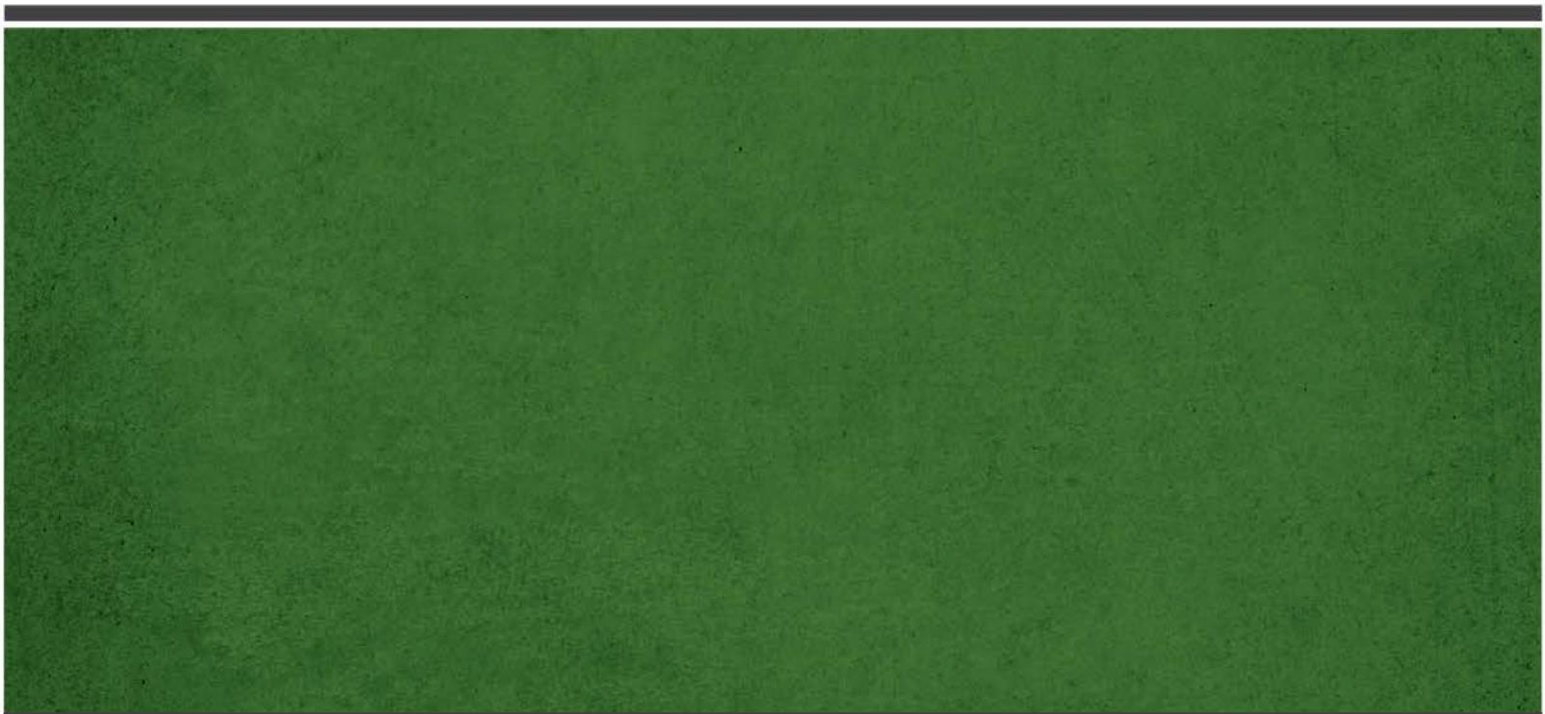
An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Updated guidance on respiratory syncytial virus (RSV) vaccines for older adults including the expanded use of RSVPreF3 for individuals 50 to 59 years of age and the use of the new mRNA-1345 vaccine



PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

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— Public Health Agency of Canada

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Déclaration du Comité consultatif (DCC) Déclaration du Comité consultatif national de l'immunisation (CCNI) : Directives mises à jour sur les vaccins contre le virus syncytial respiratoire (VSR) chez les personnes âgées, y compris l'utilisation élargie du RSVPreF3 chez les individus de 50 à 59 ans et l'utilisation du nouveau vaccin mRNA-1345

To obtain additional information, please contact:
Public Health Agency of Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
E-mail: publications-publications@hc-sc.gc.ca

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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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Summary of information contained in this NACI Statement

The following highlights key information for immunization providers. Please refer to the remainder of the Statement for details.

What

Respiratory syncytial virus (RSV) is a common respiratory virus, and infants and older adults are at higher risk of severe outcomes due to RSV. RSV can cause serious respiratory disease in older adults, particularly those at increased risk due to chronic medical conditions. RSV has a seasonal pattern of activity where infections are usually more common in the winter with variation in the timing and magnitude of the peak.

