 75%; 95% CI 67 to 81%). Maternal RSVpreF immunization also shows robust protection, particularly when administered at least 14 days prior to delivery, with VE estimates ranging from 57% (95% CI 30.0 to 74.4%) to 82% (95% CI 75.1 to 87.3%) for hospitalizations and from 64% (95% CI 0.7 to 87.0%) to 87% (95% CI 52.6 to 97.0%)[34] for ICU admissions, as well as from 54% (95% CI 35 to 67%)[35] to 64% (95% CI 37 to 79%)[36] for medically attended RSV infections. While both interventions significantly reduce the burden of medically attended RSV-associated respiratory tract infections, a head-to-head population-based cohort study suggests nirsevimab may offer an advantage over maternal vaccination for both hospitalization (aHR 0.74; 95% CI 0.61 to 0.88) and ICU admission (aHR 0.58; 95% CI 0.42 to 0.80), although data of this nature is limited to a single study.[36] Data regarding effectiveness of both interventions against death due to RSV are currently limited. Overall, the available RWE supports both strategies as highly effective measures for preventing critical RSV-related morbidity and healthcare utilization. Available data are described in more detail below. Available data are described in more detail below.

Data regarding the real-world effectiveness of nirsevimab in infants is derived from several sources. A recent systematic review and meta-analysis included 32 studies conducted in five countries (Spain [n=18], France [n=8], USA [n=4], Luxembourg [n=1] and Italy [n=1]), primarily during the 2023 – 2024 RSV season. The primary outcomes of the review included RSV-related hospitalisation, admission to ICU, lower respiratory tract infection (LRTI) incidence, and length of hospital stay.[37] Additional real-world data have become available since the publication of this systematic review, from countries such as Ireland, Italy, Spain, France, Chile and the USA.[35,38-45] A recent pre-print of a Canadian test-negative study also evaluated the effectiveness of nirsevimab against RSV-associated hospitalization and ICU admission.[46]

Data regarding the real-world effectiveness of RSVpreF in infants is derived from several observational studies.[47,48] The BronchStop vaccine effectiveness sub-study was a prospective, multi-centre, test-negative study from the UK which analyzed the effectiveness of maternal RSVpreF vaccination against hospitalisation for RSV-associated acute lower respiratory infection (ALRI) in infants during the 2024 – 2025 RSV season. Pregnant women at 28 or greater weeks gestation were offered RSVpreF vaccination in a routine program implemented in the UK. In total, 537 infants were enrolled (391 RSV-positive case patients and 146 RSV-negative controls).[48] The BERNI study was a retrospective, multi-centre, test-negative case-control study from Argentina which analyzed the effectiveness of maternal RSVpreF vaccination against RSV-associated lower respiratory tract disease (LRTD) requiring hospitalization and RSV-associated severe LRTD requiring hospitalization during the 2024 RSV season. Pregnant women were offered RSVpreF vaccination between $32^{+0/7}$ weeks and $36^{+6/7}$ weeks gestation. In total, 505 infants were enrolled (286 RSV-positive case patients and 219 RSV-negative controls).[47] Additionally, observational studies conducted by the United States (US) Centers for Disease Control and Prevention (CDC) using the Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION) and New Vaccine Surveillance Network (NVSN) datasets have evaluated the effectiveness of RSVpreF vaccination in preventing RSV-associated hospitalizations in infants in their first RSV season,[35] as have observational studies from Scotland and Argentina.[34,49,50]

IV.3.1 Effectiveness of nirsevimab or RSVpreF against infant death due to RSV

Currently, there is very limited evidence on the effectiveness RSVpreF in prevention of death due to RSV infection among infants. In the BERNI study, there were three in-hospital, RSV-associated deaths. All three of these deaths occurred among infants whose mothers had not received RSVpreF during pregnancy (n=235 RSV-positive case patients); there were no RSV-associated deaths among infants whose mother received RSVpreF during pregnancy (n=51 RSV-positive case patients). There is no evidence on the effectiveness of nirsevimab against death due to RSV.[47]

IV.3.2 Effectiveness of nirsevimab or RSVpreF against infant RSV respiratory tract infection with ICU admission

A pooled analysis of nine studies, reporting 176 ICU admissions among 79,545 infants in the nirsevimab group and 618 ICU admissions among 48,023 infants in the control group, demonstrated that nirsevimab was effective at reducing RSV-related ICU admissions (VE 81%; 95% CI 71 to 88%). Some variability in treatment effect by country was observed. In a subgroup analysis by country, studies conducted in the United States saw the largest treatment effect (VE 93%; 95% CI 84 to 96%), followed by Spain (VE 88%; 95% CI 64 to 96%) and France (VE 78%; 95% CI 61 to 80%). In addition to the meta-analysis, US CDC observational data reported effectiveness against ICU admission ranging from 80% to 88%, depending on the surveillance network.[35,37] Adjusted VE estimates were 82% (95% CI: 57 to 93%) in VISION, 88% (95% CI: 63 to 96%) in NVSN, and 80% (95% CI: 73 to 85%) in Overcoming. Recent Canadian data from a Quebec study of 1,758 hospitalizations during the 2024-2025 RSV season (549 of which were RSV-positive) recorded 34 RSV-related ICU admissions, three in infants who had received nirsevimab.[46] This corresponded to an estimated VE against ICU admission of 88% (95% CI 65 to 92%). More recent, additional data demonstrate consistent results.[39,41-44]

Data on effectiveness of RSVpreF for the prevention of RSV RTI with ICU admission are available from both the BronchStop and BERNI studies. In the BronchStop study, in RSV-positive infants, 5 of 33 infants (15%) whose mothers had been vaccinated with RSVpreF more than 14 days prior to delivery required admission to the ICU, compared to 43 of 129 infants (33%) whose mothers had not been vaccinated with RSVpreF, corresponding to an unadjusted VE against RSV-associated ICU admission of 64.1% (95% CI 0.7 to 87.0%).[48] In the BERNI study, 59 of 235 RSV-positive infants (25%) whose mothers did not receive RSVpreF during pregnancy were admitted to the ICU for more than four hours, compared to 10 of 51 RSV-positive infants (20%) whose mothers did receive RSVpreF during pregnancy. Vaccine effectiveness for severe hospitalization (defined as RSV-associated LRTD with ICU admission for more than 4 hours, oxygen saturation below 90%, need for high-flow oxygen or mechanical ventilation, or failure to respond or loss of consciousness) was 76.9% (95% CI 45.0 to 90.3%) from birth to 6 months. An additional nested, test-negative case-control study from Argentina estimated VE against RSV-associated pediatric ICU admission to be 87.2% (95% CI 52.6 to 97.0%) among hospitalized infants ≤6 months of age (n=323).[34,47]

Data directly comparing the real world effectiveness of RSVpreF and nirsevimab for the prevention of RSV RTI with ICU admission are available from a single study.[51] A population-based cohort study using the French National Health Data System estimated the effectiveness of both RSVpreF and nirsevimab for the 2024-2025 RSV season. Infants born to a mother vaccinated with the RSVpreF vaccine were matched to an infant who received nirsevimab on the same maternity discharge day (as well as sex, gestational age and geographical region). Hospitalizations requiring pediatric ICU admission were rare in both the nirsevimab (55/21,280, [0.3%]) and RSVpreF groups (101/21,280 [0.5%]) groups, however they were less frequent in the nirsevimab group compared with the RSVpreF vaccine group (adjusted hazard ratio [HR], 0.58 [95% CI 0.42 to 0.80]).

