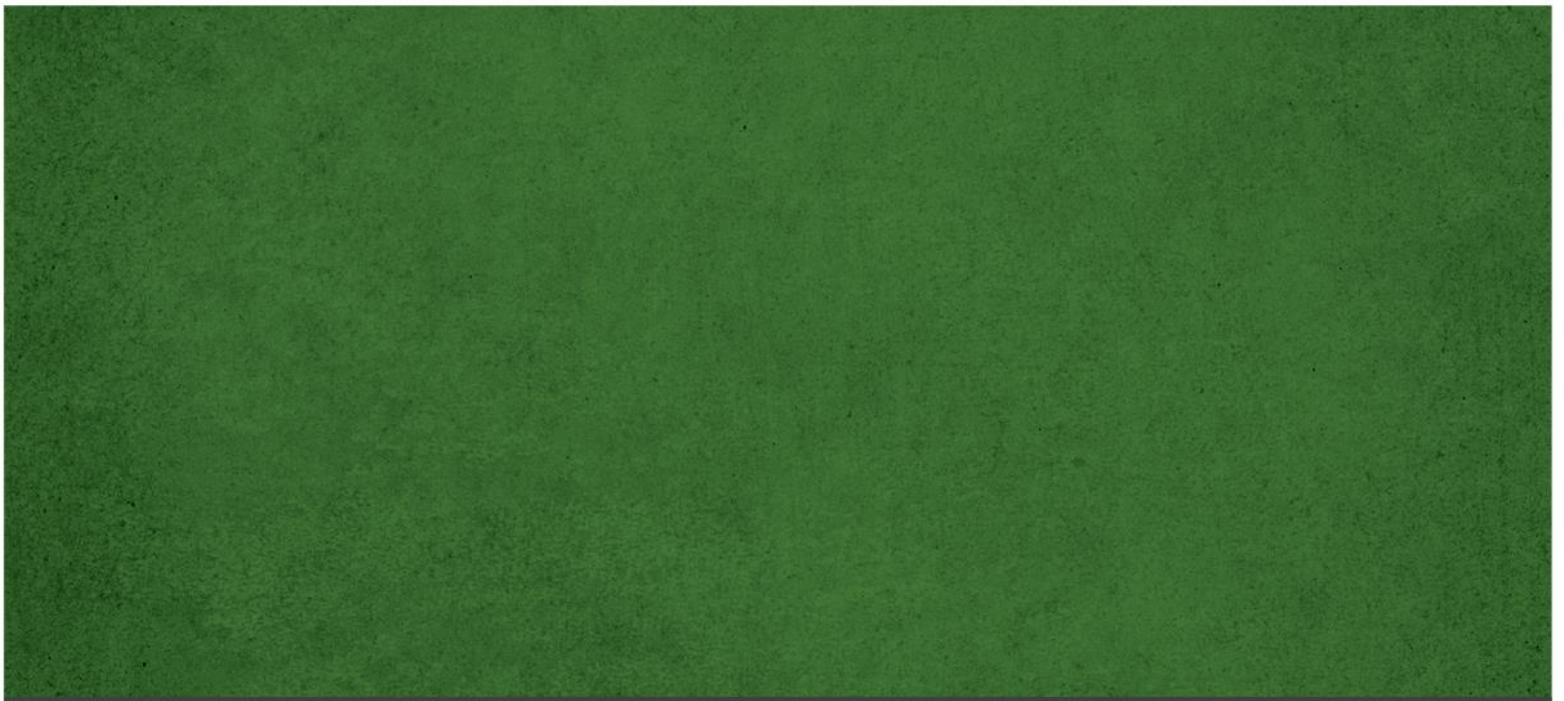
An Advisory Committee Statement (ACS)

National Advisory Committee on Immunization (NACI)

Updated guidance on respiratory syncytial virus (RSV) vaccines for older adults and for adults at high risk of severe RSV disease



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Recommandations mises à jour sur les vaccins contre le virus respiratoire syncytial (VRS) chez les adultes âgés et les adultes à risque élevé de maladie grave liée au VRS.

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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.

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I. Introduction

Guidance Objective:

Since 2023, Health Canada has approved three vaccines to prevent RSV in adults: RSVpreF (Abrysvo® by Pfizer for adults aged 60 years and older), RSVPreF3 (Arexvy by GSK for adults aged 60 years and older and adults aged 50 to 59 years of age at increased risk of RSV disease) and mRNA-1345 (mRESVIA® by Moderna for adults aged 60 years and older). The need for updated NACI guidance on RSV adult vaccines arose from additional regulatory decisions on these products. On October 17, 2025, Health Canada approved an expanded age indication for the use of RSVpreF in adults aged 18 to 59 years at increased risk for lower respiratory tract disease (LRTD) caused by RSV.[1] On January 14, 2026, Health Canada approved an expanded age indication for the use of mRNA-1345 in adults aged 18 to 59 years at increased risk for LRTD caused by RSV.[2]

This is the third NACI statement providing recommendations for the prevention of RSV in adults, further to two previous statements dedicated to older adults (released on July 12, 2024 and March 13, 2025).

The primary objectives of this statement are to:

- review the evidence on the potential benefits (immunogenicity/efficacy/effectiveness) and potential harms (e.g. safety) of RSVPreF and mRNA-1345 for adults 18 to 59 years of age at increased risk of RSV disease along with updated data among adults 60 years of age and older
- review the evidence on the cost-effectiveness of RSV immunization programs for older adults aged less than 75 years
- provide updated recommendations for the use of RSV vaccines (RSVpreF, RSVPreF3, and mRNA-1345) for adults under 75 years of age at increased risk of RSV disease in Canada

NACI publishes separate recommendations on the protection of infants and children from respiratory syncytial virus (RSV) disease using monoclonal antibodies (nirsevimab and clesrovimab) and the RSVpreF vaccine in pregnancy.

II. Methods

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

- Analysis of the burden of disease caused by RSV in adults
- Retrieval, quality assessment, and synthesis of individual studies on the benefits and harms of RSV adult vaccines
- 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[3]
- Use of an environmental scan and model-based economic evaluation of RSVpreF, RSVPreF3, and mRNA-1345 vaccines for the prevention of RSV-related outcomes in Canadian adults to generate economic evidence
- Review of vaccine guidance from international and domestic bodies through an environmental scan
- Consideration of vaccine principles
- 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.[4] The 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, including such considerations as the burden of RSV disease in the target populations; safety, immunogenicity, efficacy, and effectiveness of the vaccines; and other aspects of the overall immunization strategy. The knowledge synthesis was performed by the NACI Secretariat and supervised by the RSV Working Group. Following critical appraisal of individual studies, clinical evidence was synthesized leveraging GRADE methodologies to inform recommendations for vaccine use.

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 on September 25, 2025 and December 9, 2025 the committee voted on specific recommendations on December 9, 2025.

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 healthcare 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

RSV is a very common respiratory pathogen that infects almost all persons by age two years and causes recurrent infections throughout life. Risk factors for severe outcomes (including hospitalization, intensive care unit [ICU] admission, and death associated with RSV) increase with increasing age, residence in chronic care or long-term facilities, presence of comorbidities (e.g. cardiorespiratory disease, metabolic disease, immunocompromise, chronic liver or kidney disease, neurologic disease or class 3 obesity), or due to factors that intersect with social determinants of health.[5-8] The burden of RSV in younger adults at high risk may be similar to older adults'.[9] In the United States, 95.5% of adults hospitalized with RSV have at least one comorbidity.[10,11] Chronic kidney disease has been identified in several studies as one of the highest risk factors for severe RSV.[5,11,12] In the United States' (US) surveillance, chronic kidney disease had the highest adjusted risk ratio for RSV-associated hospitalization (6.5).[12] In a Canadian study of RSV-associated hospitalization, incidence was higher for those with comorbidities, including chronic kidney disease (receiving dialysis) (494.7/100,000; 95% CI, 410.7–595.8) and transplant recipients (370.9/100,000; 95% CI, 318.0–432.6).[5] In addition, patients attending hospital for haemodialysis may be at increased risk of acquiring respiratory viruses.

Recent data suggest a higher burden of RSV associated hospitalization than previously reported.[13] In a Canadian study over 2 respiratory seasons, incidence of RSV-associated hospitalizations increased from 2.0 (95% CI, 1.8–2.3) per 100 000 for those aged 18–49 years to 43.7 (95% CI, 41.0–46.6) per 100 000 for those aged 70–79 years, with a sharp increase to 134.7 (95% CI, 128.6–141.1) per 100 000 for those aged ≥ 80 years.[5] Incidence was higher for those with comorbidities. In a multicenter study done prior to COVID-19, RSV had a burden comparable to influenza in hospital admission and mortality, with slower recovery than influenza B.[14] Approximately 10% of older adults hospitalized with RSV infection require ICU admission and the case fatality ratio (CFR) among those admitted to hospital varies between 5% and 10%.[5,8] Some studies suggest that RSV burden may be close to the influenza burden in older adults.[8] In a recent Canadian study among hospitalized patients, there were higher rates of 30-day mortality and ICU admission, and longer hospital lengths of stay for RSV compared with influenza.[15] There are emerging longer-term risks associated with RSV infection in adults including a recent study identifying a significant excess risk of cardiovascular events (ischemic heart disease, stroke, and heart failure, and any cardiovascular event, comprising major adverse cardiovascular events together with arrhythmias, venous thromboembolism, and inflammatory heart disease) during the year following RSV infection (comparable in magnitude to influenza infection).[16] Among older adults, RSV infection may also lead to complications such as Guillain-Barré syndrome (GBS) particularly in those aged 75 years and older.[17] In a recent self-controlled case series among individuals aged 65 years and older, the adjusted incidence rate ratio (IRR) for GBS following RSV disease was 2.11 (95% CI: 1.01-4.37) and remained consistent across sensitivity analyses. After ICD-10 code adoption, IRR increased to 2.59 (95% CI: 1.17-5.73) with a marked rise among patients aged ≥75 years (95% CI: 3.98 [1.45-10.91]). [17]

IV. Vaccines

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

Characteristics of the RSV vaccines currently authorized for use in Canada are summarized in Table 1.