This statement focuses on the protection of adults at risk for severe RSV disease due to age, medical conditions, setting and other potential factors. In 2023 Health Canada approved two products to prevent RSV in older adults 60 years of age and older, RSVpreF (Abrysvo™, Pfizer) and RSVPreF3 (Arexvy, GSK). Health Canada has recently made two regulatory decisions for products that protect adults from RSV:

- mRNA-1345 (mResvia, Moderna) is an mRNA vaccine authorized on November 6, 2024, with an indication for all adults 60 years of age and over.
- RSVPreF3 (Arexvy, GSK) is an $AS01_E$ adjuvanted vaccine with a recently expanded age indication for adults 50 to 59 years of age at increased risk for RSV disease. RSVPreF3 was previously approved for use in adults aged 60 and older.

Who

NACI continues to recommend RSV 1-dose immunization programs for adults 75 years of age and older, particularly for older adults with chronic health conditions who are at increased risk of severe RSV disease. NACI also recommends RSV immunization programs for adults 60 years of age and older who are residents of nursing homes and other chronic care facilities. Severe RSV disease in adults is most common in advanced age and in those with certain chronic health conditions or other risk factors. Adults with chronic health conditions who are at increased medical risk for severe RSV disease are highlighted in List 1. In addition, adults may be at increased risk of severe RSV disease due to factors that intersect with social determinants of health.

For individuals who may seek vaccination outside of a public health program, NACI now recommends that some RSV vaccines may be considered as an individual decision by adults 50 to 74 years of age in consultation with their health care provider. This is a change from the previous recommendation of 60 to 74 years of age, as RSVPreF3 has been newly authorized for the 50 to 59 year old age group for individuals at increased risk of RSV disease. It is unknown at this time if these vaccines can be boosted by subsequent doses, and therefore healthy individuals who are less than 75 years of age may want to discuss with their health care providers deferring vaccination to a future time when they may be at greater risk. If an individual over the age of 75 is not included in a publicly funded program, NACI recommends vaccination for these individuals, particularly for those adults at increased risk of severe RSV disease.

How

The RSV vaccine (RSVpreF3, RSVpreF or mRNA-1345) is optimally administered just before the start of the RSV season. Jurisdictions are encouraged to define the RSV season and administer RSV vaccines based on local epidemiology (the RSV season is typically November to April in Canada).

mRNA-1345 is administered intramuscularly using prefilled syringes of 50 mcg of mRNA encoding RSV F glycoprotein stabilized in the prefusion conformation. A single 0.5 mL dose of mRNA-1345 is authorized for administration in adults 60 years of age and older.

RSVPreF3 is administered intramuscularly using single dose vials of lyophilized powder which is reconstituted at the time of use with the accompanying vial of $AS01_E$ adjuvant suspension. A single 0.5 mL dose of RSVPreF3 is authorized for administration in adults 60 years of age and older and adults at increased risk 50 to 59 years of age.

RSVpreF is administered intramuscularly using single dose vials of lyophilized powder which is reconstituted with sterile water (diluent) in a prefilled syringe at the time of use. A single 0.5 mL dose is authorized for administration in adults 60 years of age and older and pregnant individuals in the third trimester of pregnancy (from 32 through 36 weeks gestation).

Given the needs of older adults to be protected from multiple vaccine preventable diseases, some of which are seasonal, concurrent administration of an RSV vaccine with other adult vaccines is acceptable and supported.

For additional information, including supporting evidence and rationale for these recommendations, please see Recommendations.

Why

RSV accounts for a significant burden of disease in older adults leading to serious complications including hospitalization, ICU admission and death. Furthermore, reducing severe outcomes from RSV in older adults at the population level may help to protect health system capacity. All RSV vaccines are expected to result in similar reductions in hospitalizations due to RSV and medically attended RSV respiratory tract infections (RTIs). The prioritization of certain populations, such as older adults with chronic health conditions, is cost-effective and anticipated to promote health equity.

I. Introduction

Guidance Objective

In 2023 Health Canada approved two products to prevent RSV in older adults 60 years of age and older, RSVpreF (Abrysvo, Pfizer) and RSVPreF3 (Arexvy, GSK). The need for updated NACI guidance for RSV older adult vaccines arose from two additional regulatory decisions for products that protect adults from RSV. On November 1, 2024, Health Canada approved an expanded age indication for the use of GSK's RSVPreF3 in adults aged 50 to 59 years at increased risk for RSV disease. This product was previously authorized in August 2023 for all adults 60 years of age and older. On November 6, 2024, Health Canada authorized the use of mRNA-1345 (mRESVIA®, Moderna), an mRNA vaccine for the protection of adults 60 years of age and older.