IV.3.3 Effectiveness of nirsevimab or effectiveness of RSVpreF against infant RSV respiratory tract infection with hospitalization

A pooled analysis of 16 studies, reporting 1,585 hospitalizations among 85,242 infants in the nirsevimab group and 3,978 hospitalizations among 51,893 infants in the control group, demonstrated that nirsevimab was effective at reducing RSV-related hospitalizations (VE 83%; 95% CI 77 to 88%). Some variability in treatment effect by country was observed. In a subgroup analysis by country, studies conducted in the US reported the greatest treatment effect (VE 93%; 95% CI 72 to 98%), followed by Spain (VE 83%; 95% CI 74 to 89%) and France (VE 76%; 95% CI 65 to 83%). Additionally, US CDC observational data from the 2024-2025 RSV season reported effectiveness against RSV-associated hospitalization ranging from 79% to 82%, depending on the surveillance network.[35,37] Adjusted VE estimates were 79% (95% CI 67 to 87%) in VISION and 82% (95% CI 71 to 88%) in NVSN. Recent Canadian data from Quebec estimated VE against RSV-related hospitalization to be 89% (95% CI 84 to 92%) during the 2024-2025 RSV season. Of the 549 RSV-positive cases admitted to hospital, 55 (10%) had been immunized with nirsevimab. Of the 1,209 RSV-negative controls admitted to hospital, 627 (51.9%) had been immunized with nirsevimab. For children with chronic diseases, VE remained high at 79% (95% CI 60 to 89%).[46] More recent, additional data demonstrate consistent results.[38,39,41-45]

In the BronchStop study, among 423 infants hospitalised with RSV-associated ALRI, 81 (19.1%) were born to vaccinated pregnant women. Among 146 RSV-negative control infants, 61 (41.8%) were born to vaccinated pregnant women. The adjusted VE against hospitalisation for RSV-associated ALRI was 57.7% (95% CI 30.0 to 74.4%). In a prespecified subgroup analysis in people

who received RSVpreF at least 14 days prior to delivery, adjusted VE increased to 71.1% (95% CI 46.7 to 84.4%). In the BERNI study, the adjusted VE against RSV-associated LRTD requiring hospitalization was 71.3% (95% CI 53.5 to 82.3%) in infants six months of age and younger. Restricting to infants three months of age and younger, adjusted VE was similar (VE 78.6%; 95% CI 62.1 to 87.9%).[48] Moreover, US CDC observational data from the 2024-2025 RSV season reported similar estimates of VE against RSV-related hospitalization of 70% (95% CI 28 to 88%) in NVSN and 79% (95% CI 55 to 90%) in VISION,[35,37] as did several observational studies from Argentina (VE 68.2% [95% CI 33.1 to 84.9%][50] and adjusted VE 66.1% [95% CI 30.1 to 83.8%])[34] and Scotland (adjusted VE 82.2% [95% CI 75.1 to 87.3%]).[49]

In the French cohort study comparing the effectiveness of RSVpreF and nirsevimab for the 2024-2025 RSV season, hospitalizations for RSV-associated RTI were rare in both the nirsevimab (212/21,280, [1.0%]) and RSVpreF groups (269/21,280 [1.3%]) groups, however they were less frequent in the nirsevimab group compared with the RSVpreF vaccine group (adjusted HR, 0.74 [95% CI 0.61 to 0.88]). Subgroup analyses exploring factors such as biological sex, gestational age, interval from maternal vaccination and intensity of RSV circulation demonstrated consistent results.[51]

IV.3.4 Effectiveness of nirsevimab or RSVpreF against medically attended RSV respiratory tract infection in infants

A pooled analysis of seven studies, reporting 396 RSV-related LRTI requiring medical attention among 48,303 infants in the nirsevimab group and 1,049 RSV-related LRTI requiring medical attention among 9,569 infants in the control group, demonstrated that nirsevimab was effective at reducing RSV-related LRTI requiring medical attention (VE 75%; 95% CI 67 to 81%). Additionally, US CDC observational data from the 2024-2025 RSV season reported VE against RSV-associated emergency department visits ranging from 63% to 76%, depending on the surveillance network.[35,37] Adjusted VE estimates were 63% (95% CI 56 to 69%) in VISION and 76% (95% CI 55 to 87%) in NVSN. Recent Canadian data from Quebec estimated VE against RSV-associated emergency room consultations to be 86% (95% CI 82 to 90%) during the 2024-2025 RSV season. For children with chronic diseases, VE remained high at 86% (95% CI 70 to 93%). More recent, additional data demonstrate consistent results.[39,45,46]

Although some data are available,[36] data on effectiveness of RSVpreF for the prevention of medically attended RSV are more limited. US CDC observational data from the 2024-2025 RSV season reported effectiveness against RSV-associated emergency department visits among infants in their first RSV season of 54% (95% CI 35 to 67%)[35] and 64% (95% CI 37 to 79%)[36] against medically attended RSV-associated acute respiratory infection.

IV.4 Vaccine safety

This statement aims to summarize the newly available safety data for clesrovimab and real-world safety data on RSVpreF. This statement also aims to update and summarize safety data on nirsevimab. Previously available safety data for RSVpreF and nirsevimab are available in the previous NACI statement on the protection of infants from RSV disease.[19]

Clesrovimab

Overall, the available evidence indicates that among infants entering their first RSV season, clesrovimab results in little to no difference in severe systemic or local adverse events (AEs) compared to placebo (moderate certainty of evidence, Table 4). Clesrovimab is well tolerated in healthy preterm and full-term infants born during or entering their first RSV season, with a safety profile comparable to placebo. In infants at increased risk of severe RSV disease, clesrovimab was also well tolerated, with a safety profile comparable to palivizumab and consistent with what was observed in healthy infants. Similarly, for infants and children entering their second RSV season, clesrovimab continued to be well tolerated, with a safety profile comparable to palivizumab. The frequency of serious adverse events (SAEs), injection-site reactions, and systemic AEs was similar between groups, and no product-related SAEs were reported.[19,52-54] Details of the available evidence are described in detail below.

IV.4.1 Local adverse events following immunization with clesrovimab

In healthy preterm and full-term infants, the rate of local AEs was similar in the clesrovimab and placebo groups; there were two severe local AEs (Grade ≥3) in the clesrovimab group (n=2,409, 0.1%), and two in the placebo group (n=1,202, 0.2%).[32] In infants at increased risk of severe RSV disease, the rate of local AEs was similar in clesrovimab and palivizumab groups; there were two severe local AEs (Grade ≥3) in the clesrovimab group (n=445, 0.4%), and two in the palivizumab group (n=450, 0.4%).[31] In both studies, injection site pain, injection site erythema and injection site swelling were the most commonly reported local AEs, and the majority of local AEs were Grade 1 or 2 There were no meaningful differences observed in the rate of severe local AEs between groups in either study.

In the SMART trial, among infants and children entering their second RSV season, the rate of local AEs following administration of clesrovimab (210 mg) was low, with injection-site AEs occurring in four infants who received clesrovimab in both seasons (n=89, 4.5%), and one infant who received palivizumab in the first season and clesrovimab in the second season (n=89, 1.1%). The specific types and severity of local AEs were not reported.[33]

IV.4.2 Systemic adverse events following immunization with clesrovimab

In healthy preterm and full-term infants, the rate of systemic AEs was similar in the clesrovimab and placebo groups, with severe systemic AEs (Grade ≥3) occurring in 217 patients in the clesrovimab group (n=2,409, 9.0%), and 112 in the placebo group (n=1,202, 9.3%).[32] In infants at increased risk of severe RSV disease, the rate of systemic AEs was similar in the clesrovimab and palivizumab groups, with 77 severe systemic AEs (Grade ≥3) in the clesrovimab group (n=445, 17.3%), and 84 in the palivizumab group (n=450, 18.7%).[31] In both studies, irritability, somnolence, decreased appetite, and fever ≥100.4F were the most commonly reported systemic AEs, and the majority of systemic AEs were Grade 1 or 2 There were no meaningful differences observed in the rate of severe systemic AEs between groups in either study.

In the SMART trial, the rate of systemic AEs unrelated to the injection site was comparable between groups in season 2. Systemic AEs were reported in 54 infants who received clesrovimab in both seasons (n=89, 60.7%) and in 61 infants who received palivizumab in the first season and clesrovimab in the second season (n=89, 68.5%). The available data did not specify the types or severity of these events.[33]

IV.4.3 Serious adverse events following immunization with clesrovimab

In healthy preterm and full-term infants, the rate of SAEs was similar in the clesrovimab (278/2,409, 11.5%) and placebo groups (149/1,202, 12.4%). There was only one SAE deemed related to study intervention in individuals receiving clesrovimab: an increased body temperature (with a rectal temperature of 38°C on Day 4 and with adenovirus detected in stool on Day 8).[32] In infants at increased risk of severe RSV disease, the rate of SAEs was similar in the clesrovimab (99/445, 22.2%) and palivizumab groups (110/450, 24.4%), and none were deemed related to the study intervention in either group. Similar results were observed in infants and children receiving clesrovimab in their second RSV season, with no SAEs being deemed related to study intervention.[31]

IV.4.4 Nirsevimab

The safety profile of nirsevimab from clinical trials has been summarized previously.[19] Briefly, available RCT evidence demonstrates that nirsevimab has an acceptable safety profile among infants entering their first RSV season. The risks of severe systemic and local AEs with nirsevimab were similar to those observed with placebo. In infants and children considered at high risk entering their first or second RSV season, nirsevimab demonstrated a safety profile similar to that of palivizumab. Moreover, no meaningful differences in SAEs were observed when nirsevimab was compared to placebo or to palivizumab. Real-world safety evidence is currently limited, but available evidence to date is consistent with prelicensure clinical trial data, reaffirming the favourable safety profile of nirsevimab.[55-59] Preliminary safety data from the 2023-2024 RSV season, based on over 36,000 nirsevimab recipients under 8 months of age in the US CDC's Vaccine Safety Datalink (VSD), showed no increased risk of seizures, immune thrombocytopenia (ITP), drug reactions, or fever/sepsis.[60] No cases of anaphylaxis were reported. A few non-serious allergic reactions, primarily urticaria, occurred.