Table 1. Comparison of vaccines authorized for use in Canada

	AREXVY (RSVPreF3)[18]	**ABRYSVO® (RSVpreF)[1]**	**mRESVIA® (mRNA-1345)[2]**
Manufacturer	GlaxoSmithKline Inc. (GSK)	Pfizer Canada ULC	Moderna Biopharma Canada Corporation
Date of authorization in Canada	August 4, 2023. Updated indication: November 1, 2024	December 21, 2023 Updated indication: October 17, 2025	November 6, 2024 Updated indication: January 14, 2026
Type of vaccine	Stabilized subunit vaccine	Stabilized subunit vaccine	mRNA vaccine
Adjuvant	$AS01_E$	N/A	N/A
Composition	Lyophilized powder containing 120 mcg of RSVPreF3 glycoprotein F antigen, trehalose dihydrate, polysorbate 80, potassium dihydrogen phosphate, and dipotassium phosphate, reconstituted with an adjuvant suspension containing 25 mcg *Quillaja saponaria Molina*, fraction 21, 25 mcg 3-O-desacyl-4'-monophosphoryl lipid A, dioleoyl phosphatidylcholine, cholesterol, sodium chloride, disodium phosphate anhydrous, potassium dihydrogen phosphate, and water for injection	Lyophilized powder containing 60 mcg of each stabilized RSV prefusion F antigens (A and B), mannitol, polysorbate 80, sodium chloride, sucrose, tromethamine, trometamol hydrochloride reconstituted with sterile water as the diluent	Pre-filled syringe containing frozen dispersion containing 50 mcg of mRNA encoding RSV F glycoprotein stabilized in the prefusion conformation, 5′(m7G-5′-ppp-5′-Gm) cap, 100-nucleotide 3′ poly(A) tail, acetic acid, cholesterol, DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), SM-102 (heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate), PEG2000-DMG (1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000), sodium acetate trihydrate, sucrose, trometamol, trometamol hydrochloride, and water for injection
Schedule	1-dose schedule	1-dose schedule	1-dose schedule
Route of administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Indications	Authorized for the prevention of lower	Authorized for the prevention of lower	Authorized for the prevention of lower

	AREXVY (RSVPreF3)[18]	ABRYSVO® (RSVpreF)[1]	mRESVIA® (mRNA-1345)[2]
	respiratory tract disease caused by RSV in adults 60 years of age and older and adults 50 to 59 years of age at increased risk of RSV disease	respiratory tract disease (LRTD) caused by RSV in individuals 60 years of age and older, individuals 18 through 59 years of age who are at increased risk for LRTD caused by RSV and in pregnant individuals from 32 through 36 weeks gestational age for the prevention of LRTD and severe LRTD caused by RSV in infants from birth through 6 months of age	respiratory tract disease caused by RSV in adults 60 years of age and older, individuals 18 through 59 years of age who are at increased risk for LRTD caused by RSV
Contraindications	Individuals who are hypersensitive to the active ingredients or to any ingredients in the formulation, including non-medicinal ingredients, or components of the container	Individuals who are hypersensitive to the active substance or to any component of the vaccine	Individuals who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container
Precautions	Safety and immunogenicity data on RSVPreF3 are not available for immunocompromised individuals. Patients receiving immunosuppressive treatment or patients with immunodeficiency may have a reduced immune response to RSVPreF3. There are no data from the use of RSVPreF3 in pregnant individuals, nor on the excretion of RSVPreF3 in human or animal milk. RSVPreF3 is not recommended for use during pregnancy or in breast-feeding/lactating individuals.	There are no data on the use of RSVPreF in immunocompromised individuals. Immunocompromised individuals, including those receiving immunosuppressive therapy, may have a diminished immune response to RSVPreF. It is unknown whether RSVPreF is excreted in human milk. No safety signals were detected in breastfed newborns of vaccinated mothers in a clinical trial.	The efficacy and safety of mRNA-1345 have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. These individuals may have a diminished immune response to mRNA-1345. There are no data on the use of mRNA-1345 in pregnant women. No human or animal data are available to assess the effects of mRNA-1345 on the breastfed infant or on milk production/excretion.
Storage Requirements	Store in a refrigerator between 2°C to 8°C. Do not freeze. Discard if the vial has been frozen. Store in the original package in order to protect from light. After reconstitution, RSVPreF3 should be used promptly; if not possible,	Store in a refrigerator between 2°C and 8°C in the original carton. Do not freeze. Discard if the carton has been frozen. RSVPreF should be administered immediately (within 4 hours) after	Store frozen between - 40°C and -15°C for up to 18 months. One (1) pre-filled syringe, thaw in a refrigerator (2°C to 8°C) for 1 hour and 40 minutes or at room temperature (15°C to

	AREXVY (RSVPreF3)[18]	ABRYSVO® (RSVpreF)[1]	mRESVIA® (mRNA-1345)[2]
	the vaccine should be stored in the refrigerator between 2°C to 8°C or at room temperature up to 25°C. If not used within 4 hours, it should be discarded.	reconstitution. Store the reconstituted vaccine between 15°C and 30°C. Do not freeze reconstituted vaccine.	25°C) for 40 minutes. Cartons of 10 pre-filled syringes, thaw in a refrigerator (2°C to 8°C) for 2 hours and 40 minutes or at room temperature (15°C to 25°C) for 1 hour and 20 minutes. After thawing, do not refreeze. Syringes should not be returned to the refrigerator after being thawed at room temperature. The pre-filled syringes may be stored at room temperature (15°C to 25°C) for a total of 24 hours after removal from refrigerated conditions. Discard the pre-filled syringe if not used within this time. Within the 18-month shelf-life, the unopened vaccine may be stored refrigerated between 2°C and 8°C, protected from light, for a maximum of 90 days. Unopened prefilled syringes may be stored at 8°C to 25°C for a total of 24 hours after removal from refrigerator conditions. Thawed prefilled syringes can be handled in room light conditions.

For complete prescribing information for AREXVY, ABRYSVO®, and mRESVIA®, consult the product leaflet or information contained within Health Canada's authorized product monographs available through the Drug Product Database.

The data on the immunogenicity, efficacy, effectiveness and safety of vaccines (RSVpreF3, RSVpreF or mRNA-1345) preventing RSV disease in adults have been described in previous NACI statements.[19,20] This updated statement provides an updated evidence summary (including recent publications) with a focus on adults aged 60-74 years and 18-59 years of age at increased risk of severe RSV disease where applicable. If needed, additional details are available in previous NACI statements: Updated guidance on respiratory syncytial virus (RSV) vaccines for older adults including the expanded use of RSVPreF3 for individuals 50-59 years of

age and use of the new mRNA-1345 vaccine and Statement on the prevention of respiratory syncytial virus in older adults.

IV.2 Immunogenicity in adults 18 years of age and older

NACI reviewed the available evidence on the immunogenicity of RSVpreF, RSVPreF3 and mRNA-1345 in adults ≥18 years of age at increased risk of severe RSV disease. Overall, available evidence shows that all three RSV vaccines trigger a strong immune response. Waning of the immune responses after the first RSV vaccine dose has been observed.[19] However, it is unknown at this time whether vaccine efficacy/effectiveness can be boosted by subsequent vaccine doses. The total duration of protection provided by the first dose and the need for revaccination at later timepoints are still under investigation.[19]

The type of underlying chronic medical conditions or immunocompromising conditions (e.g. cardiovascular diseases, chronic lung diseases, diabetes, solid organ transplant [SOT] recipients, autoimmune inflammatory disorders) assessed varied across studies and a limited number of adults under 60 years of age were included. In total, there were 5,264 participants aged 18 to 59 years with an underlying chronic medical condition or immunocompromising condition (884 for RSVPreF, 3,377 for RSVPreF3 and 1,003 for mRNA-1345). The median age of participants was generally closer to the upper age range in trials. For trials with an 18 to 59 year age group, the median age was around 50 years, and for trials among adults aged ≥18 years the median age was around 60 years. The immune response among adults under 60 years at high risk due to underlying conditions was similar to the response observed in individuals aged 60 years and older. The robust response observed following the first dose was also observed across the immunocompromised subgroups assessed. Immunogenicity data are described in more detail below. None of the clinical trials in adults 18 to 59 years of age at increased risk of severe RSV disease described below were designed to measure vaccine efficacy.

The immunogenicity of RSVpreF in adults ≥18 years of age at increased risk of severe RSV disease has been evaluated in clinical trials.[21,22] A randomized, double-blinded, placebo-controlled trial in adults 18 to 59 years of age with chronic medical conditions (most commonly chronic pulmonary conditions and diabetes) randomized participants 2:1 to receive either RSVpreF (n=453) or placebo (n=225). The primary immunogenicity objective was to demonstrate non-inferiority of the immune response (measured via geometric mean titer ratio [GMR], and seroresponse rate [SRR]) in participants 18 to 59 years of age with chronic medical conditions compared to adults ≥60 years of age from the pivotal RSVpreF efficacy trial.[23] One month following RSVpreF administration, the immune response in the adults 18 to 59 years of age with chronic medical conditions was non-inferior to adults ≥60 years of age, for both RSV-A and RSV-B. The immune response was also similar across subgroups of both age (18 to 49 years of age and 50 to 59 years of age) and prespecified medical condition (chronic pulmonary disease, diabetes, cardiovascular disease, or other condition).