This is the second NACI statement to provide recommendations for the prevention of RSV in older adults, further to initial guidance released on July 12, 2024. NACI has also made recommendations for the prevention of RSV disease in infants in 2024.

The primary objectives of this statement are to:

- review the evidence on the potential benefits (efficacy), potential harms (safety) and cost-effectiveness of mRNA-1345 for programs in Canada and for RSVPreF3 for adults 50 to 59 years of age at increased risk of RSV disease.
- describe the feasibility considerations for mRNA-1345 for programs in Canada and for RSVPreF3 for adults 50 to 59 years of age at increased risk of RSV disease. Acceptability, equity and ethics considerations are anticipated to be similar to those discussed in previous NACI guidance.
- provide recommendations for the use of mRNA-1345 for programs in Canada and for RSVPreF3 for adults 50 to 59 years of age at increased risk of RSV disease vaccines in Canada, including identifying groups that may be at increased risk of severe RSV disease and therefore would benefit the most from these products.

II. Methods

In brief, the broad stages in the preparation of this NACI advisory committee statement are:

1. Analysis of burden of disease of RSV in older adults and adults considered at high risk of severe infection
2. Retrieval and summary of individual studies of RSV vaccines, evidence synthesis, including meta-analysis when appropriate and assessment of the quality of the evidence by the NACI Secretariat – summarized in Tables 3 to 8
3. Synthesis of the body of evidence of benefits and harms of RSV vaccines, considering the quality of the synthesized evidence and magnitude of effects observed across the studies
4. Use 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
5. 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
6. Translation of evidence into a recommendation.

Further information on NACI's evidence-based methods is available elsewhere.

A framework has been developed to facilitate systematic consideration of programmatic factors (now included in NACI's mandate, including: ethics, equity, feasibility, acceptability) in developing clear, evidence-based recommendations for timely, transparent decision-making[1]. This framework provides a clear outline with accompanying evidence informed tools to consider relevant aspects of each programmatic factor that may have an impact on the implementation of NACI recommendations. These tools have been completed by the NACI Secretariat and presented to the RSV Working Group and NACI and integrated into the statement. For details on the development and application of NACI's EEFA Framework and evidence-informed tools, please see A framework for the systematic consideration of ethics, equity, feasibility, and acceptability in vaccine program 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.

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 illness of the disease to be prevented and the priority populations, safety, immunogenicity, efficacy, effectiveness, economic evaluation of the RSV vaccines, vaccine schedules, and other aspects of the overall immunization strategy. The knowledge synthesis was performed by the NACI Secretariat and supervised by the RSV Working Group. When at least two trials reported data for a specific outcome, results of individual trials were pooled in a meta-analysis, where appropriate, using random effects model in RevMan by the NACI Secretariat (e.g., safety analyses for older adults 60 years and older)[2].

An assessment using the Evidence to Decision (EtD) framework was prepared for the main program decision on age and risk were developed[3]. To synthesize the recommendations, other factors and decisions were also included. Where excluded from the GRADE analysis, it is indicated in the text. The Working Group chair and PHAC medical specialist presented the evidence and proposed recommendations to NACI on November 19, 2024. Following a thorough

review of the evidence, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in this statement.

The policy question addressed in this statement is: What is the best use of RSV vaccines (i.e., RSVpreF, RSVPreF3 and mRNA-1345) for adults 60 years of age and older?

A note on language

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 marginalising or erasing the experience of women within the healthcare environment. 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.

In addition, much of the research available currently refers only to “women” when discussing pregnancy. When citing research, NACI refers to the language used in the study. In these cases, “woman” refers to someone who was assigned female at birth and “maternal” is used to identify the person who is pregnant or postpartum. For the purposes of this statement, the terms “woman”, “women”, and “maternal” 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/chest feeding the infant.

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 common respiratory agent that causes recurrent infections throughout life[4]. Primary infection does not confer immunity, and recurrent infection tends to occur throughout lifetime[4]. Risk of serious clinical outcomes in adults, including hospitalization, intensive care unit (ICU) admission, and death, increase with increasing age, presence of chronic medical conditions, residence in chronic care and long-term facilities, and due to factors that intersect with social determinants of health[5]. Chronic medical conditions that increase risk include cardiac or pulmonary disorders, diabetes mellitus and other metabolic diseases, immunocompromise, chronic liver or kidney disease, neurologic or neurodevelopmental conditions and class 3 obesity[5]. Although evidence is more limited, studies suggest that the incidence of severe RSV outcomes in younger adults with underlying conditions is in the same range as for older adults[5].

IV. Vaccine

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

Characteristics from the product monographs of the RSV vaccine(s) currently authorized for use in Canada are summarized in Table 1.