IV.4.5 RSVpreF

The safety profile of RSVpreF has been previously summarized.[19] Clinical trial evidence suggests that RSVpreF does not increase the risk of severe systemic AEs in pregnant individuals or their infants, although it appears to be associated with a higher frequency of severe local reactions compared to placebo. The frequency of SAEs remained similar across groups.

In earlier analyses of the phase 3 RCT (MATISSE), an imbalance in preterm births between RSVpreF and placebo recipients was noted and the uncertainty around a potential causal relationship was highlighted.[19,52-54,61] Preterm birth (e.g. <37 weeks gestational age [wGa]) occurred in 5.7% of infants in the RSVpreF group and 4.7% in the placebo group (relative risk [RR] 1.20; 95% CI 0.98 to 1.46)). Most preterm births were late preterm and occurred more than 30 days after vaccination. When stratified by country income level, no difference in preterm birth

rates was observed in high-income countries (5.0% in both groups), but a higher rate was observed in non–high-income countries (7.0% in RSVpreF vs 4.0% in placebo; RR 1.73; 95% CI 1.22 to 2.47). In addition, the overall preterm birth rate was below background national rates in countries with robust participant numbers.

Real-world safety data on RSVpreF vaccination during pregnancy are available from two non–Pfizer-sponsored, US-based, retrospective cohort studies conducted during the 2023–24 RSV season as well as from surveillance data presented at the June 2025 Advisory Committee on Immunization Practices (ACIP) meeting using the US CDC's VSD, and preliminary data from the UK maternity services dataset. In most of these studies the vaccine was given at 32-36 weeks gestation; in one study the vaccine was given at 28-36 weeks gestation. Overall, real-world data, some of which are summarized below, have not demonstrated an increased risk of preterm birth following vaccination.[62-66]

In the study by Blauvelt *et al*., 414 of 647 (64.0%) eligible pregnant individuals received RSVpreF between 32 and 36 weeks gestation. Vaccinated individuals delivered at a later mean gestational age compared to non-vaccinated individuals (39.0 [standard deviation (SD) 1.2] vs. 38.3 [SD 2.8] weeks) and had a lower rate of preterm birth (e.g. <37 wGA, 8.5% vs. 18.5%). After adjusting for relevant covariates using multivariable conditional logistic regression, there was no significant association between RSVpreF vaccination and preterm birth (adjusted OR, 1.03; 95% CI 0.55 to 1.93). No safety concerns were identified in this study.[62]

In the second study, Son *et al*. reported that 1,011 of 2,973 pregnant individuals received RSVpreF at a mean gestational age of 34.5 weeks (SD 1.4). Preterm birth (e.g. <37 wGA) occurred in 60 (5.9%) vaccinated individuals versus 131 (6.7%) non-vaccinated. No increased risk of preterm birth was observed after adjusting for confounders (adjusted OR, 0.87; 95% CI 0.62 to 1.20) or when accounting for immortal time bias using a time-dependent model (HR 0.93; 95% CI, 0.64 to 1.34). No significant differences in maternal or perinatal outcomes were observed overall between vaccinated and non-vaccinated individuals. However, an increased risk of hypertensive disorders of pregnancy (HDP) associated with RSVpreF was observed in the time-dependent model only (HR, 1.43; 95% CI, 1.16 to 1.77).[63]

In an analysis using data from the US CDC's VSD, 13,966 matched pairs of pregnant women vaccinated with RSVpreF and non-vaccinated controls were evaluated. Among women vaccinated between 32 and 36 weeks gestation, no increased risk of preterm birth (e.g. <37 wGa, aRR 0.90; 95% CI 0.80 to 1.00), small for gestational age at birth (adjusted RR 0.99; 95% CI 0.90 to 1.09) or stillbirth was observed (adjusted RR 1.09; 95% 0.46 to 2.58). A slightly increased risk of HDP was identified in the time-dependent model only (HR, 1.43; 95% CI 1.16 to 1.77).[66] There was not an increased risk noted of preterm birth or other adverse outcomes. The severity of HDP appeared similar between groups based on caesarean delivery rates and post-birth admissions for HDP. Acute safety outcomes were assessed across multiple post-vaccination windows (e.g., 1 to 6, 1 to 21, and 1 to 42 days), including fever, local reactions, and medically attended events such as neurologic, cardiovascular and thromboembolic events. No safety signals were identified, and event rates were low and similar between vaccinated and non-vaccinated women. In addition, a preliminary analysis of safety data from the UK maternity services dataset by the UK Health security Agency presented to the Joint Committee on Vaccination and Immunisation (JCVI) in November 2025, found no signal for an association between RSVpreF administration and preterm birth.[67]

Increased risk of HDP and preterm premature rupture of membranes (PPROM) have been inconsistently observed in RSVpreF-exposed pregnancies compared to the concurrent comparator cohort.[54,59,68,69] Additional analyses are planned to further investigate these potential safety signals. Interim analysis of an ongoing large retrospective cohort study did not identify statistically significant increases in preterm birth, HDP, PROM, or preterm PROM.[70] NACI will continue to monitor safety data as they emerge.

IV.5 Immunogenicity and duration of protection

There is no correlate of protection for prevention of RSV disease in infants. However, binding and neutralizing antibody titres have been measured and may give some indication as to the duration of protection offered by passive immunization. Based on available evidence, passive immunization via a vaccine administered in pregnancy or a long-acting monoclonal antibody (mAb) administered to infants may last up to 6 months. There is some evidence that the protection offered by long-acting mAbs is longer in duration than for gestational immunization.

The need for revaccination of pregnant women and pregnant people with RSVpreF in subsequent pregnancies has not been established. No data are available on the efficacy or safety of additional doses of RSVpreF administered during subsequent pregnancies. NACI will update this information as needed as more evidence becomes available.

IV.6 Contraindications and precautions

Clesrovimab is contraindicated in individuals with a known hypersensitivity or history of a severe allergic reaction (e.g., anaphylaxis) to any component of the product. There are no notable differences in contraindications and precautions between clesrovimab and nirsevimab. For additional information on nirsevimab and RSVpreF, see previous NACI statement.[19]

Special caution should be taken to ensure that products are administered to the right populations. For example, RSVpreF vaccine should not be given to children and mAbs should not be given to adults.

IV.7 Concurrent administration with other vaccines

Clesrovimab can be administered on the same day, or any time before or after, routine childhood vaccines. Given that the monoclonal antibody targets a specific RSV antigen, clesrovimab would not be expected to interfere with immunizations for protection from other infections. The manufacturer also reported that routine vaccinations were concurrently administered during the phase 3 clinical trials (CLEVER and SMART trials), and preliminary results indicated that the safety profile of the concurrently administered regimen was generally comparable to when clesrovimab or routine vaccines were given alone.[71]

Nirsevimab can be administered on the same day, or any time before or after, routine childhood vaccines. See previous NACI guidance for additional information.[19]

Concurrent administration of RSVpreF during pregnancy with other recommended vaccines can be considered according to basic vaccine principles outlining that, in general, non-live vaccines may be administered concurrently with, or at any time before or after, other vaccines.[19]

IV.8 Immunization of specific populations

See previous NACI statement for guidance for these populations for use of RSVpreF and nirsevimab.

IV.8.1 Immunization of people who are immunocompromised

Clesrovimab is authorized for the prevention of RSV LRTD in children less than 12 months of age, including those who are immunocompromised. The efficacy and safety of clesrovimab is currently being evaluated in clinical trials in immunocompromised infants and children less than 24 months of age.

IV.8.2 Immunization in pregnancy and breastfeeding

There is no evidence to suggest that the transfer of antibodies in human milk affects the efficacy of monoclonal antibodies to prevent RSV infection in breastfed infants.