The second study, a single-arm, open-label study, evaluated RSVpreF's immune response in adults 18 years of age and older with immunocompromising and high-risk conditions (most

commonly autoinflammatory disorders and SOT recipients). Participants (n=203) were stratified by age group (18 to 50 years of age and ≥60 years of age) and received two doses of RSVpreF, with an interval of one month between doses. The primary immunogenicity objective was to determine RSV-A and RSV-B neutralizing antibody titers after vaccination. A robust immune response, similar to that observed in the pivotal efficacy study, was observed, one month following the first dose, for both RSV-A and RSV-B. One month following the second dose, no increase in immune response was observed. The robust response observed following the first dose was observed across age and immunocompromised subgroups. However, SOT recipients who were also receiving mycophenolate had a lower neutralizing antibody response compared to SOT recipients who were not receiving mycophenolate.[21] The implication of these data are not yet clear as there is no established immune correlate of protection and no threshold of immunity that correlates with protective efficacy has been established.[24]

Similarly, several clinical trials evaluating the immunogenicity of RSVPreF3 in adults ≥18 years of age at increased risk of severe RSV disease have been conducted to date. A phase IIb, randomized, open-label trial in lung and renal transplant patients ≥18 years of age randomized participants in a 1:1 ratio to either one (n=131) or two (n=130) doses (30 to 60 days following dose one) of RSVPreF3.[25] These individuals were compared to a control group of healthy adults ≥50 years of age who received a single dose of RSVPreF3 (n=125). The majority of SOT recipients were ≥50 years of age (93%). The primary outcome measure was the neutralizing antibody titers of RSV-A and RSV-B, one month following each dose. A robust immune response was observed following administration of one dose of RSVPreF3, although the magnitude of the response was lower than that observed in the healthy adults ≥50 years of age. In those receiving a second dose, neutralizing antibody titer levels were similar to the levels seen in healthy adults ≥50 years of age, one month following administration of the second dose. Similar results were observed after six months of follow-up, although the magnitude of the difference in immune response between the one dose group and the two dose and ≥50 years of age groups was decreased. Similar to what was observed in the RSVpreF trials, the immune response induced by RSVPreF3 in participants who were receiving mycophenolate was less robust than in those who were not.

A separate, phase IIIb, non-randomized, open-label study evaluated the non-inferiority of the immune response of a single dose of RSVPreF3 in non-immunocompromised adults 18 to 49 years of age at increased risk for RSV (n=1,029) compared to older adults ≥60 years of age (n=429).[26] The mean age in the 18 to 49 years of age group was 38.4 (standard deviation 8.4). The majority of participants (68.8%) had one pre-existing chronic condition, the remaining participants had at least two chronic conditions. Cardiopulmonary diseases and diabetes were the most common chronic conditions. GMT ratio and SRR analyses were conducted one month following RSVPreF3 administration, and the immune response in the adults 18 to 49 years of age at increased risk for RSV was non-inferior to adults ≥60 years of age, for both RSV-A and RSV-B. After six months of follow-up, similar results were observed, and the immune response remained non-inferior.[26] An additional study, an observer-blind, phase III, non-inferiority trial, compared the immune response in adults 50 to 59 years of age (with [n=386] and without [n=383] predefined, stable, chronic medical conditions) to a control group of adults ≥60 years of age (n=381). All participants received a single dose of RSVPreF3. In the group of adults 50 to 59 years

of age with chronic medical conditions, chronic cardiovascular disease, chronic cardiopulmonary disease and diabetes mellitus were the most common chronic medical conditions. One month following vaccination, the immune response in adults 50 to 59 years of age with chronic medical conditions was non-inferior to that in those ≥60 years of age in terms of RSV-A and RSV-B neutralization titers and in seroresponse rates.[27] Over time, levels of neutralizing titers and seroresponse rates declined in adults 50 to 59 years of age with chronic medical conditions and in adults ≥60 years of age, but remained above levels observed at baseline and in placebo groups at 6 and 12 months following vaccination.[28]

The immunogenicity of mRNA-1345 has been evaluated in a single trial, a phase III, randomized, double-blind trial. Participants 18 to 59 years of age at high risk for RSV were randomized in a 1:1 ratio to a single dose of either 30µg (n=497) or 50µg (n=502) of mRNA-1345 and compared to older adults ≥60 years of age[29] who received a single 50µg dose of mRNA-1345 in the pivotal efficacy trial.[30] Risk conditions included coronary artery disease, congestive heart failure, chronic lung disease (i.e., COPD and asthma), and diabetes (type 1 or 2). The median age in those 18 to 59 years of age was 52 (range 19 to 59). The primary immunogenicity objective was to demonstrate non-inferiority of the immune response (measured by neutralizing antibody titers and seroresponse rate) of both RSV-A and RSV-B elicited by 50ug of mRNA-1345 in participants 18 to 59 years compared to the immune response in adults ≥60 years of age from the pivotal efficacy trial. One month following administration of mRNA-1345 (50µg), the immune response for both RSV-A and RSV-B was non-inferior in adults 18 to 59 years of age at high risk of RSV, compared to older adults ≥60 years of age. Neutralizing antibody titers were generally similar across subgroups of age (18 to 49 years of age, 50 to 59 years of age), and prespecified risk factors (coronary artery disease and/or congestive heart failure, chronic lung disease, diabetes).

Details on the immunogenicity of RSV vaccines following revaccination have been provided in previous Updated guidance on respiratory syncytial virus (RSV) vaccines for older adults including the expanded use of RSVPreF3 for individuals 50-59 years of age and use of the new mRNA-1345 vaccine. To date, while additional vaccine doses increased antibody titers, they did not improve the overall efficacy. The need for subsequent vaccine doses and optimal strategy for boosting are still under investigation and NACI will continue to monitor emerging evidence as it becomes available.

IV.3 Efficacy in adults 60 years of age and older

There are currently no efficacy data available in adults aged less than 60 years. Evidence on vaccine efficacy of RSVpreF, RSVPreF3 and mRNA-1345 in adults 60 years of age and older (with and without stable chronic medical conditions) is available from clinical trials.[23,30-34] As summarized in previous NACI statements,[19,20] a single dose of RSV vaccine (RSVpreF, RSVPreF3 or mRNA-1345) has been shown to reduce laboratory confirmed RSV respiratory tract infection (RTI) associated hospitalizations and medically attended RSV RTI for adults 60 years of age and older. Available evidence suggests that a single dose of RSV vaccine provides protection from RSV disease for at least three years;[35] however, it is not yet known if the efficacy can be boosted with further vaccine doses.[19,36] When available, vaccine efficacy stratified by age or risk

was comparable across groups but imprecise (i.e. wide confidence intervals) due to the small sample sizes. However, in immunogenicity studies, all three RSV vaccines provided robust immune responses and one dose of RSV vaccine was shown to be immunogenic in most of the high-risk conditions assessed (see Table S1, S2 and S3).

Further details on efficacy are provided below. Of note, season 1 of Pfizer's RENOIR and GSK's AReSVi-006 trials was conducted in the 2021-2022 RSV season when public health measures due to the COVID-19 pandemic were in place and respiratory viral transmission was limited, which could explain the low rate of RSV-associated outcomes.

IV.3.1 Efficacy of RSV vaccines against death due to RSV

Currently, there is no available data on the efficacy of RSV vaccines for the prevention of death due to RSV in adults 60 years of age and older. There were no deaths due to RSV in any of the efficacy trials conducted to date among adults 60 years of age and older[23,30-34]; these trials were not adequately powered to detect differences in this outcome.

IV.3.2 Efficacy of RSV vaccines against RSV respiratory infection with ICU admission

Available data on the efficacy of RSV vaccines for the prevention of RSV RTI with ICU admission in adults ≥60 years of age are currently limited. In the pivotal efficacy trials for both RSVpreF and mRNA-1345 in adults ≥60 years of age, there were no ICU admissions in either group of the studies.[23,30] In the phase III efficacy trial of RSVPreF3 in adults ≥60 years of age (n=24,960; 12,466 in the RSVPreF3 group and 12,494 in the placebo group), there was one participant in the placebo group admitted to ICU (between the ages of 60 and 74), and none in the RSVPreF3 group.[31,37]

IV.3.3 Efficacy of RSV vaccines against RSV respiratory infection with hospitalization

In the pivotal efficacy trial of mRNA-1345 in adults ≥60 years of age, there were two cases of RSV RTI with hospitalization reported in the placebo group (n=18,045) and none in the mRNA-1345 group (n=18,112). One of these cases occurred in a participant 75 years of age and older, the other in a participant 60 to 74 years of age.[30] The pivotal efficacy trial of RSVpreF in adults ≥60 years of age recorded two RSV RTIs with hospitalization in the placebo group (n=18,076) and none in the RSVpreF group (n=18,058). Both of these hospitalizations were in participants 60 to 74 years of age.[23] For the pivotal efficacy trial of RSVPreF3 in adults ≥60 years of age, there were three hospitalizations in the placebo group (n=12,494) and none in the RSVPreF3 group (n=12,466). All three of these hospitalizations were in individuals 60 to 74 years of age.[31]

IV.3.4 Efficacy of RSV vaccines against medically attended RSV respiratory tract infection

In the pivotal efficacy trial of mRNA-1345 in adults ≥60 years of age, there were 18 cases of medically attended RSV RTI; 5 in the mRNA-1345 group (n=18,112) and 13 in the placebo group