Table 1. Comparison of vaccines authorized for use in Canada

	AREXVY (RSVPreF3)[6]	ABRYSVO™ (RSVpreF)[7]	mRESVIA (mRNA-1345)[8]
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	November 6, 2024
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 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	Authorized for the prevention of lower respiratory tract disease (LRTD) caused by RSV in individuals 60 years of age and older 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	Authorized for the prevention of lower respiratory tract disease caused by RSV in adults 60 years of age and older
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 Arexvy are not available for immunocompromised individuals. Patients receiving immunosuppressive treatment or patients with immunodeficiency may have a reduced immune response to Arexvy. There are no data from the use of Arexvy in pregnant individuals, nor on the excretion of Arexvy in human or animal milk. Arexvy is not recommended for use	There are no data on the use of Abrysvo in immunocompromised individuals. Immunocompromised individuals, including those receiving immunosuppressive therapy, may have a diminished immune response to Abrysvo. There are no data on the excretion of Abrysvo in human or animal milk.	The efficacy and safety of mRESVIA have not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. These individuals may have a diminished immune response. There are no data on the use of mRESVIA in pregnant women. No human or animal data are available to assess the effects of mRESVIA on the breastfed infant or on milk production/excretion.

	during pregnancy or in breast-feeding/lactating individuals.		
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, Arexvy should be used promptly; if not possible, 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.	Store in a refrigerator between 2°C and 8°C in the original carton to protect from light. Do not freeze. Discard if the vaccine has been frozen. Abrysvo should be administered immediately (within 4 hours) after reconstitution. Store the reconstituted vaccine between 15°C and 30°C. Do not store reconstituted vaccine under refrigerated conditions between 2°C and 8°C. Do not freeze reconstituted vaccine.	Store frozen between -40°C and -15°C for up to 18 months. Prefilled syringes in blister pack can be thawed in a refrigerator (2°C to 8°C) for 60 minutes or at room temperature (15°C to 25°C) for 45 minutes. Cartons of 10 can be thawed in a refrigerator (2°C to 8°C) for 155 minutes or at room temperature (15°C to 25°C) for 140 minutes. Once thawed, the vaccine should not be refrozen. 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 30 days. Unopened pre-filled syringes may be stored at 8°C to 25°C for a total of 24 hours after removal from refrigerator conditions. Thawed pre-filled 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.

IV.2 Efficacy

Evidence on vaccine efficacy of RSVpreF and RSVPreF3 in adults 60 years of age and older is available from clinical trials and ongoing national and international post-marketing surveillance of effectiveness. As summarized in previous NACI statement[9], data are limited, however in clinical trials[10,11], a single dose of RSV vaccine (RSVpreF or RSVPreF3) has been shown to reduce laboratory confirmed RSV RTI associated hospitalizations and medically attended RSV RTI for adults 60 years of age and older. The efficacy of these vaccines across multiple seasons is not yet clear. However, early data suggests that through subsequent RSV seasons, efficacy against RSV disease may be maintained[12-14]. For more information, please see the section on Immunogenicity, efficacy, and effectiveness in the RSV vaccines chapter of the CIG.

On November 1, 2024, Health Canada approved an expanded age indication for the use of GSK's RSVPreF3 in adults aged 50 to 59 years at increased risk for RSV disease. This authorization was based on immunogenicity data and non-inferiority of the vaccine in adults 50 to 59 years as compared to adults 60 years of age and older and is discussed below (see IV.4 Immunogenicity below). No efficacy data in this population is currently available.

Evidence on the efficacy of mRNA-1345, a lipid nanoparticle dispersion of mRNA sequences encoding the prefusion F protein administered for the prevention of severe lower respiratory outcomes due to RSV in older adults is derived from one phase II/III RCT[15]. The ConquerRSV study was conducted among older adults 60 years of age and older, including persons with stable chronic medical conditions such as chronic obstructive pulmonary disease (COPD), asthma, chronic respiratory or pulmonary disease, diabetes, CHF, advanced liver disease, or advanced renal disease, who received mRNA-1345 (n=18,112) or placebo (n=18,045) [median follow-up of 8.6 months]. Of these participants, 6,562 were 75 years of age and older (n=3,280 who received placebo and n=3,282 who received mRNA-1345).

Of note, season 1 of Pfizer's RENOIR, GSK's AReSVi-006, and Moderna's ConquerRSV 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.2.1 Efficacy of mRESVIA vaccine against death due to RSV

There is no evidence on the efficacy of mRNA-1345 for the prevention of death due to RSV infection among adults 60 years of age and older. In the phase II/III RCT evaluating the efficacy of mRNA-1345 in adults 60 years of age and older, VE of mRNA-1345 to prevent death due to RSV infection was not a study outcome. No deaths due to RSV occurred in the RCT through median follow-up 8.6 months (n=36,157; 18,112 in the mRNA-1345 group and 18,045 in the placebo group)[15-17] . Although RSV vaccines are most likely to benefit the oldest age groups and individuals with more numerous and less stable chronic conditions, these groups have not been adequately represented in randomized controlled trials conducted to date.