Due to a lack of data, NACI currently has no recommendations for repeat vaccine dosing for subsequent pregnancies. To provide RSV protection to infants born in subsequent pregnancies, administration of a mAb to the infant after birth should be considered.

Preliminary data suggest that mAbs may have a longer duration of protection and may have slightly higher efficacy against severe RSV in the infant compared to RSVpreF. For infants not at increased risk of severe RSV disease, mAbs are not expected to provide additional protection to an infant born of a vaccinated pregnancy.

IV.8.3 Immunization of individuals previously infected with RSV

A previous RSV infection is not a contraindication to administration of clesrovimab or nirsevimab. However, clesrovimab or nirsevimab is not typically necessary or recommended for an infant who has a current or previous laboratory-confirmed RSV infection in the current RSV season. The additional benefit of clesrovimab or nirsevimab after an infant has recovered from RSV infection is unknown but is expected to be low, as the risk of rehospitalization in the same RSV season is very low.

Infants who are severely immunocompromised and get an RSV infection may not mount an immune response to the infection. In this case, administration of a mAb may provide additional protection.

IV.8.4 Immunization of pregnant adults 18+ at increased risk of RSV disease

If a pregnant woman or pregnant individual is at high risk of RSV disease due to medical comorbidities, RSVpreF vaccination may be considered for protection of both the pregnant

woman or pregnant individual and the infant. Refer the NACI Statement for Protection of Adults at High Risk of RSV disease[1] for more information.

IV.8.5 Immunization with mAbs to prevent outbreaks in NICU

There is very limited evidence for palivizumab in preventing outbreaks in neonatal intensive care units (NICU)[72] and there are no data yet for nirsevimab or clesrovimab. Consult an expert in infection prevention and control for advice on use in NICU or hospital outbreaks.

V. Ethics, equity, feasibility and acceptability considerations

The ethics and equity considerations for these populations and products are similar to those articulated in the previous NACI statement on the prevention of RSV in infants. However, it is important to emphasize the ongoing need to consider specific contexts in which social and structural determinants of health heighten the risk of severe RSV outcomes, particularly for some individuals in or from First Nations, Inuit, and Métis communities. Jurisdictions should continue to prioritize equity in program implementation.

V.1 Feasibility considerations

The Canadian Immunization Committee (CIC) was asked to consider a number of issues related to the feasibility of various RSV immunization program options. Many jurisdictions noted that procuring just one monoclonal antibody that could be used for both first and second RSV seasons would be preferable and reduce the risk of administration errors. Noting that clesrovimab is only authorized for infants in their first RSV season. With regard to a monoclonal antibody program vs. a pregnancy vaccine program, a monoclonal antibody program delivered at birth could achieve broader coverage since most births in Canada are in hospital or otherwise medically attended whereas the number, consistency and gestational timing of prenatal care visits may vary across jurisdictions and populations. Most jurisdictions expressed that a seasonal program including administration for children born before the beginning of the RSV season is feasible but has complexities, necessitating clear communication and awareness.

V.2 Acceptability considerations

There remains a lack of generalizable evidence on RSV immunization acceptability, and with current program implementation varying across jurisdictions, available uptake data are limited. Recently published Canadian literature is limited to three studies. In the first study, conducted in Quebec, RSVpreF was preferred over a monoclonal antibody due to perceptions of greater safety and reduced invasiveness for the infant.[73] In the second study, a national survey, the same preference was reported but with ease of receipt cited as the primary reason.[74] In the third study, a national survey, there was no clear preference between products.[75] Within the context of these studies, RSVpreF appeared to be the favoured option. However, all studies were conducted prior to product availability and the release of NACI recommendations, and their findings are not generalizable to the larger or more diverse Canadian population. Further surveillance and new research will be important to monitor uptake and acceptability, although no significant issues have been reported to date.

VI. Economics

An environmental scan and an economic evaluation using a previously described Canadian cost-utility model were used to generate economic evidence on RSV immunization programs for infants. This evidence supplemented that previously used to assess the cost-effectiveness of infant programs.[19]

VI.1 Environmental scan

An environmental scan was conducted to identify recently published economic evaluations of RSV immunization programs for infants, building on previous reviews.[19] Earlier reviews identified 11 studies, including two from Canada. Results were heterogeneous; programs using nirsevimab or RSVpreF, alone or in combination, ranged from being cost-saving to having incremental cost-effectiveness ratios (ICERs) well above common thresholds. Nirsevimab programs focused on infants at high risk or infants living in regions with higher RSV burden and healthcare costs were more likely to be cost-effective. Overall, these studies consistently found that lower product prices than were assumed in the primary analyses were needed for RSV immunization programs offered to all infants to be cost-effective.

The search, updated to June 28, 2025, identified any new economic evaluations reviewed by other National Immunization Technical Advisory Groups (NITAGs), as well as any published studies and preprints specific to Canada not included in the previous reviews. Five new economic evaluations were identified, comprising three Canadian model-based analyses[76,77] and two that modelled a US setting and were presented to the ACIP.[78] For clarity, the economic evaluations presented to the ACIP are referred to by the names of the model authors.[79,80] For the US studies, costs were converted to 2024 Canadian dollars (exchange rate of 1.3698).[81] Two of the five economic evaluations were industry funded.[76,77,80] and one preprint and two that modelled a US setting and were presented to the ACIP.[78] For clarity, the economic evaluations presented to the ACIP are referred to by the names of the model authors.[79,80] For the US studies, costs were converted to 2024 Canadian dollars (exchange rate of 1.3698).[81] Two of the five economic evaluations were industry funded.[76,80] All studies used static decision analytic models. Results for three studies are reported for the societal perspective,[76,79,80] and two are reported for the healthcare system perspective.[77,82] Time horizons ranged from one to two years.

Two studies evaluated programs that incorporated RSVpreF and nirsevimab, either alone or in combination.[77,82] One analysis evaluated nine immunization strategies, dividing Canada into four regions (southern Canada, Northwest Territories, Nunavik, and Nunavut) with varying RSV burden and healthcare costs and used a $100,000 per quality-adjusted life year (QALY) threshold to identify the optimal strategy in each region.[77] Of the strategies evaluated, programs using nirsevimab were identified as optimal in all regions but the scope of the optimal program varied, including: only palivizumab-eligible infants in southern Canada, all preterm infants (36 wGA or less) in the Northwest Territories, all infants under 6 months in Nunavik, and all infants under 12 months in Nunavut. Combined RSVpreF and nirsevimab programs were not optimal at assumed product prices ($533 for nirsevimab and $299 for RSVpreF). Threshold analysis showed that for a nirsevimab infant program for all infants aged under 6 or 12 months to be cost-effective, the product price needed to be less than $170 or $112, respectively, for southern Canada, with higher allowable prices for other regions. The second analysis, conducted in British Columbia, compared five strategies and used a $50,000 per QALY threshold to identify the optimal strategy.[82]

Nirsevimab for infants at high and moderate risk was identified as the optimal strategy at assumed product prices ($450 for nirsevimab and $125 for RSVpreF). A program offering nirsevimab to all infants during their first RSV season, including doses for infants born before the start of the RSV season, was not optimal unless the product price was reduced to approximately $110 per dose. A strategy offering seasonal RSVpreF to all pregnant women and pregnant individuals along with nirsevimab for infants at high risk was optimal for certain combinations of product prices, particularly when nirsevimab prices were higher or RSVpreF prices were lower than assumed in the base case analysis.

A third Canadian analysis conducted a price threshold analysis of nirsevimab programs only and estimated that for a nirsevimab program for all infants born during and prior to their first RSV season to be cost-effective compared to palivizumab for infants at high risk, the price would need to be less than $536 per dose using a $50,000 per QALY threshold, or $706 per dose using a $100,000 per QALY threshold.[76] Unlike the two previously described Canadian studies, this study did not examine multiple program options and therefore did not include a sequential analysis.

Two US economic evaluations presented to ACIP assessed the cost-effectiveness of clesrovimab programs for all infants during their first RSV season, including immunization for those born before the season, compared to palivizumab in infants at high risk. For a price of $626 per dose, ICERs were $50,184[80] and $143,203[79] per QALY. Differences in ICERs were attributed to different assumptions about initial effectiveness, waning of protection, coverage rate for palivizumab, medical costs, and adverse events.[78]

Overall, these evaluations showed that while infant RSV immunization programs can reduce RSV disease and associated costs, their cost-effectiveness is sensitive to the disease burden, population risk, and product price. Of note, although the three Canadian studies reviewed specifically looked at nirsevimab, the results would expect to be applicable to clesrovimab, assuming a similar product price.