(n=18,045), corresponding to an estimated VE of 59% (95% CI: -3 to 84%). VE was similar in a subgroup analysis of adults 60 to 74 years of age, with 2 cases in the mRNA-1345 group (n=14,830) and 11 in the placebo group (n=14,765).[30] The pivotal efficacy trial of RSVpreF in adults ≥60 years of age recorded 27 medically attended RSV RTIs in the placebo group (n=18,076) and eight in the RSVpreF group (n=18,058), corresponding to a VE of 66% (95% CI: 34 to 83%). VE was similar in a subgroup analysis of adults 60 to 74 years of age, with 20 medically attended RSV RTIs in the placebo group (n=15,173) and seven in the RSVpreF group (n=15,164).[23,38] For the pivotal efficacy trial of RSVPreF3 in adults ≥60 years of age, there were 24 medically attended RSV RTIs in the placebo group (n=12,494) and three in the RSVPreF3 group (n=12,466), corresponding to a VE of 88% (95% CI: 59 to 98%). VE was similar in a subgroup analysis of adults 60 to 74 years of age, with 20 medically attended RSV RTIs in the placebo group (n=9,848) and 1 in the RSVPreF3 group (n=9,795).[31,39]

IV.3.5 Longer term efficacy during subsequent RSV seasons

Available evidence on the efficacy of RSV vaccines over multiple RSV seasons show that a single dose of some RSV vaccines may provide protection from RSV disease for at least three RSV seasons.[35,36,40-43] Waning of the immune responses after the first RSV vaccine dose has been observed.[19] However to date, vaccine efficacy/effectiveness has not been boosted with additional vaccine doses .[19,35,36] The total duration of protection, need of boosters and dynamics of waning of immune responses for all three RSV vaccines are still under investigation and the vaccines may not provide the same duration of protection. NACI will continue to monitor emerging evidence as it becomes available.

IV.4 Effectiveness in adults 60 years of age and older

NACI reviewed the available data on the effectiveness of RSVPreF and RSVPreF3 in adults ≥60 years of age. Currently, there are no effectiveness data available in adults aged less than 60 years nor for mRNA-1345 (at any age).

Multiple observational studies from the US and the UK have demonstrated the effectiveness of both RSVpreF and RSVPreF3 in adults ≥60 years of age, against various outcomes, including RSV infection, RSV-associated hospitalizations, and RSV-associated emergency department (ED) visits.[26,44-49] Under real-world conditions, vaccination with an RSV protein subunit vaccine (either RSVpreF or RSVPreF3) provided protection against severe RSV disease similar to what was observed in pivotal phase III efficacy trials. The populations studied in these real-world effectiveness studies are also more representative of those at high risk of severe RSV disease and for more severe outcomes (i.e., adults ≥80 years of age, those with immunocompromising conditions, etc.). Several of these studies also compared effectiveness in adults 60 to 74 years of age to the effectiveness in adults ≥75 years of age, and have found comparable results. Several key studies are described below. Data are also beginning to emerge on effectiveness over multiple RSV seasons, and are summarized below.

A test-negative case-control study conducted from October 2023 to March 2024, using the Influenza and Other Viruses in the Acutely Ill (IVY) Network data evaluated vaccine effectiveness against RSV-associated hospitalization in patients ≥60 years of age (n=265) receiving either RSVPreF3 or RSVpreF.[44] Almost all vaccine recipients (96.6%) had at least one chronic condition, and 31.7% of vaccinees were immunocompromised (defined as having an active solid tumor or hematologic malignancy, solid organ or hematopoietic cell transplant, or conditions that cause moderate to severe immunosuppression). VE against RSV-associated hospitalization was 75% (95% CI: 50 to 87%) and was similar in adults 60 to 74 years of age (75%; 95% CI: 31 to 91%) and adults ≥75 years of age (76%; 95% CI: 40 to 91%).

A second test-negative case-control study conducted from October 2023 to March 2024, using Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION) network data evaluated vaccine effectiveness against RSV-associated hospitalization, ED visits, and critical illness (defined as ICU admission or death) in patients ≥60 years of age (n=3,275) receiving either RSVPreF3 or RSVpreF.[45] Age-stratified results were provided for both RSV-associated hospitalization and RSV-associated ED visits. Vaccine effectiveness was high for both RSV-associated hospitalizations (80%; 95% CI 71 to 85%) and RSV-associated ED visits (77%; 95% CI 70 to 83%) in adults without immunocompromising conditions, and was also similar in adults 60 to 74 years of age and adults ≥75 years of age. VE estimates were similar between vaccine types (RSVPreF3 and RSVpreF), and VE against RSV-associated hospitalization was also similar in those with immunocompromising conditions (71%; 95% CI 46 to 85%).

A GSK-sponsored, test-negative, case-control study using Kaiser Permanente Southern California health system data matched RSV-positive cases (n=281) to RSV-negative controls (n=1,108) in a 4:1 ratio and estimated VE of RSVpreF3 against RSV-associated LRTD hospitalization in adults ≥60 years of age.[26] The mean age of the RSV-positive cases was 78.4 (SD 9.3) years, and almost all (n=256, 91%) had at least one comorbidity of interest (kidney disease, heart disease, lung disease, liver disease, diabetes, autoimmune diseases, neurologic or neuromuscular conditions, hematologic conditions, or immunocompromising conditions). Preliminary results demonstrate high VE against RSV-associated LRTD hospitalization (82%; 95% CI: 62 to 92%). When stratified by age group, VE was similar in adults 60 to 74 years of age (83%; 95% CI: 27 to 96%) and adults ≥75 years of age (82%; 95% CI: 55 to 93%). VE estimates were also similar across subgroups of comorbidities and immunocompromised status.

A multicentre test-negative case-control study conducted in England from September 2023 to March 2024 evaluated the effectiveness of RSVpreF against RSV-associated hospital admission among adults aged 75–79 years using the Hospital-based Acute Respiratory Infection Sentinel surveillance (HARISS) network data (n=1,006; 173 RSV-positive cases and 833 RSV-negative controls).[48] Almost all participants (91%) had at least one chronic condition. Mean age was 77.8 years (SD 1.44) in individuals who were RSV positive. VE against RSV-associated hospitalization was 82% (95% CI: 71 to 90%), and VE against severe disease (defined as requirement of oxygen supplementation, high-flow nasal oxygen, non-invasive ventilation or continuous positive airway pressure, invasive ventilation or mechanical ventilation, and admission to the ICU on hospital admission and adults who died within 30 days of hospital admission), was 86% (95% CI: 75 to

94%). In individuals with immunosuppression, vaccine effectiveness against hospital admission was 73% (95% CI: 40 to 89).

VE over two RSV seasons in adults ≥60 years of age has been assessed by two studies conducted in the US.[49,50] In both studies, VE against RSV-associated hospitalization was numerically higher in the first RSV season compared to the second, indicating that protection appears to be waning over time. The first study, a multicentre, test-negative, case-control study using data from the IVY Network across 26 hospitals in 20 U.S. states,[49] estimated VE (primarily a mix of RSVpreF and RSVPreF3) against RSV-associated hospitalization at 58% (95% CI: 45 to 68%) over two RSV seasons. Estimates were lower (VE 48%; 95% CI: 27 to 63%) for prior-season vaccination compared to same-season vaccination (VE 69%; 95% CI: 52 to 81%), although the difference was not statistically significant. Overall VE was also significantly lower amongst immunocompromised individuals (compared to immunocompetent individuals) and among individuals with cardiovascular conditions (compared to those without). When stratified by age group, VE was similar among immunocompetent adults 60 to 74 years of age and immunocompetent adults ≥75 years of age. The second study was a target trial emulation study using the Veterans Health Administration (VHA), which estimated VE against RSV-associated hospitalization. Protection was estimated at 88.9% (95% CI; 77.9 to 95.7%) over 0 to 1 month and decreased to 57.3% (95% CI; 47.3 to 66.4%) over 0 to 18 months. Similar reductions in VE against other outcomes such as documented RSV infection, RSV-associated ED or urgent care (UC) visits and RSV-associated ICU admissions were also observed. Estimates of VE were numerically lower in individuals with immunocompromising conditions and decreased more rapidly, compared to those without immunocompromise. When stratifying by age, reductions in VE over time were observed in all age groups, except for those 60 to 64 years of age, where protection remained stable.