IV.2.2 Efficacy of mRESVIA vaccine against RSV respiratory tract infection with ICU admission

There is no evidence on the efficacy of mRNA-1345 for the prevention RSV RTI with ICU admission among adults 60 years of age and older. In the phase II/III RCT evaluating the efficacy of mRNA-1345 in adults 60 years of age and older, VE of mRNA-1345 to prevent RSV RTI with ICU admission was not a study outcome. No ICU admissions occurred in the RCT through median 8.6 months of follow-up (n=36,157; 18,112 in the mRNA-1345 group and 18,045

in the placebo group)[15-17]. Although RSV vaccines are most likely to benefit the oldest age groups and in individuals with more numerous and less stable chronic conditions, these groups have not been adequately represented in randomized controlled trials conducted to date.

IV.2.3 Efficacy of mRESVIA vaccine against RSV respiratory tract infection with hospitalization

The available evidence from one season of data (median 8.6 months of follow-up), suggest that compared to placebo, RSV vaccines may result in a reduction in laboratory confirmed RSV RTI with hospitalization in older adults, but the evidence for efficacy is very uncertain, including the possibility that this vaccine may have different efficacy from other RSV vaccines[18,19]. The evidence is limited due to the small number of events reported in each trial.

One phase II/III RCT evaluating the efficacy of mRNA-1345 vaccine against RSV RTI with hospitalization reported 2 cases among 18,045 placebo recipients and none in mRNA-1345 recipients (VE: 86%; 95% CI: -116 to 99%)[15-17] (Table 2). One of these cases occurred in a participant 75 years of age and older; the VE in this age group was 86% (95% CI: -582 to 100%)[15,16].

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

The available evidence from one season of data, suggests that all available RSV vaccines may result in a similar reduction in the risk of medically attended RSV RTI in older adults, though this is still uncertain[18,19]. The evidence is limited due to the small number of events reported for each vaccine. For mRNA-1345, the manufacturer outcome of RSV lower respiratory tract disease with two or more symptoms and emergency room/urgent care visit was used to represent cases of medically attended RSV RTI.

In adults 60 years of age and older, one phase II/III RCT evaluating the efficacy of mRNA-1345 vaccine reported 18 cases of medically attended RSV RTI; 5 in the mRNA-1345 group and 13 in the placebo group, which corresponds to a VE of 59% (95% CI: -3 to 84%)[15,16]. In adults 75 years of age and older, 3 cases were observed in the mRNA-1345 group (n=3,282) compared to 2 cases in the placebo (n=3,280)[15,16].

IV.2.5 Longer term efficacy during subsequent RSV seasons

Although not included in the GRADE analysis, NACI reviewed the available data on the efficacy of RSV vaccines over multiple RSV seasons[12-14,18,20]. Disease surveillance and follow-up for outcomes of interest continued over 16.4 months, 30.6 months, and 18 months median follow-up for RSVpreF, RSVPreF3, and mRNA-1345 respectively. Evidence is limited; however, early data suggests that through two RSV seasons, efficacy against RSV disease remains. The timing and dynamics of waning of immune responses for all three RSV vaccines is still under investigation and the vaccines may not provide the same duration of protection.

For mRNA-1345, the manufacturer outcome of first episode of RSV-associated lower respiratory tract disease with at least two lower respiratory signs or symptoms was used to assess efficacy. Over a median follow-up of 18 months (range: 0.5 to 24 months), adults 60 years of age and older who received mRNA-1345 vaccine in advance of season 1 had a VE against first episode of RSV-associated lower respiratory tract disease of 50.3% (95% CI: 37.5 to 60.7%)[18].

The duration of efficacy of RSV vaccines are not yet clear and NACI will continue to monitor emerging evidence as it becomes available.

IV.3 Effectiveness

IV.3.1 Observational RSV vaccine effectiveness

Preliminary observational effectiveness data for two RSV vaccines, RSVpreF (Pfizer) and RSVPreF3 (GSK) vaccines in US adults aged 60 years and older were derived from several sources, including data from the Influenza and Other Viruses in the Acutely Ill (IVY) Network, Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION), Veterans Health Association (VHA), and Medicare/end stage renal disease (ESRD) patients[21]. These observation studies are more representative of individuals who benefit most from RSV vaccination than clinical trials; of all included adults, more than 25% were aged 80 years or older, more than 94% had a chronic condition, and immunocompromised adults were included. During the 2023/2024 RSV season, over 400,000 individuals were included across these networks and observational vaccine effectiveness against RSV-associated emergency department (ED) visits, hospitalization, critical illness (ICU admission or death) was established.