VI.2 Cost-utility analysis

A Canadian cost-utility model was updated to assess the cost-effectiveness of RSV prevention strategies using RSVpreF during pregnancy and/or monoclonal antibodies (nirsevimab or clesrovimab) administered to infants.[19,83,84] The analysis evaluated how these strategies could reduce RSV-related outcomes in Canadian infants during their first RSV season. Key updates to the model included: (i) incorporating new strategies, such as seasonal RSVpreF alone or combined with monoclonal antibodies, (ii) removing previously dominated strategies (e.g., year-round programs), and (iii) updating key parameter inputs including product list prices, RSV incidence rates, and effectiveness and waning assumptions. Effectiveness estimates were informed by recent clinical trial efficacy data and protection was assumed to follow a sigmoidal decay curve, reaching 0% after six months.[19,84] All costs were updated to 2024 Canadian dollars.

In the primary analysis, monoclonal antibodies were modelled as a single product based on average effectiveness estimates. List prices were informed by manufacturer-provided information available at the time of the analysis: $750 for monoclonal antibodies (based on nirsevimab, as a clesrovimab list price was not available) and $230 for RSVpreF. A secondary analysis focused on settings where combination programs involving RSVpreF were not under consideration, and compared only monoclonal antibody strategies to each other. Cost-effectiveness was assessed using a cost-effectiveness threshold of $50,000 per QALY gained.

All of the modelled strategies were assumed to be seasonal, defined as protection provided during the Canadian RSV season (November through April). Monoclonal antibody strategies included two components: (i) in-season dosing for infants born during the RSV season, and (ii) dosing at the start of the RSV season for infants born before the RSV season to ensure protection when the RSV season began. In both cases, the monoclonal antibody could be offered to all infants or targeted to specific groups (based on their RSV risk as defined by gestational age at birth). RSVpreF was modelled as a seasonal program, administered between $32^{0/7}$ and $36^{6/7}$ weeks of pregnancy for those with expected in-season deliveries (November to April). For combination programs of RSVpreF plus monoclonal antibody, it was assumed that infants would receive protection from either RSVpreF or monoclonal antibody, but not both. Programs were considered universal if all infants born or entering their first RSV season were protected by either product. The reference strategy was a seasonal monoclonal antibody program for infants at moderate risk ($33^{0/7}$ to $36^{6/7}$ wGA) or high risk (born before 33 wGA), with administration occurring at season start for moderate or high risk infants born prior to RSV season start. The model definition of moderate- and high-risk was limited to prematurity, and therefore differs from NACI's 2024 recommendation, which prioritizes all infants born <37 wGA as well as term infants with certain chronic medical condition (e.g., chronic lung or cardiac disease) to receive mAb.[19] A sequential analysis was conducted, comparing strategies in order of increasing cost to exclude dominated options and calculate ICERs relative to the next most efficient strategy. Scenario and sensitivity analyses were performed to examine the impact of model input uncertainties. Results are presented for the health system perspective, and additional results including those from the societal perspective are provided in a preprint publication.[84]

In the primary analysis, the most cost-effective strategy was a combination program of seasonal RSVpreF administered at $32^{0/7}$ to $36^{6/7}$ weeks of pregnancy for those with in-season deliveries, plus seasonal monoclonal antibody for infants at high risk, including immunization at season start for infants at high risk born prior to the RSV season, with an ICER of $35,408 per QALY compared to the reference strategy of seasonal monoclonal antibody for infants at moderate or high risk, including administration at season start for those born prior to the RSV season (Figure 1).

Expanding this combination strategy to include monoclonal antibody for non-high risk infants born to non-vaccinated pregnant women and pregnant people during the RSV season increased the ICER to $132,131 per QALY. Universal strategies offering monoclonal antibody to all infants regardless of risk, with or without RSVpreF, were not cost-effective at current list prices, with ICERs far exceeding commonly used cost-effectiveness thresholds. Seasonal RSVpreF alone was dominated by other program options (i.e., other programs had lower expected costs and higher QALYs compared to seasonal RSVpreF alone). In areas with higher RSV hospitalization rates and medical costs, such as those involving complex transportation requirements to access care, seasonal monoclonal antibody for all infants born during the RSV season, with immunization at season start for infants at high risk born prior to the RSV season, was the most cost-effective strategy at current list prices.

In a secondary analysis that compared monoclonal antibody-only programs and excluded programs with RSVpreF, seasonal monoclonal antibody for infants at moderate or high risk, including administration at season onset for those born prior to the RSV season, was the most cost-effective strategy. A broader program offering seasonal monoclonal antibody for all infants born during the RSV season, with administration at season onset for infants at high risk born prior to the RSV season, resulted an ICER of $131,668 per QALY and would require a price reduction of at least 55% (i.e., to below $341 per dose) to be cost-effective at a $50,000 per QALY threshold.

However, in settings experiencing a higher RSV burden and higher costs, this broader monoclonal antibody program was the most cost-effective option at current list prices.

Results were sensitive to assumed product prices. A two-way sensitivity analysis (Figure 2) indicated that the combined program of seasonal RSVpreF plus monoclonal antibody for infants at high risk, including administration at season onset for infants at high risk born prior to the RSV season, remained optimal when the price of monoclonal antibody exceeded $350 per dose. At monoclonal antibody prices below $100 per dose, seasonal monoclonal antibody for all infants born during the RSV season, with administration at season onset for infants at high risk born prior to the RSV season, became the optimal strategy. Within an intermediate monoclonal antibody price range ($100 to $350 per dose), the optimal strategy shifted with RSVpreF pricing: a combination strategy (seasonal RSVpreF plus monoclonal antibody for all infants born to non-vaccinated pregnant women and pregnant people, with administration at season onset for infants at high risk born prior to the RSV season) was more favourable at lower RSVpreF prices, while seasonal monoclonal antibody for all infants born during the season, with administration at season onset for infants at high risk born prior to the RSV season, became more cost-effective as the RSVpreF price increased.

The assumption of extended duration of protection led to lower ICERs across all strategies, but it did not change the overall conclusions. ICERs from the societal perspective were generally lower than those from the health system perspective but this did not qualitatively change the conclusions.