IV.5 Safety

Evidence on the safety of RSV vaccines (RSVPreF3, RSVpreF and mRNA-1345) is available from clinical trials and ongoing national and international post-marketing surveillance and has been described in previous NACI statements.[19,20,51] In this statement, an updated evidence summary is provided with a focus on evidence relevant to assess the safety of RSV vaccines among individuals at high risk aged 18-59 years. This includes data from clinical trials (assessing RSVpreF, RSVPreF3 or mRNA-1345) and post-market surveillance data on the safety of protein subunit RSV vaccines among pregnant women and pregnant individuals (RSVpreF) and among individuals aged 60 years and older (RSVPreF3, RSVpreF). Overall, clinical trials show that all three RSV vaccines have an acceptable safety profile including among adults aged 18 to 59 years with underlying conditions putting them at higher risk of severe RSV disease. No safety signal was identified but these clinical trials were not powered to assess rare adverse events. International post-market safety surveillance continue to show an increased risk of Guillain-Barré Syndrome (GBS) following protein subunit RSV vaccination (RSVpreF and RSVPreF3) in adults aged 65 years and older. To date, pregnant women and pregnant individuals are the largest group aged less than 60 years who have received RSV vaccination and no increased risk of GBS was observed following administration of RSVpreF in pregnancy.[52]

IV.5.1 Local and systemic adverse events following immunization

Several clinical trials have assessed the safety of RSVpreF,[21,22] RSVPreF3,[25,27,28,53-55] and mRNA-1345.[56,57] The types of underlying chronic medical conditions and immunocompromising conditions (e.g. cardiovascular diseases, chronic lung diseases, diabetes, SOT recipients, autoimmune inflammatory disorders) assessed varied by studies and a limited number of adults aged under 60 years was included. In total, there were 2,551 participants aged 18 to 59 years with an underlying chronic medical condition (549 for RSVpreF, 1500 for RSVPreF3 and 502 for mRNA-1345) and 190 with an immunocompromising condition) included in safety analyses. Overall in these clinical trials, all RSV vaccines were well tolerated, including in adults at high risk aged 18 to 59 years. Most local and systemic adverse events (AEs) were comparable or more frequent in the vaccine groups compared to placebo but were generally mild to moderate. The proportions of severe (Grade 3 or Grade 4) events were comparable in the placebo and vaccine groups. A GRADE assessment comparing severe systemic and severe local adverse events (i.e., Grade ≥3) following vaccination determined that there was little to no difference in severe local adverse events in adults 18 to 59 years of age at high risk for severe RSV disease, compared to adults ≥60 years of age, for either RSVpreF, RSVPreF3 or mRNA-1345. For RSVPreF3 and mRNA-1345, vaccination was associated with a small increase in the risk of severe systemic adverse events (e.g. fatigue, myalgia, arthralgia) in those 18-59 years compared to those 60 years of age and older (5.5% vs 2.1% and 5.8% vs 4.0% respectively, see Tables S2 and S3). In the study by Almeida et al., local reactions after RSVpreF doses 1 and 2 (administered 1 month apart) were more common among the younger (18 to 59 years of age; 56.3%) versus older (≥60 years of age; 43.0%) age groups and were more common after Dose 2 than after Dose 1 in both the younger (46.8% after Dose 2 vs. 26.0% after Dose 1) and older (34.3% after Dose 2 vs. 19.6% after Dose 1) age groups.[21]

IV.5.2 Serious adverse events following immunization

In the clinical trials, no safety signal was identified in adults at high risk aged 18 to 59 years following administration of each RSV vaccine. Reported serious adverse events (SAEs) (such as atrial fibrillation, transplant rejection) were deemed unrelated to the study intervention (REFs). Related SAEs occurred at similar rates (less than 1%) in both the vaccine and placebo groups, with no GBS, atrial fibrillation or death reported in this age group.

Post-market safety surveillance

For individuals aged 60 years and older, post-market safety surveillance data from the United Kingdom (UK) and multiple systems from the US show an increased risk of Guillain-Barré Syndrome (GBS) following the administration of protein subunit RSV vaccines (either RSVpreF or RSVPreF3).[12,52,58-60] Among individuals aged 65 years and older, US data estimate 9 and 7 excess GBS cases per million doses for RSVpreF and RSVPreF3 respectively.[12] UK data estimate 23 (95% CI: 17–26) excess GBS cases per million RSVpreF doses among individuals aged 75-79 years.[61] In the UK, as of May 26, 2025 no suspected case of GBS had been reported following RSVPreF3, however there has been very limited use of RSVPreF3 in the UK.[52] Preliminary results

from the US Vaccine Safety Datalink (VSD) suggested a possible increased risk of immune thrombocytopenic purpura (ITP) following RSVPreF3 administration, but re-analysis following medical record review did not confirm an association.[58,62]

For pregnant women and pregnant individuals, post-market safety surveillance from the UK and US has not shown an increased risk of GBS or preterm birth following administration of RSVpreF.[52,63-65] However, increased risks of hypertensive disorders of pregnancy (HDP)[64,65] and preterm premature rupture of the membranes (PROM) have been inconsistently observed in studies and these numerical imbalances are currently being investigated.[38,66] NACI will continue to monitor safety data as they emerge.

For additional information on the safety of RSV vaccines among individuals aged 50 years and older and among pregnant women and pregnant individuals, refer to NACI statements on the prevention of respiratory syncytial virus disease in infants and older adults: Updated guidance on respiratory syncytial virus (RSV) vaccines for older adults including the expanded use of RSVPreF3 for individuals 50-59 years of age and use of the new mRNA-1345 vaccine, Statement on the prevention of respiratory syncytial virus in older adults, Statement on the prevention of respiratory syncytial virus disease in infants, Updated guidance on the prevention of respiratory syncytial virus disease in infants.

IV.6 Contraindications and precautions

RSV vaccines are contraindicated in individuals with known hypersensitivities or history of a severe reaction (e.g., anaphylaxis) to any components of the products. RSVPreF3 and mRNA-1345 have not been tested in pregnant women and pregnant people, and RSVpreF has only been studied in pregnant women and pregnant people from 24 through 36 weeks of gestation.
There have been documented administration errors, where some new RSV vaccines have been administered to populations for which they are not authorized, including young children, pregnant women and pregnant people.[67,68] Given the increasingly complex product environment for RSV vaccines and immunizing agents in Canada, it will be important for programs to take steps to minimize potential administration errors. Please see Table 1 for details on the indications for each product. Full information on each vaccine can be found in their respective product monographs available through the Drug Product Database.

IV.7 Concurrent administration with other vaccines

Given the needs of older adults and adults at high risk to be protected from multiple vaccine preventable diseases, some of which are seasonal, concurrent administration is an important consideration. Concurrent administration of an RSV vaccine with other adult vaccines is acceptable and supported. RSVpreF, an unadjuvanted recombinant protein subunit vaccine, RSVPreF3, an adjuvanted recombinant protein subunit vaccine, and mRNA-1345, an mRNA vaccine, are not live. Concurrent administration of these RSV vaccines 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.

If possible, RSV vaccines should be given at least six weeks before or after non-seasonal vaccines such as shingles or diphtheria-tetanus vaccines, to avoid inadvertently attributing an adverse event from another vaccine to the RSV vaccine or vice versa. For more information regarding concurrent administration of vaccines, please refer to the chapter on Timing of vaccine administration in the Canadian Immunization Guide (CIG).
Additional research is ongoing to further inform guidance on same-day administration of the RSV vaccine and other adult vaccines, including COVID-19 vaccines, the co-administration of two mRNA vaccines targeting different pathogens and same-day administration of two adjuvanted vaccines targeting different pathogens. For detailed information on the evidence available on concurrent administration of RSV vaccines with other vaccines, refer to the corresponding section of previous NACI statements: Updated guidance on respiratory syncytial virus (RSV) vaccines for older adults including the expanded use of RSVPreF3 for individuals 50-59 years of age and useof the new mRNA-1345 vaccine, Statement on the prevention of respiratory syncytial virus in older adults.

IV.8 Vaccination of specific populations

IV.8.1 Immunization of people who are immunocompromised or have a chronic medical condition

Persons with immunocompromising conditions or chronic medical conditions such as cardiopulmonary disease, metabolic diseases, chronic renal and liver disease, neurologic or neurodevelopmental conditions and class 3 obesity are at higher risk of serious outcomes associated with RSV including hospitalization, ICU admission and death. Although evidence is limited, studies suggest that serious outcomes associated with RSV are also higher among younger adults (18 to 59 years) considered at high risk of complications and is somewhat similar to adults ≥65 years.[69] In a systematic review, among all RSV-positive immunodeficient patients (including community-based and medically attended), 38.30% (95% CI 29.26–48.23%) were hospitalized and 24.09% (95% CI 16.35–34.01%) were admitted to the ICU.[9] In another systematic review, immunocompromised status was significantly associated with a higher risk of mortality from RSV infection,[70] Some immunocompromised populations may be at higher risk than others. Data from substudy B of the ongoing pivotal Phase 3 clinical trial (NCT05842967) MONeT focused on those with non-small cell lung cancer, those on hemodialysis due to end-stage renal disease, those with autoimmune inflammatory disorder receiving active immunomodulator therapy, and SOT recipients. RSV infection may induce specific risks for lung transplant patients such as graft versus host disease, decline in lung function and bronchiolitis obliterans.[71] However, there is not a lot of literature or surveillance that, at present, compares risk of severe RSV outcomes with immunocompromise compared to other risk groups. Limitations to the available literature include which conditions are categorized within immunocompromise, heterogeneity of study populations and lack of information for some clinical outcomes of interest. Some immunocompromised populations may also have reduced benefit to vaccination as a result of diminished immunological capacity and to date there is limited data on RSV vaccine immunogenicity, safety or efficacy in this population. The efficacy and effectiveness of vaccines

for those with immunocompromise may vary by specific condition and/or use of medication, both of which influence degree of immunosuppression.

The increased risk of severe RSV disease is likely variable depending on the severity of the immunocompromise or chronic medical condition with individuals at more severe stages of the disease expected to be at highest risk. Each person who is immunocompromised or has chronic medical condition(s) is different and presents unique factors to consider regarding immunization such as age, presence of one or multiple risk factors, increased risk of exposure to RSV disease or structural and social determinants like limited access to care. For adults younger than 60 years of age, the currently recommended single dose should be administered at a time when maximal clinical benefit is anticipated as there is still uncertainty about whether RSV vaccines' efficacy/effectiveness can be boosted with additional vaccine doses.

V. Ethics, equity, feasibility and acceptability

V.1 Ethics, equity and acceptability considerations

The ethics, equity and acceptability considerations for these populations and products are similar to those articulated in the previous NACI Statement on the prevention of RSV in older adults.[20] 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, or Métis communities. Jurisdictions should continue to prioritize equity in program implementation.