Under real-world conditions and across multiple networks, vaccination with an RSV vaccine (either RSVpreF or RSVPreF3) provided protection against severe RSV disease not only among adults 60 years of age and older, but also in a population that is more representative of those at high-risk of severe RSV disease and for more severe outcomes which were not able to be evaluated in clinical trials. Vaccine effectiveness was similar to results from Phase 3 trials and no substantial differences in effectiveness were observed between products.

IVY Network data

From October 1, 2023, to March 31, 2024, 265 IVY Network patients were vaccinated against RSV. Among them, 137 received RSVPreF3, 89 received RSVpreF, and 39 were unsure of the specific vaccine received. This network used a test-negative, case-controlled design to assess vaccine effectiveness against RSV associated hospitalization among US adults 60 years of age and older. In adults 60 years of age and older, RSV vaccines were 75% (95% CI: 50 to 87%) effective at preventing RSV-associated hospitalizations, and similar in adults 75 years of age and older (76%; 95% CI: 40 to 91%)[21,22].

VISION Network

From October 1, 2023, to March 31, 2024, 3,275 VISION Network patients were vaccinated against RSV. Among them, 2,409 received RSVPreF3 and 865 received RSVpreF. This network used a test-negative, case-controlled design to assess vaccine effectiveness against RSV-associated ED visits, hospitalization, and critical illness among US adults 60 years of age and older. Vaccine effectiveness was 77% (95% CI: 70 to 83%) against RSV-associated ED visits, 80% (95% CI: 71 to 85%) against RSV-associated hospitalizations, and 81% (95% CI: 52 to 92%) against RSV-associated critical illness, defined as ICU admission or death. Point effectiveness estimates were similar between products across outcomes and decreased with increased time since RSV vaccination. RSV vaccines provided protection against RSV-associated hospitalization among people with immunocompromise (Vaccine effectiveness, 73%; 95% CI: 48 to 85%)[21,23].

VHA

From September 1, 2023, to March 31, 2024, 146,852 VHA patients were vaccinated against RSV. Among them, 43,875 received RSVPreF3, 101,623 received RSVpreF, and 1,345 were unsure of the specific vaccine received. This network used a target trial emulation design which emulated a target randomized controlled trial of RSV vaccination to assess vaccine effectiveness against RSV-associated ED visits and hospitalization among US veterans 60 years of age and older. Vaccine effectiveness was 77% (95% CI: 71 to 82%) against RSV-associated ED visits and 82% (95% CI: 69 to 89%) against RSV-associated hospitalizations. Point effectiveness estimates were similar between products across outcomes. Effectiveness against documented RSV infection was similar in adults aged 80 years or older (72%; 95% CI: 59 to 81%) and those with immunocompromise (71%; 95% CI: 52 to 83%), defined as receipt of immunosuppressive (excluding steroids) or cancer medications within 90 days or 1 year of the index date (depending on the medication), HIV with most recent CD4 ≤2 years prior to index date ≤200 cells/mm3, or hematologic malignancy documented ≤2 years prior to index date[21].

Medicare/ESRD

From October 1, 2023, to February 24, 2024, 6,731 Medicare/ESRD patients were vaccinated against RSV. Among them, 4,559 received RSVPreF3 and 2,172 received RSVpreF. This network used a retrospective cohort design to assess vaccine effectiveness against RSV-associated hospitalization among US adults 65 years of age and older with ESRD. Vaccine effectiveness was 72% (95% CI: 41 to 87%) against RSV-associated hospitalizations. In individuals with additional immunocompromise (e.g., hematologic malignancy, solid tumor malignancy, transplant, rheumatologic/inflammatory disorders, other intrinsic immune conditions or immunodeficiency), vaccine effectiveness was 83% (95% CI: 45 to 95%)[21].

IV.4 Immunogenicity

IV.4.1 Immunogenicity of RSVPreF3 in adults 50 to 59 years of age

NACI reviewed the available evidence on immunogenicity of RSVPreF3 in adults 50 to 59 years of age, although this outcome was not included in the GRADE analysis. One phase III study evaluated the safety and immunogenicity of RSVPreF3 in adults 50 to 59 years of age[24,25]. This study was intended to demonstrate the non-inferiority of RSVPreF3 vaccine in adults 50 to 59 years, including those at increased risk of severe RSV disease, compared to adults 60 years of age and older. In total, 769 adults 50 to 59 years of age received RSVPreF3 (n=386 with comorbidities and n=383 without comorbidities). The ratio of geometric mean titres and the difference in seroresponse rate for both RSV-A and RSV-B neutralizing antibodies were evaluated. Compared to baseline, the humoral response one month (i.e., day 31) following vaccination elicited by RSVPreF3 vaccine in adults 50 to 59 years of age was non-inferior for all outcomes, groups, and RSV subtypes as compared to adults 60 years of age and over[24,25]. There is no data on the efficacy of this vaccine in adults 50 to 59 years of age, and no ongoing clinical trials to establish the efficacy of RSV vaccines in this population. While efficacy data is preferable, especially given there is no immunologic correlate of protection against RSV disease, the non-inferiority data suggest that the vaccine efficacy of RSVPreF3 in adults 50 to 59 years with and without chronic conditions at high risk of severe RSV disease will be similar to efficacy demonstrated among adults 60 years and older. Efficacy data from clinical trials is not anticipated in this age and risk group.