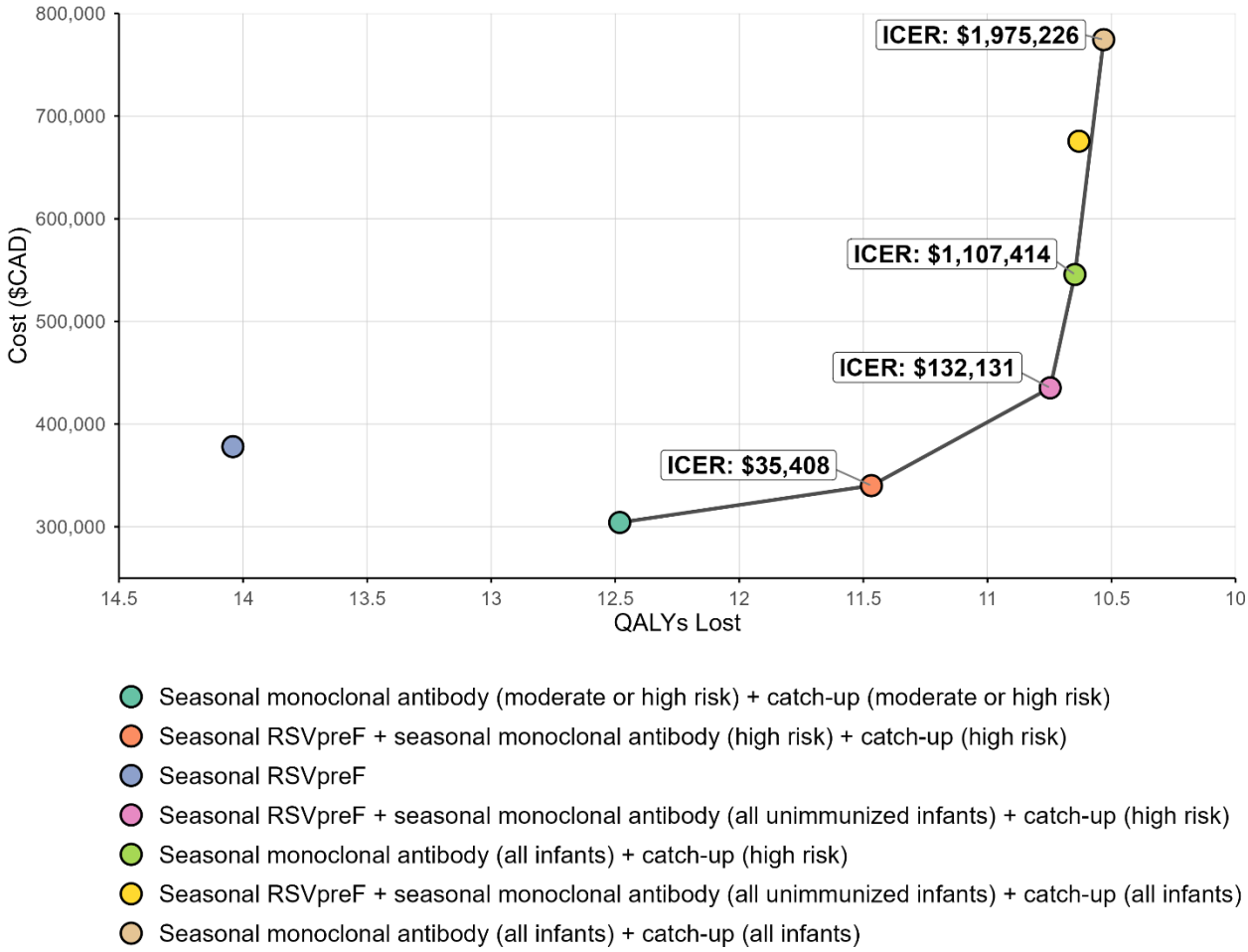

Figure 1. Results of the base case cost-utility analysis showing costs, QALY losses, and sequential incremental cost-effectiveness ratios, in which monoclonal antibody and/or RSVpreF programs are compared stepwise to identify the most efficient options from a health system perspective. All RSVpreF programs are seasonally administered between $32^{0/7}$ and $36^{6/7}$ weeks of pregnancy to those with in-season due dates (November to April) i.e., all infants born outside of the RSV season and high risk infants (born before 32 wGA) born during the RSV season were not protected by the RSVpreF pregnancy vaccine. Seasonal monoclonal antibody for all unimmunized infants refers to administration of monoclonal antibody (nirsevimab or clesrovimab) both to infants at high risk and to those not at high risk who were born to non-vaccinated pregnant women and pregnant people during the RSV season. Catch-up refers to administration of monoclonal antibody at season start to infants born prior to RSV season start. For combination programs, infants received protection from either product (RSVpreF or monoclonal antibody), not both.

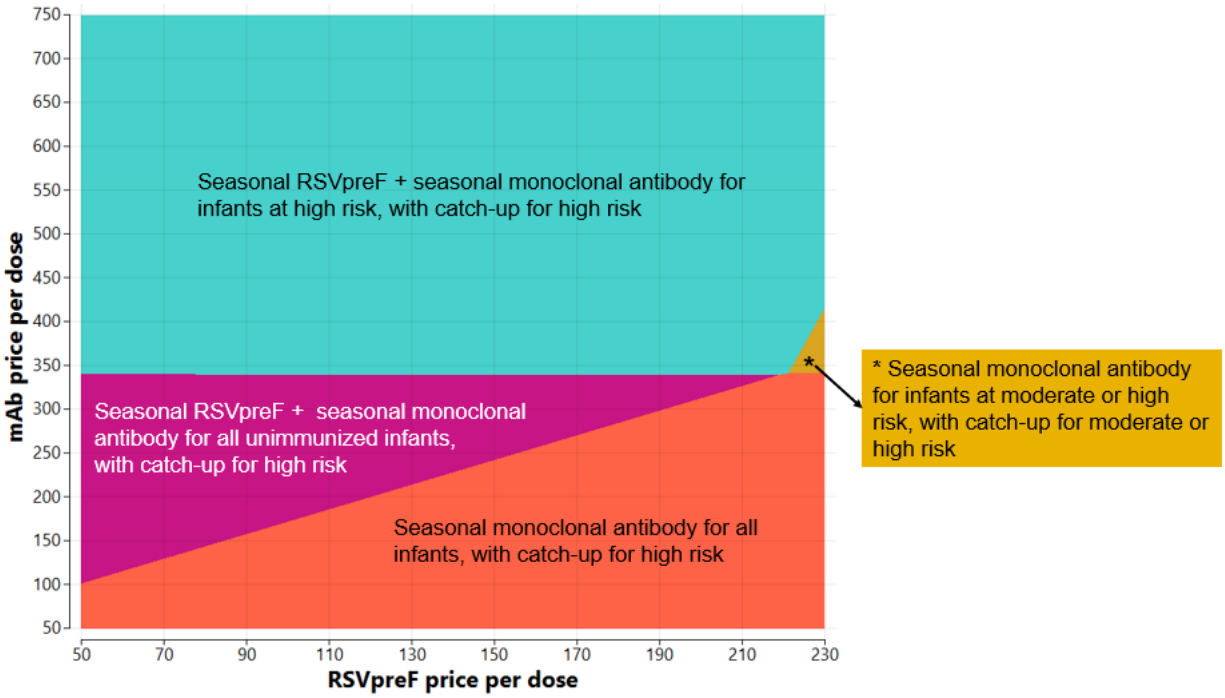

Figure 2. Two-way sensitivity analysis showing the impact of varying prices for monoclonal antibody and RSVpreF on the cost-effectiveness of all evaluated strategies, using a $50,000 per QALY cost-effectiveness threshold. The colored areas indicate the most cost-effective strategy for a given combination of prices, showing how product pricing influences the optimal program choice. All RSVpreF programs are seasonally administered between $32^{0/7}$ and $36^{6/7}$ weeks of pregnancy to those with in-season due dates (November to April) i.e., all infants born outside of the RSV season and high risk infants (born before 32 wGA) born during the RSV season were not protected by the RSVpreF pregnancy vaccine. Seasonal monoclonal antibody for all unimmunized infants refers to administration of monoclonal antibody (nirsevimab or clesrovimab) both to infants at high risk and to those not at high risk who were born to non-vaccinated pregnant women and pregnant people during the RSV season. Catch-up refers to administration of monoclonal antibody at season start to infants born prior to RSV season start. For combination programs, infants received protection from either product (RSVpreF or monoclonal antibody), not both.

VI.3 Summary

In summary, the model-based economic analyses found that seasonal combination programs (RSVpreF plus monoclonal antibody) generally offered the best value for money in protecting infants against RSV disease. Cost-effectiveness was primarily influenced by the selected target population, product prices, infant age at product administration, and regional variations in RSV-related hospitalization rates and healthcare costs. For jurisdictions not considering the use of RSVpreF to prevent RSV in infants, targeted seasonal monoclonal antibody programs were preferred, with universal monoclonal antibody programs only cost-effective with substantial price reductions. Across analyses, broader programs protecting all infants (with monoclonal antibody alone or combined with RSVpreF) were not cost-effective at common cost-effectiveness thresholds unless products are below current list prices. The model distinguishes between high- and moderate-risk infants based on prematurity, whereas NACI recommendations group both high- and moderate-risk infants within the definition of infants at increased risk of severe RSV disease. This difference should be considered when interpreting the economic results.

These findings were consistent with the results of an environmental scan of economic evaluations. Across studies, results were sensitive to assumptions about disease burden, immunization product price, initial efficacy and protection duration. Monoclonal antibody programs focused on infants at high risk or implemented in regions with higher RSV burden were cost-effective or even cost-saving. By contrast, programs for all infants generally exceeded common cost-effectiveness thresholds and required lower product prices to be economically favourable.

VII. Recommendations

Following the thorough review of available evidence summarized above, NACI makes the following recommendations for public health level and individual level decision-making.

Please note:

A **strong recommendation** applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present

A **discretionary recommendation** may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable

Please see Table 5 for a more detailed explanation of strength of NACI recommendations and grade of the body of evidence.

Recommendations for public health program decision-making

(i.e. Recommendations for Provinces/Territories making decisions for publicly funded immunization programs)

In considering these recommendations and for the purposes of publicly funded program implementation, provinces and territories may take into account local programmatic factors (e.g. current immunization programs, resources). Recognizing that there are differences in operational contexts across Canada, jurisdictions may wish to refer to the Management Options Table below for a summary of the relative merits of vaccinating different age cohorts, with different immunizations or schedules, high risk groups, etc., if prioritization of targeted immunization programs is required for implementation.