V.2 Feasibility considerations

Given that mRNA-1345 shelf life at 2°C to 8°C was extended from 30 days to 90 days, consultation was sought with the Canadian Immunization Committee (CIC) on May 8, 2025. It was noted that the lower temperature storage conditions required for mRNA-1345 remains a feasibility concern. Vaccine wastage may occur as thawed vaccine may not be used in time. In addition, there may be feasibility challenges transporting vaccines at frozen temperature.

VI. Economics

An environmental scan and an economic evaluation using a previously described Canadian cost-utility model were used to generate economic evidence related to RSV vaccination for adults at increased risk of severe RSV disease aged less than 75 years. This evidence supplemented the one previously used to assess the cost-effectiveness of RSV vaccination programs for older adults.[19,20] All costs are presented in 2024 Canadian dollars.

VI.1 Environmental scan

An environmental scan was conducted to identify recently published economic evaluations of RSV vaccination in adult populations at increased risk of RSV, building on a previous environmental scan.[19] The search included publications up to May 15, 2025 and sought to identify any new economic evaluations conducted by other national immunization technical advisory groups (NITAGs), as well as any published studies and preprints specific to the Canadian population.

Four relevant economic evaluations were identified, all of which were presented to the US Advisory Committee on Immunization Practices (ACIP). For clarity, the economic evaluations summarized to ACIP are referred to by the names of the investigators who conducted them. All costs were converted from 2024 US to Canadian dollars (exchange rate of 1.3698). Three of the evaluations were industry funded and all estimated incremental cost-effectiveness ratios (ICERs) from the societal perspective, with a 3% discount rate. Vaccine prices per dose were $384 for RSVPreF3, $397 for mRNA-1345, and $404 for RSVpreF. Although some evaluations considered multiple time horizons, for comparability, results are summarized for a 3-year time horizon, except for Sato,[72] which is presented for a 3.5-year time horizon.

All studies evaluated the cost-effectiveness of RSV vaccination in adults at high risk aged 50 to 59 years with specific medical conditions, and three also assessed broader population groups with one or more chronic medical conditions). Across evaluations, vaccination for adults aged 50 to 59 with one or more chronic medical conditions was generally not cost-effective using a $50,000 per QALY threshold, with the exception of one industry-funded analysis. However, when focusing on select high-risk conditions, vaccination was frequently cost-effective, and in some cases, cost-saving, compared to no vaccination. Conditions evaluated in two or more models and consistently identified as cost-saving or cost-effective included chronic obstructive pulmonary disease, chronic kidney disease, and cardiovascular disease (including coronary artery disease and heart failure). Findings for people with asthma or diabetes mellitus varied across evaluations. For asthma, two studies identified vaccination as cost-saving[73] or cost-effective[74], while a third estimated an ICER above $130,000 per QALY.[75] For diabetes mellitus, results ranged from cost-saving[72,73] to above $78,000 per QALY. Overall, industry-funded models tended to report more favourable cost-effectiveness results than the non-industry funded model. Differences in model assumptions about incidence of medically attended RSV, vaccine effectiveness and waning, and hospitalization costs may have contributed to variability across evaluations.

Hutton et al. also evaluated cost-effectiveness of RSV vaccination in adults at high risk aged 60 to 74 years, reporting more favourable results than for the 50 to 59 age group. ICERs for adults aged 60 to 74 years with one or more chronic medical conditions were $29,750 per QALY for the protein subunit vaccines and $69,670 for the mRNA vaccine, compared to $59,000 and $130,380 respectively, for the younger group. For adults aged 60 to 74 with specific high-risk conditions, RSV vaccination was generally cost-effective using a $50,000 per QALY threshold. Both the protein subunit and mRNA vaccines were cost-effective for individuals with chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), obesity, heart failure, asthma, and coronary artery disease (CAD). Diabetes was the only condition to exceed a $50,000 per QALY threshold, and only for the mRNA vaccine ($71,085 per QALY); for the subunit vaccines, the ICER remained below the threshold at $30,971 per QALY. This contrasts with findings for adults aged 50 to 59 with diabetes, where ICERs for both vaccine types exceeded $50,000 per QALY.

VI.2 Cost-utility analysis

A Canadian cost-utility model previously used to estimate the cost-effectiveness of RSV vaccination in older adults[76] was updated to assume three seasons of protection following vaccination, with waning occurring between seasons. Estimates of waning of vaccine protection between the second and third RSV season were based on data for RSVPreF3.[77] In the absence of similar data for RSVpreF and mRNA-1345 at the time of the analysis, similar waning rates were assumed for these two vaccines. Vaccine effectiveness (VE) was assumed to decline further to two-thirds of the average third season value by the end of that season. For RSVPreF3, VE against medically-attended RSV was 83% in season 1 (7-month follow-up), 56% in season 2 (6-month follow-up), and 48% in season 3 (7-month follow-up), while VE against hospitalized RSV was 94%, 64%, and 43% over the same follow-up periods. For RSVPreF, VE against outpatient RSV was 65% in season 1 (7-month follow-up), 49% in season 2 (4-month follow-up), and 16% in season 3 (7-month follow-up assumed), while VE against hospitalized RSV was 89%, 79%, and 26% over the same periods. For mRNA-1345, VE against outpatient RSV was 56% in season 1 (11-month follow-up), 30% in season 2 (7-month follow-up), and 26% in season 3 (7-month follow-up assumed), while VE against hospitalized RSV was 75% in season 1 (9-month follow-up), 41% in season 2 (7-month follow-up), and 28% in season 3 (7-month follow-up assumed). Costs were updated to 2024 Canadian dollars and demographic estimates were updated to the most recently available data. All other parameters were unchanged from the previous analyses and all vaccines were assumed to cost $230 per dose in the primary analysis. Results are presented for the health system perspective and a 1.5% discount rate was applied. Vaccination strategies were evaluated for population subgroups aged 50 to 59, 60 to 69, and 70 to 74 years with one or more chronic medical conditions, defined in this analysis as adults at increased risk of RSV, incrementally added to a strategy of vaccination for all adults aged 75 years and older.

Compared to NACI recommendation at the time of the analysis of vaccination for all adults aged 75 years and older, vaccination of adults at increased risk aged 70 to 74 years resulted in ICERs of $23,900, $30,630, and $59,270 per QALY gained for vaccines with characteristics based on RSVpreF, RSVPreF3, and mRNA-1345, respectively. Program expansion to include vaccination for adults at increased risk aged 60 to 69 years resulted in ICERs ranging from $66,940 to

$117,560 per QALY gained. Adding adults at increased risk aged 50 to 59 years resulted in ICERs ranging from $128,470 to $205,930 per QALY gained. For all population groups, ICERs were lower for vaccines with characteristics based on the protein subunit vaccines (RSVpreF and RSVPreF3) than for mRNA-1345, reflecting higher assumed VE for the protein subunit vaccines. For a program that includes vaccination of adults at increased risk aged 60 to 74 years to be cost-effective at a $50,000 per QALY threshold, the vaccine price would need to be reduced to less than $190 per dose, representing a 17% reduction from the base case price $230 per dose, with a larger price reduction (48%) required for a vaccine with characteristics based on mRNA-1345.

Scenario analyses showed that results were sensitive to assumptions about RSV burden. The primary analysis assumed a 1.5-fold under-detection of medically attended RSV cases. If there is no under-detection, ICERs for expanding the current program to include adults at increased risk aged 70 to 74 years were $56,600 to $109,140 per QALY gained, and ICERs for including younger age groups exceeded $115,000 per QALY gained. For a setting with higher RSV incidence and higher medical costs, as may been seen in some remote and isolated communities, a program for adults at increased risk aged 50-74 years and all adults aged 75 years and older was the optimal strategy for a cost-effectiveness threshold of $50,000 per QALY. Overall conclusions did not change when assumptions about prevalence of chronic medical conditions in the population or among people hospitalized with RSV were varied.

VI.3 Summary

Previous economic analyses have demonstrated the cost-effectiveness of RSV vaccination for all adults aged 75 years and older].[19,51] Building on this evidence, an updated economic evaluation using Canadian data suggests that RSV vaccination for adults at increased risk aged 70 to 74 years is likely to be cost-effective. Together, these findings indicate that extending immunization programs to include younger adults at increased risk of severe RSV disease may provide good value for money. Vaccination of adults at increased risk aged 60-69 years may be cost-effective at lower vaccine prices. Vaccination of adults at increased risk aged 50-59 years is unlikely to be cost-effective, even with a substantial reduction in price, but may be cost-effective in settings with elevated RSV disease burden and medical costs, such as some remote and isolated communities. Four US studies reinforced the finding of improved cost-effectiveness for older age groups and identified specific medical conditions for which RSV vaccination may be cost-effective in adults aged 50 to 59. None of the economic evaluations assessed cost-effectiveness of RSV vaccines in adults at increased risk aged less than 50 years. Differences in cost-effectiveness across vaccine products reflect variations in assumed vaccine effectiveness and comparisons should be interpreted with caution pending further data.

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 2 for a more detailed explanation of strength of NACI recommendations.

Recommendations for public health program decision-making

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

1. NACI continues to recommend that RSV immunization programs should include all adults 75 years of age and older.

(Strong NACI recommendation)

2. NACI recommends that RSV immunization programs should include adults 65 to 74 years of age who are at increased risk of severe RSV disease (List 1).