IV.4.2 Immunogenicity of RSV vaccines following revaccination

NACI reviewed the available evidence on immunogenicity of RSV vaccines in the context of revaccination schedules, although this outcome was not included in the GRADE analysis. Studies for RSVpreF, RSVPreF3, and mRNA-1345 demonstrate waning of immune responses after the first dose. 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[26]. In addition, several trials have studied the immunogenicity of RSV vaccines following revaccination, however clarity around the boostability of this immune response, including potential differences between protein and mRNA-vaccines, remains unclear. Longer intervals between doses (e.g., revaccination at 24 months post-dose 1) are being explored.

In Pfizer's phase I/II RCT[27], an additional dose of RSVpreF 12 months after dose one increased neutralizing antibody titre levels, but they remained below increases observed following dose one[28]. Similarly, in a phase III immunogenicity RCT evaluating revaccination with RSVPreF3 at 12-months post-dose one[29], a smaller booster effect was observed. Serum neutralizing antibody titres were slightly boosted, but they were below titres observed one month after the first dose[30,31]. Lastly, a phase III study of revaccination with mRNA-1345 at 12 months led to a neutralizing antibody response similar to that seen after the primary vaccination; the geometric mean ratio (GMR) following revaccination versus the first dose met the prespecified non-inferiority criterion for both RSV-A and RSV-B[18].

The need for subsequent vaccine doses and optimal strategy for boosting these vaccine responses are not yet clear and NACI will continue to monitor emerging evidence as it becomes available.

IV.5 Vaccine administration and schedule

RSVpreF is supplied as a single dose vial of lyophilized powder that is reconstituted with sterile water (diluent) in a prefilled syringe. A 0.5 mL dose of RSVpreF should be administered intramuscularly. The standard schedule for individuals 60 years of age and older is one dose. Please see the product monograph for more details[7].

RSVPreF3 is supplied as a single dose vial of lyophilized powder which is reconstituted at the time of use with the accompanying vial of $AS01_E$ adjuvant suspension. A 0.5 mL dose of RSVPreF3 should be administered intramuscularly. The standard schedule for individuals 50 years of age and older is one dose. Please see the product monograph for more details[6].

mRNA-1345 is supplied as a single dose frozen dispersion in a pre-filled syringe. It must not be reconstituted, mixed with other medicinal products, or diluted prior to administration. A 0.5 mL dose of mRNA-1345 should be administered intramuscularly. The standard schedules for individuals 60 years of age and older is one dose. Please see the product monograph for more details[8].

There is limited efficacy and immunogenicity data supporting the need for revaccination. Studies of RSV vaccines demonstrate waning of immune responses after the first dose. Whether booster doses will be required to maintain a sufficient level of protection is not known (see IV.4 Immunogenicity above). At this time, RSV vaccines are approved and recommended to be administered as a single dose.

IV.6 Concurrent administration with other vaccines

Given the needs of older adults to be protected from multiple vaccine preventable diseases, some of which are seasonal, 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. For more information regarding concurrent administration of vaccines, please refer to the chapter on Timing of vaccine administration in the CIG.

According to the results of coadministration studies of RSV vaccines with influenza vaccines, common side effects, such as fever and soreness at the injection site, may be increased when these two vaccines are administered on the same day. Some studies also suggest that the RSV and influenza vaccines may not produce as strong of an immune response if they are given on the same day, but the clinical significance of this is unknown[19,30].

One phase III study looked at concurrent administration of mRNA-1345 with either quadrivalent influenza or bivalent COVID-19 vaccines. Concurrent administration of mRNA-1345 with a quadrivalent inactivated influenza vaccine (IIV4), in adults 50 years of age and older has been shown to be safe and immunogenicity data demonstrated non-inferiority was met for all components of the IIV4 and mRNA-1345 vaccines. The GMRs at 1 month after vaccination for concurrent (mRNA-1345 and IIV4) to non-concurrent (mRNA-1345 and placebo/IIV4 and placebo) were 0.89 (95% CI: 0.77 to 1.03) for A/Victoria/2570/2019 (H1N1), 0.97 (95% CI: 0.86 to 1.00) for A/Darwin/9/2021 (H3N2), 0.91 (95% CI: 0.86 to 1.09) for B/Phuket/3073/2013 (B/Yamagata lineage), 0.93 (95% CI: 0.82 to 1.05) for B/Austria/1359417/2021 (B/Victoria lineage), 0.81 (95% CI: 0.67 to 0.97) for RSV-A, and 0.85 (95% CI: 0.73 to 1.00) for RSV-B[32,33]. Thus, compared with the pre-specified criterion of a lower CI limit of 0.67, non-inferiority was established for all components of both IIV4 and mRNA-1345.