1. NACI recommends universal RSV immunization programs to protect infants, using seasonal administration.

(Strong Recommendation)

2. NACI recommends that jurisdictions implement a seasonal RSV immunization program, based on local context, feasibility and program priorities:

- **Infant monoclonal antibody (mAb) program**
  - Offering nirsevimab or clesrovimab to all infants during their first RSV season and to infants at continued increased risk during their second RSV season (see Recommendation 3 for infants at increased risk).

- **Combined pregnancy vaccine and infant mAb program**
  - Offering RSVpreF during pregnancy to protect infants born during the RSV season
  - Offering nirsevimab or clesrovimab to infants:
    - who are at increased risk of severe RSV according to Recommendation 3, including infants at increased risk born to women or individuals who received RSVpreF during pregnancy.

- who are born to women or individuals who did not receive RSVpreF during pregnancy, regardless of the infant's risk status, or who are born less than two weeks after RSVpreF administration.

(Strong Recommendation)

Considerations:

mAbs:

- Monoclonal antibody products (nirsevimab, clesrovimab) are administered to infants. RSVpreF is administered in pregnancy. Refer to the Clinical mAb Recommendations Table by Infant Characteristics (Table 2) and Management Options Table by Program (Table 3) for considerations regarding product and program use.
- Infants who are at increased risk of severe RSV disease are recommended to receive mAbs in their first and second season if at ongoing risk (nirsevimab or clesrovimab). Refer to Recommendation 3 for complete details.
- Infants recommended to receive a mAb in their first RSV season are usually below 8 months of age.
- A program using mAbs alone is one of the proposed approaches based on product effectiveness, safety of the product, expected longer duration of protection, acceptability and successful implementation in several provinces.

RSVpreF:

- NACI recommends RSVpreF vaccine can be given during pregnancy from 28 to 36 weeks gestation. RSVpreF vaccine is authorised in Canada at 32 to 36 weeks gestation. The off-label recommendation from NACI is supported by safety and efficacy data, supports broader access and opportunities for immunization and aligns with the recommendations by the World Health Organization.
- Due to a lack of data, NACI currently has no recommendations for repeat vaccine dosing for subsequent pregnancies. To provide RSV protection to infants born in subsequent pregnancies, administration of a mAb to the infant after birth should be considered.

Cost-effectiveness:

- At current product list prices, neither of the recommended program approaches is cost-effective using commonly applied cost-effectiveness thresholds. Substantial reductions in mAb price are required for either of these programs to be considered cost-effective. Of the two approaches evaluated, the most cost-effective option at current list prices is a combined pregnancy vaccine and infant mAb program.
- Within the combined program approach, a more cost-effective implementation may be achieved by narrowing the scope of mAb administration to infants at increased risk of severe RSV (including season-start immunization for infants at high risk born prior to the RSV season), in combination with RSVpreF vaccination in pregnancy to protect infants born during the RSV season. Given this, it would be reasonable for jurisdictions to initially implement this more targeted approach, while maintaining the longer-term objective of protecting all infants against RSV disease. Jurisdictions taking this approach could reassess broader program options as product prices and real-world effectiveness data evolve.
- Administration of mAbs to healthy infants born before the start of the RSV season is not cost-effective at expected product prices because the incremental health gains per dose decline as baseline risk decreases with increasing age. Programs implementing

immunization for healthy infants born prior to season start could prioritize the youngest healthy term infants (i.e., less than 3-6 months at the start of the RSV season), recognizing that cost-effectiveness declines as infant age at season onset increases. Inclusion of these infants would depend on product price and budget impact considerations.

Timing of immunization:

- Seasonal administration of RSV immunization is recommended as it provides optimal protection to infants during the RSV season and is more cost effective than other program options considered (including year-round administration). mAb duration of protection is expected to be 6 months.
- Jurisdictions are encouraged to define the RSV season based on local epidemiology. Prior to the COVID-19 pandemic, the RSV season was typically November to April. For nirsevimab and clesrovimab, administration should begin at the start of the RSV season. For administration of RSVpreF, consideration should be given to gestational timing and the start of the RSV season, allowing for the development of a humoral immune response and passive antibody transfer (e.g., at least two weeks). For example, RSVpreF could be administered starting in September to protect infants expected to be born during the RSV season in November, if gestational age is at least 28 weeks at the time of administration.
- For infants admitted to hospital immediately after birth during the RSV season and who are eligible for a mAb, the mAb should be administered before discharge, with flexibility for clinical judgment regarding timing.

Immunization outside of public programs:

- If neither RSVpreF nor mAbs are available through publicly-funded immunization programs, individuals, parents or guardians may consider immunization options (mAbs or RSVpreF) available as part of the private market in consultation with their healthcare provider.
- Parents considering immunization outside of publicly-funded programs to protect infants should consider factors that put infants at risk for severe RSV disease. The youngest infants (i.e., infants aged less than 3-6 months at the start of the RSV season, and infants born during the RSV season) are most at risk of severe RSV disease. Certain infants are at increased risk of severe RSV disease during their first or second RSV season as defined in Recommendation 3.

<u>Summary of evidence and rationale:</u>

- Respiratory syncytial virus (RSV) is one of the most common respiratory viruses in infants and young children, infecting almost all children in Canada by two years of age. Although infants with certain underlying medical conditions are at increased risk of severe disease, the majority of infants hospitalized with RSV each year are otherwise healthy.
- Based on evidence of efficacy/effectiveness and safety, RSVpreF, nirsevimab or clesrovimab are expected to offer protection against severe RSV disease in infants.
- For most infants not at increased risk of severe RSV disease, mAbs are not expected to offer additional protection if the infant is born to a vaccinated woman or individual, provided that birth happened more than 2 weeks since vaccination and there is no reason to believe transplacental antibody transfer was disrupted.
- Based on currently available efficacy and effectiveness data, there is no meaningful difference between nirsevimab and clesrovimab in protection to infants in their first season.

- No data are available about the duration of protection for RSVpreF for subsequent pregnancies. Due to a lack of data, NACI currently has no recommendations for repeat vaccine dosing for subsequent pregnancies. To provide RSV protection to infants born in subsequent pregnancies, administration of a mAb to the infant after birth should be considered.

3. NACI recommends that infants at increased risk of severe RSV disease receive monoclonal antibodies (mAbs).

Infants at increased risk include:

- **Infants in their first RSV season with certain medical conditions (List 1), even if they are born to a woman or individual who received RSVpreF during pregnancy.**
- **Infants and children in their second RSV season with certain medical conditions (List 1).**
- **Infants in their first RSV season whose transportation for severe RSV disease treatment is complex, and/or whose risk of severe RSV disease intersects with established social and structural health determinants such as those experienced by some individuals in or from First Nations, Inuit and Métis communities.**

(Strong Recommendation)

List 1. Infants and children at increased medical risk of severe RSV disease:

- Chronic lung disease, including bronchopulmonary dysplasia, requiring ongoing assisted ventilation, oxygen therapy or chronic medical therapy in the 6 months prior to the start of the RSV season
- Cystic fibrosis with respiratory involvement and/or growth delay
- Haemodynamically significant chronic cardiac disease
- Severe immunodeficiency
- Severe congenital airway anomalies impairing clearing of respiratory secretions
- Neuromuscular disease impairing clearing of respiratory secretions
- Down syndrome
- Premature infants less than 32 wGA

Considerations:

- The following infants born to a woman or person immunized with RSVpreF during pregnancy should still receive a mAb in their first RSV season, to ensure they are optimally protected for the RSV season:
    - Infants with a medical condition on List 1 (including those born at less than 32wGA).
    - Infants who are born less than 2 weeks after the pregnant woman or pregnant individual received the vaccine
- Clesrovimab is not authorized for infants and children at ongoing risk in their second RSV season but could be considered off-label based on evidence of immunogenicity and safety at a dose of 210 mg (2 x 105 mg/0.7 mL) as per the clinical trial. Infants and children who received a passive immunization (i.e., directly received a mAb or were born to a pregnant woman or pregnant individual who received RSVpreF) in their first season who are at continued risk in their second season should receive a mAb in their second season

(nirsevimab or clesrovimab can be used regardless of which product was received in the first season).

- Infants in their first RSV season are usually below 8 months of age and infants and children in their second RSV season are usually between 8 and 19 months of age.
- Consideration should be made for diverse contexts of equity-denied communities. One example where diverse contexts may apply is with individuals in or from First Nations, Inuit, and Métis communities across various settings (e.g., urban, rural, remote, northern).