(Strong NACI recommendation)

List 1. Clinically significant chronic health conditions for which RSV vaccination is particularly important

- Cardiac or pulmonary disorders (includes chronic obstructive pulmonary disease, asthma, cystic fibrosis, and conditions affecting ability to clear airway secretions)
- Diabetes mellitus and other metabolic diseases
- Moderate and severe immunodeficiency (refer to the list of immunocompromising conditions developed for COVID-19)
- Chronic renal disease
- Chronic liver disease
- Neurologic or neurodevelopmental conditions (includes neuromuscular, neurovascular, neurodegenerative [e.g., dementia], neurodevelopmental conditions, and seizure disorders, but excludes migraines and psychiatric conditions without neurological conditions)
- Class 3 obesity (defined as BMI of 40 kg/m^2 and over)

3. NACI recommends that RSV immunization programs should include adults 18 years of age and older, who:

- **are residents of nursing homes and other chronic care facilities**
- **have had a lung transplant**
- **have had a hematopoietic stem cell transplant (in the previous two years or who remain on immunosuppression)**
- **are on home oxygen or require chronic oxygen therapy regardless of living at home or elsewhere**
- **are receiving dialysis**

(Strong NACI recommendation)

Additional considerations:

- Jurisdictions and communities may consider vaccinating individuals in or from First Nations, Inuit and Métis communities at a younger age given the available evidence on the increased burden of illness due to intersecting structural and social determinants of health. Autonomous decisions should be made by Indigenous Peoples with the support of culturally safe public health and healthcare partners in accordance with the United Nations Declaration on the Rights of Indigenous Peoples Act (UNDRIP).
- A single dose of RSVPreF3, RSVpreF or mRNA-1345 can be used within the authorized age groups. Although NACI judged that all three vaccines work well from a clinical perspective, there are less available data for the safety and efficacy/effectiveness of mRNA-1345 compared to the protein subunit vaccines.
- An increased risk of Guillain-Barré Syndrome (GBS) has been identified in individuals aged 65 years and older following receipt of the RSVpreF and RSVPreF3 vaccines. However, it should be noted that RSV infection may also increase the risk of Guillain-Barré Syndrome (GBS) in adults aged 65 years and older. At this time, it is unclear whether an increased risk of GBS will also be seen among adults aged less than 65 years, given that no increased risk of GBS has been identified in pregnant women and pregnant individuals following receipt of the RSVpreF vaccine. NACI will continue to monitor safety data on all RSV vaccines (RSVpreF, RSVPreF3 mRNA-1345) as they become available.
- Economic evidence supports that RSV immunization programs are cost-effective for all adults aged 75 years and older and those aged 70-74 years at increased risk of severe RSV disease. Immunization programs may also be cost effective for adults aged 60-69 years at increased risk of severe RSV disease. Using currently available vaccine efficacy data, mRNA-1345 may be less cost-effective than other authorized RSV vaccines. If the assumption of lower vaccine efficacy for mRNA-1345 compared to protein subunit vaccines is accurate, a lower vaccine price for mRNA-1345 would reduce the difference in cost-effectiveness. However, true differences in efficacy remain uncertain.
- There is still uncertainty about the total duration of protection and the need for and timing of any potential booster doses with any of the authorized adult RSV vaccine products. Therefore, a single dose is currently recommended.
- NACI acknowledges the feasibility concerns of the different storage temperature for mRNA-1345 and supports jurisdictions to weigh this alongside other vaccine characteristics when considering product selection and program design.

Summary of evidence and rationale:

- Recent evidence from Canada and other countries identifies individuals with certain medical conditions as being at higher risk of severe RSV disease. While NACI continues to recommend an RSV program for all individuals aged 75 years and older, the vaccine should also be offered to some adults under 75 years of age at high risk who have a good balance of clinical benefits, safety and feasibility.
- Indigenous Peoples may experience a disproportionate burden of illness due to social, environmental, and economic factors, rooted in the history of colonization and systemic racism (i.e., structural inequity).
- Residents of nursing homes and other chronic care facilities have a higher likelihood of severe clinical outcomes of RSV disease compared to those with other living situations.
- Home oxygen requirement or chronic oxygen therapy is an indication of respiratory disease severity.
- RSVPreF3, RSVpreF or mRNA-1345 have demonstrated protection against hospitalization and medically attended RSV in clinical trials among individuals aged 60 years and older. Post-market studies have also shown effectiveness of RSVPreF3 and RSVpreF in this age group.
- Data from clinical trials indicate that RSV vaccines have a favourable safety profile among individuals aged 18-59 years. NACI will monitor post-market safety data among individuals aged 18-59 years as they become available.

Recommendations for individual decision-making

(i.e. clinicians wishing to advise individual patients about preventing a vaccine preventable disease.)

4 . NACI recommends that RSV vaccines may be considered by adults 18-64 years of age at increased risk of severe RSV disease as an individual decision informed by discussion with their health care provider.

(Discretionary NACI recommendation)

Additional considerations:

- A single dose of RSVPreF3, RSVpreF or mRNA-1345 can be used within the authorized age groups. Consult the product leaflet or information contained within Health Canada's authorized product monographs available through the Drug Product Database for the latest information on the age indication of each vaccine product.
- A careful assessment of benefits versus potential harms is warranted, as most younger adults may benefit more from vaccination at an older age or if their risk of severe RSV disease increases (e.g. worsening of an existing condition, addition of new risk factors). Each person is different and will present unique factors to consider such as age, type, severity and number of underlying medical conditions or risk factors, increased risk of

exposure to RSV disease or structural and social determinants like limited access to care. See below for more information on factors to consider including vaccine benefits and risks.

- NACI has identified clinically significant chronic health conditions that place individuals at increased risk of severe RSV disease (List 1). The conditions on List 1 should be considered along with other factors as mentioned above.
- A single dose of vaccine is recommended at this time and is expected to provide protection from RSV disease for at least three years. For adults under 60 years of age at increased risk, the currently recommended single dose should be administered at a time when maximal clinical benefit is expected as there is still uncertainty about whether RSV vaccines' efficacy/effectiveness can be boosted with additional vaccine doses.
- An increased risk of GBS has been identified in individuals aged 65 years and older following receipt of the RSVPreF and RSVPreF3 vaccines. However, it is unclear whether an increased risk will be noted among adults aged less than 65 years given that the increased risk of GBS has not been identified in pregnant women and pregnant individuals following receipt of the RSVPreF vaccine. Safety monitoring of all RSV vaccines (mRNA-1345, RSVpreF, RSVPreF3) is ongoing.
- For pregnant women or pregnant persons considering RSV immunization to protect their infant, please consult NACI's updated guidance to protect infants and children from RSV disease.

VIII. Research needs and gaps

Research to address the following outstanding questions is encouraged:

- Any similarities and differences between RSV vaccines using different vaccine platforms (i.e. protein subunit vs mRNA)
- Burden of RSV disease, vaccine efficacy, effectiveness and safety in adults 18 years of age and older with medical conditions
    - Further exploration of vaccine effectiveness and safety in people who are immunocompromised, or previously underrepresented populations
- Impact of RSV infection and disease on cardiovascular events, including myocardial infarction, heart failure, and stroke, especially among individuals with pre-existing cardiac disorders, and the implications of prevention of cardiovascular events offered by RSV vaccination
- Effectiveness of RSV vaccines for older adults outside of the RCT setting, particularly in the oldest and highest-risk adults, such as those with more numerous and less stable chronic conditions (including lung transplant and hematopoietic stem cell transplant patients), those who are more frail, and highest risk patients under 60 years of age
- Vaccine efficacy/effectiveness overtime and following revaccination
- Safety of RSV vaccines outside of the RCT setting
- Whether or not there is an association between GBS and RSV vaccination, or conversely between GBS and RSV infection, and safety of RSV vaccination for patients with a history of GBS
- Safety, efficacy and effectiveness of concurrent administration of RSV vaccines with other vaccines for adults
- Impacts on equity due to programs for RSV vaccines for adults or lack thereof
- Acceptability and uptake of RSV vaccines for adults

Tables

Table 2. Strength of NACI recommendations

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 3. GRADE Certainty of evidence 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
AESI	Adverse events of special interest
AReSVi-006	Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults Study
CAD	Coronary artery disease
CFR	Case fatality ratio
CI	Confidence interval
CIC	Canadian Immunization Committee
CIG	Canadian Immunization Guide
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
ED	Emergency department
EEFA	Ethics, equity, feasibility, and acceptability
GBS	Guillain-Barré syndrome
GMR	Geometric mean titer ratio
GMT	Geometric mean titer
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HARISS	Hospital-based Acute Respiratory Infection Sentinel Surveillance
HDP	Hypertensive disorders of pregnancy
HSCT	Hematopoietic stem cell transplantation
ICD-10	International Classification of Diseases, 10th Revision
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IRR	Incidence rate ratio
ITP	Immune thrombocytopenic purpura
IVY network	Influenza and other Viruses in the AcutelY ill network
LRTD	Lower respiratory tract disease
MONET	Study to Assess the Safety, Tolerability, and Immunogenicity of RSVpreF in Adults at High Risk of Severe RSV Disease
mRNA	messenger Ribonucleic Acid
mRNA-1345	Respiratory Syncytial Virus mRNA Vaccine
N	Number of Participants
NACI	National Advisory Committee on Immunization
NITAGs	National immunization technical advisory groups
NOC	Notice of Compliance
PHAC	Public Health Agency of Canada
PPROM	Preterm premature rupture of the membranes
QALY	Quality-adjusted life year
RCT	Randomized controlled trial

RENOIR	RSV Vaccine Efficacy Study in Older Adults Immunized against RSV Disease
RR	Rate ratio
RSV	Respiratory syncytial virus
RSVpreF	Respiratory syncytial virus prefusion F subunit vaccine
RSVPreF3	Respiratory syncytial virus prefusion F3 subunit vaccine
RTI	Respiratory tract infection
SAE	Serious adverse event
SRR	Seroresponse rate
SOT	Solid Organ Transplant
UC	Urgent care
UK	United Kingdom
UNDRIP	United Nations Declaration on the Rights of Indigenous Peoples
US	United States (of America)
VE	Vaccine efficacy
VHA	Veterans Health Association
VISION	Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network
VSD	Vaccine Safety Datalink