Summary of evidence and rationale:

- When interpreting the epidemiological trends to inform the recommendations, equity considerations include acknowledgement that available evidence for some populations is limited and may be biased, for example due to systemic limitations in available data for racialized groups.
- Early preterm infants and young children (born at <32 weeks gestational age), not exclusive of other comorbidities, have significantly higher rates of severe RSV. Risk increases with increasing prematurity and is higher if infants are born at <28 weeks gestational age.[14,85]
- Infants with a medical condition on List 1 born to a woman or person immunized with RSVpreF should still receive a mAb due to immunological waning of protection offered by RSVpreF. These infants are at the most increased risk of severe RSV disease, and immunization with a mAb at the start of the RSV season ensures optimal protection during the seasonal window of the highest risk of exposure.

Table 2. Clinical mAb recommendations table by infant characteristics

Age of infant	Has a condition listed in List 1 (including prematurity less than 32 weeks gestational age)	Pregnancy immunization status (RSVpreF)	Recommendation for nirsevimab or clesrovimab
Below 8 months *First RSV Season*	Yes	Any	Yes
	No	Yes	No
		No	Yes[1,2]
8-19 Months *Second RSV Season*	Yes	Any	Yes
	No		No

[1]Infants born during the RSV season should be prioritized. The youngest infants at the start of RSV season (i.e.; = less than 3-6 months old) could also be prioritized for mAb administration, noting that cost-effectiveness decreases with increasing infant age at the start of the RSV season.

[2]NACI is preferentially recommending a mAb for all infants in their first RSV season whose transportation for severe RSV disease treatment is complex, and/or whose risk of severe RSV disease intersects with established social and structural health determinants such as those experienced by some individuals in or from First Nations, Inuit and Métis communities.

Table 3. Management options table by program

Strategy	Description of options	Benefits	Challenges	Comments
1) mAbs only	mAbs for infants born during the RSV season (administration shortly after birth) and before the season (administration at the beginning of the season)	• Reduction of the burden of RSV disease • Simpler program	• Provides less value for money and does not represent optimal use of resources compared to combined program at current list prices	• Not including some or all healthy term infants (<8 months of age) born before the start of RSV season could be considered to increase the cost-effectiveness of the strategy.
2) Combined pregnancy vaccine and infant mAb program	RSVpreF to all pregnant women and pregnant people whose infant is expected to be born during the RSV season mAbs to infants at increased risk of severe RSV disease (administered shortly after birth for those born during RSV season, and administered at start of RSV season for those born before RSV season) Seasonal mAbs to infants who are born to women or individuals who did not receive the RSVpreF vaccine during pregnancy	• Reduction of the burden of RSV disease • Provides better value for money for protecting infants against RSV disease at current list prices	• Durability of protection provided by RSVpreF may be less than mAbs • Safety of RSVpreF (hypertension) still under investigation • More complicated program (e.g. HCW need to determine if there was vaccination during pregnancy)	• Not including some or all healthy term infants (<8 months of age) born before the start of RSV season could be considered to increase the cost-effectiveness of the strategy. • Not recommended to receive RSVpreF in subsequent pregnancies (mAb for those infants).

VIII. Research needs and gaps

In addition to the previously identified research gaps and needs, research to address the following outstanding questions is encouraged:

- Safety and effectiveness of mAbs in infants at high risk and children in their second RSV season
- Safety and effectiveness of mAbs outside of clinical trial settings
- Durability of protection of mAbs
- Safety and efficacy or effectiveness of concurrent administration of mAbs with childhood vaccines and/or other monoclonal antibodies
- Impacts on equity due to mAb immunization programs or lack thereof
- Acceptability and uptake of mAb
- Impact of RSV vaccination on reduction in severe respiratory disease in pregnancy, and/or pregnancy complications
- Durability of protection of the infant following vaccination in pregnancy
- Efficacy and safety of repeat vaccination in subsequent pregnancies and for pregnant women and pregnant people who may benefit from RSV protection in the future, including boostability of immune responses
- Added benefit of immunizing an infant with a long-acting monoclonal antibody against RSV if RSV vaccination was administered during pregnancy.

Tables

Table 4. Summary of findings comparing clesrovimab to placebo for all infants entering their first RSV season

Outcome	No. of studies (study design)	No. of events/ No. of participants		Effect		Certainty	Comments
		Clesrovimab	Placebo	Relative effect (95% CI)	Absolute effect (95% CI)		
Critical outcomes							
Death due to RSV	No data						
RSV RTI with ICU admission (follow-up: 150 days)	1 (RCT)	0/2398 (0%)	4/1201 (0.3%)	RR 0.063 (0.0003 to 1.183)	3 fewer per 1,000 (3 fewer to 1 more)	Moderate[a]	Clesrovimab is likely effective at reducing RSV RTI with ICU admission in infants entering their first RSV season
RSV RTI with hospitalization (follow-up: 150 days)	1 (RCT)	9/2398 (0.4%)	28/1201 (2.3%)	RR 0.16 (0.08 to 0.34)	20 fewer per 1,000 (21 fewer to 15 fewer)	High	Clesrovimab is effective at reducing RSV RTI with hospitalization in infants entering their first RSV season
Severe systemic adverse events (follow-up: 150 days)	1 (RCT)	217/2409 (9.0%)	112/1202 (9.3%)	RR 0.967 (0.778 to 1.201)	3 fewer per 1,000 (21 fewer to 9 more)	Moderate[b]	Clesrovimab likely results in little to no difference in severe systemic adverse events in infants entering their first RSV seasons
Important outcomes							
Medically-attended RSV RTI (follow-up: 150 days)	1 (RCT)	60/2398 (2.5%)	74/1201 (6.2%)	RR 0.96 (0.281 to 0.559)	37 fewer per 1,000 (44 fewer to 27 fewer)	High	Clesrovimab is effective at reducing medically attended RSV RTI in infants entering their first RSV season
Severe local adverse events (follow-up: 150 days)	1 (RCT)	2/2409 (0.1%)	2/1202 (0.2%)	RR 0.499 (0.070 to 3.538)	1 fewer per 1,000 (2 fewer to 4 more)	Moderate[a]	Clesrovimab likely results in little to no difference in severe local adverse events in infants entering their first RSV season

[a] Downrated by one level due to imprecision. The sample size did not meet the optimal information size for this outcome, nor was the study properly powered to detect differences in this outcome
[b] Downrated by one level due to imprecision. The width of the 95% confidence interval of the absolute effect encompasses potential benefit, no effect, and a potential harm.

Table 5. NACI recommendations: strength of recommendation

Strength of recommendation	Strong	Discretionary
Wording	"should/should not be offered"	"may/may not be offered"
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages ("should"), OR Known/Anticipated disadvantages outweigh known/anticipated advantages ("should not")	Known/anticipated advantages are closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists
Implication	A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.	A discretionary recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

Table 6. GRADE certainty of evidence rating for NACI recommendations

GRADE certainty of evidence rating	Description
High	Very confident that the true effect lies close to that of the effect estimate.
Moderate	Moderately confident: the true effect is likely to be close to the effect estimate, but there is a possibility that it is substantially different.
Low	Limited confidence in the effect estimate: the true effect may be substantially different from the effect estimate.
Very low	Very little confidence in the effect estimate: true effect likely to be substantially different from the effect estimate.

List of abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
ALRI	Acute lower respiratory infection
CDC	Centers for Disease Control and Prevention (United States)
CHD	Congenital heart disease
CIC	Canadian Immunization Committee
CLD	Chronic lung disease of prematurity
GRADE	Grading of recommendations, assessment, development and evaluation
HDP	Hypertensive disorders of pregnancy
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratios
ICU	Intensive care unit
IR	Incidence rate
ITP	Immune thrombocytopenia
LRTD	Lower respiratory tract disease
LRTI	Lower respiratory tract infection
mAb	Monoclonal antibody
MALRI	Medically attended lower respiratory tract infection
NACI	National Advisory Committee on Immunization
NITAG	National Immunization Technical Advisory Group
NVSN	New Vaccine Surveillance Network
PHAC	Public Health Agency of Canada
PHECG	Public health ethics consultative group
QALY	Quality-adjusted life year
RSV	Respiratory syncytial virus
RSV WG	Respiratory syncytial virus working group
RTI	Respiratory tract infection
SAE	Serious adverse events
SD	Standard deviation
US	United States
VE	Vaccine efficacy
VISION	Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network
VSD	Vaccine Safety Datalink
wGA	Weeks gestational age
WHO	World Health Organization

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