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Appendix

Table S1. Summary of findings comparing RSVpreF for adults 18 to 59 years of age with high-risk conditions to adults 60 years of age and older

Outcome	No. of studies (study design)	No. of events/ No. of participants		Effect		Certainty	Comments
		18 – 59 years of age	≥60 years of age	Relative effect (95% CI)	Absolute effect (95% CI)		
Critical outcomes							
Death due to RSV (follow-up: 1 month)	2 (non-RCT)	527	508[a]	- In adults 18 – 59 with *chronic medical conditions*, non-inferiority criteria were met when comparing to adults ≥60 years of age for RSV-A and RSV-B neutralizing titers and seroresponse rates - In adults 18 – 59 with *immunocompromising conditions*, a robust immune response was observed, similar to adults ≥60 years of age in the pivotal phase III efficacy trial		Very low[b]	RSVpreF administration may have a similar effect on death due to RSV in adults 18 to 59 years of age with high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.
RSV RTI with ICU admission (follow-up: 1 month)	2 (non-RCT)[21,22]	527	508[a]			Very low[b]	RSVpreF administration may have a similar effect on RSV RTI with ICU admission in adults 18 to 59 years of age with high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.
RSV RTI with hospitalization	2 (non-RCT)	527	508[a]			Very low[b]	RSVpreF administration may have a similar effect on RSV RTI with hospitalization due to RSV in adults 18 to 59 years of age with

(follow-up: 1 month)							high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.
Severe systemic adverse events (follow-up: 7 days)	1 (non-RCT)[21]	2/96 (2.1%)	6/107 (5.6%)	RR 0.37 (0.08 to 1.80)	35 fewer per 1,000 (52 fewer to 45 more)	Very low[c]	RSVpreF administration may result in little to no difference in severe systemic adverse events in adults 18 to 59 years of age with high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.
Important outcomes							
Medically-attended RSV RTI (follow-up: 1 month)	2 (non-RCT)	527	508[a]	- In adults 18 – 59 with chronic medical conditions, *non-inferiority criteria were met* when comparing to adults ≥60 years of age for RSV-A and RSV-B neutralizing titers and seroresponse rates - In adults 18 – 59 with immunocompromising conditions, a robust immune response was observed, similar to adults ≥60 years of age in the pivotal phase III efficacy trial		Very low[b]	RSVpreF administration may have a similar effect on medically-attended RSV RTI in adults 18 to 59 years of age with high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.
Severe local adverse	1 (non-RCT)	0/96 (0%)	0/107 (0%)	1.11 (0.02 to 55.58)	0 fewer per 1,000 (0 fewer to 0 more)	Very low[c]	RSVpreF administration may result in little to no difference in severe local adverse events in adults 18 to 59 years of age with

events (follow-up: 7 days)							high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.

[a] The control group used for one of the included studies (accounting for approximately 80%) of the total sample size, is a historical control group from the pivotal efficacy trial of RSVpreF[23]

[b] Downgraded by one level due to indirectness. Immunogenicity studies were used as surrogate markers of efficacy, as no efficacy data is available. In addition, there is no established correlate of protection.

[c] Downgraded by one level due to imprecision of the effect estimate. Optimal information size not met.

Table S2. Summary of findings comparing RSVPreF3 for adults 18 to 59 years of age with high-risk conditions to adults 60 years of age and older

Outcome	No. of studies (study design)	No. of events/ No. of participants		Effect		Certainty	Comments
		18 – 59 years of age	≥60 years of age	Relative effect (95% CI)	Absolute effect (95% CI)		
Critical outcomes							
Death due to RSV (follow-up: 1 month)	2 (non-RCT)	737	759	- In non-immunocompromised adults 18 to 49 years of age at increased risk for RSV disease *non-inferiority criteria were met* when comparing to adults ≥60 years of age for RSV-A and RSV-B neutralizing titers and seroresponse rates - The humoral immune response elicited by RSVPreF3 in adults 50-59 years of age at increased risk was non-inferior compared to adults ≥ 60 years of age for RSV-A and RSV-B neutralizing titers and seroresponse rates		Very low[a]	RSVPreF3 administration may have a similar effect on death due to RSV in adults 18 to 59 years of age with high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.
RSV RTI with ICU admission (follow-up: 1 month)	2 (non-RCT)[27]	737	759			Very low[a]	RSVPreF3 administration may have a similar effect on RSV RTI with ICU admission in adults 18 to 59 years of age with high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.
RSV RTI with hospitalization (follow-up: 1 month)	2 (non-RCT)	737	759			Very low[a]	RSVPreF3 administration may have a similar effect on RSV RTI with hospitalization due to RSV in adults 18 to

							59 years of age with high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.
Severe systemic adverse events (follow-up: range 4 days to 7 days)	2 (non-RCT)[25,26]	61/1122 (5.5%)	14/674 (2.1%)[25]	RR 2.39 (1.26 to 4.51)	29 more per 1,000 (5 more to 73 more)	Very low[b]	RSVPreF3 administration in adults 18 to 59 years of age with high-risk conditions may lead to a small increase in severe systemic adverse events compared to adults 60 years of age and older; however the evidence is very uncertain.
Important outcomes							
Medically-attended RSV RTI (follow-up: 1 month)	2 (non-RCT)	737	759	- In non-immunocompromised adults 18 to 49 years of age at increased risk for RSV disease *non-inferiority criteria were met* when comparing to adults ≥60 years of age for RSV-A and RSV-B neutralizing titers and seroresponse rates - The humoral immune response elicited by RSVPreF3 in adults 50-59 years of age at increased risk was non-inferior compared to adults ≥ 60 years of age for RSV-A and RSV-B		Very low[a]	RSVPreF3 administration may have a similar effect on medically-attended RSV RTI in adults 18 to 59 years of age with high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.

				neutralizing titers and seroresponse rates			
Severe local adverse events (follow-up: range 4 days to 7 days)	2 (non-RCT)	16/1120 (1.4%)	3/674 (0.4%)	RR 2.40 (0.20 to 28.84)	6 more per 1,000 (4 fewer to 124 more)	Very low[b]	RSVPreF3 administration may result in little to no difference in severe local adverse events in adults 18 to 59 years of age with high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.

[a] Downgraded by one level due to indirectness. Immunogenicity studies were used as surrogate markers of efficacy, as no efficacy data is available. In addition, there is no established correlate of protection.

[b] Downgraded by one level due to imprecision. Optimal information size not met.

Table S3. Summary of findings comparing mRNA-1345 for adults 18 to 59 years of age with high-risk conditions to adults 60 years of age and older

Outcome	No. of studies (study design)	No. of events/ No. of participants		Effect		Certainty	Comments
		18 – 59 years of age	≥60 years of age	Relative effect (95% CI)	Absolute effect (95% CI)		
Critical outcomes							
Death due to RSV (follow-up: 1 month)	1 (non-RCT)	494	1515[a]	Non-inferiority criteria were met in adults 18 to 59 years of age at high risk compared to adults ≥60 years of age for RSV-A and RSV-B neutralizing antibody titers and seroresponse rates.		Very low[b]	mRNA-1345 administration may have a similar effect on death due to RSV in adults 18 to 59 years of age with high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.
RSV RTI with ICU admission (follow-up: 1 month)	1 (non-RCT)	494	1515[a]			Very low[b]	mRNA-1345 administration may have a similar effect on RSV RTI with ICU admission in adults 18 to 59 years of age with high-risk conditions compared to adults 60 years of age and older; however the

							evidence is very uncertain.
RSV RTI with hospitalization (follow-up: 1 month)	1 (non-RCT)	494	1515[a]			Very low[b]	mRNA-1345 administration may have a similar effect on RSV RTI with hospitalization due to RSV in adults 18 to 59 years of age with high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.
Severe systemic adverse events (follow-up: 7 days)	1 (non-RCT)	29/502 (5.8%)	718/18160 (4.0%)	1.46 (1.02 to 2.10)	18 more per 1,000 (1 more to 43 more)	Very low	mRNA-1345 administration in adults 18 to 59 years of age with high-risk conditions may lead to a small increase in severe systemic adverse events compared to adults 60 years of age and older; however the evidence is very uncertain.
Important outcomes							

Medically-attended RSV RTI (follow-up: 1 month)	1 (non-RCT)	494	1515[a]	- Non-inferiority criteria were met in adults 18 to 59 years of age at high risk compared to adults ≥60 years of age for RSV-A and RSV-B neutralizing antibody titers and seroresponse rates.		Very low[b]	mRNA-1345 administration may have a similar effect on medically-attended RSV RTI in adults 18 to 59 years of age with high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.
Severe local adverse events (follow-up: 7 days)	1 (non-RCT)	10/502 (2.0%)	560/18160 (3.1%)	RR 0.65 (0.35 to 1.20)	11 fewer per 1,000 (20 fewer to 6 more)		mRNA-1345 administration may result in little to no difference in severe local adverse events in adults 18 to 59 years of age with high-risk conditions compared to adults 60 years of age and older; however the evidence is very uncertain.

[a] The control group is a historical control group based on the pivotal efficacy trial of mRNA-1345.[30]

[b] Downgraded by one level due to indirectness. Immunogenicity studies were used as surrogate markers of efficacy, as no efficacy data is available. In addition, there is no established correlate of protection.