Concurrent administration of mRNA-1345 with Moderna's bivalent (original strain and Omicron BA.1) Spikevax COVID-19 vaccine (mRNA-1273.214), in adults 50 years of age and older has been shown to be safe and immunogenicity data demonstrated non-inferiority was met for all components of the COVID-19 and RSV vaccines. The GMRs at 1 month after vaccination for concurrent (RSV mRNA-1345 and COVID-19 mRNA-1273.214) to sequential (RSV mRNA-1345 alone 1 month before COVID-19 mRNA-1273.214) were 0.96 (95% CI: 0.87 to 1.06) for the SARS-CoV-2 original (D614G) strain, 1.01 (95% CI: 0.89 to 1.14) for the SARS-CoV-2 Omicron BA.1 strain, 0.80 (95% CI: 0.70 to 0.90) for RSV-A and 0.89 (95% CI: 0.79 to 1.00) for RSV-B[32,33]. Thus, compared with the pre-specified criterion of a lower CI limit of 0.67, non-inferiority was established for all components of both mRNA-1345 and mRNA-1273.214.

Concurrent administration of RSVPreF3 with the adjuvanted recombinant zoster vaccine (RZV) in adults 50 years of age and older has been shown to be safe and immunogenicity data demonstrated non-inferiority was met for all components of the RZV and RSV vaccines. The GMRs at 1 month after vaccination for sequential (RZV alone 1 month before RSVPreF3) to concurrent (RSVPreF3 and RZV) were 1.24 (95% CI: 1.08 to 1.42) for anti-glycoprotein E, 1.14 (95% CI: 0.97 to 1.35) for RSV-A and 0.98 (95% CI: 0.84 to 1.15) for RSV-B[34]. Thus, compared with the pre-specified criterion of an upper CI limit of 1.50, non-inferiority was established for all components of both RSVPreF3 and RZV. There were no clinically meaningful differences in reactogenicity or safety when comparing sequential administration of RZV and RSV vaccines to concurrent administration.

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. If possible, RSV vaccines should be given at least six weeks before or after non-seasonal vaccines, for example, 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 on concurrent administration of RSVpreF and RSVpreF3 with other vaccines, please see the section on Administration practices in the Respiratory syncytial virus (RSV) vaccines chapter of the CIG.

IV.7 Vaccine safety

In this updated statement, safety data on the mRNA RSV vaccine mRNA-1345 (Moderna) and new safety data following the expanded age indication of RSVPreF3 (GSK) to include adults aged 50 to 59 years has been obtained from two randomized controlled trials[15,25]. This statement also provides updated post-market safety data for the RSVpreF (Pfizer) and RSVPreF3 (GSK) vaccines in adults aged 60 years and older.

In the clinical trials, mRNA-1345 was generally well tolerated in older adults aged 60 years and older (n= 17,734), and RSVPreF3 was well tolerated in adults aged 50 to 59 years (n=769). Most local and systemic adverse events (AEs) were 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 (see Tables 5 and 7). Related serious adverse events (SAEs) occurred at similar rates (less than 0.7%) in both the vaccine and placebo groups, with no deaths reported (see Tables 6 and 8).

Evidence from RCTs on the safety of RSVpreF and RSVPreF3 vaccines in adults 60 years of age and older was previously summarized[9]. Updated post-market surveillance among individuals aged 60 years and older continues to suggest a potential increased risk of Guillain-Barré Syndrome (GBS) following the administration of either RSVpreF or RSVPreF3 vaccines. While safety monitoring is ongoing, the FDA recently released a label change update for RSVPreF3 and RSVpreF[35] to include GBS as a potential adverse event. Overall, these vaccines have demonstrated an acceptable safety profile.

NACI will continue to monitor emerging safety data for these vaccines and update guidance as needed. For more detailed information, refer to the previous Statement on the prevention of respiratory syncytial virus in older adults and the corresponding section of the Respiratory Syncytial Virus (RSV) vaccines chapter of the Canadian Immunization Guide (CIG).

IV.7.1 Local adverse events following immunization

In the phase III trial for RSVPreF3 among adults aged 50 to 59 years and 60 years and older[25], local AEs were reported within 4 days after vaccine or placebo administration. Injection-site pain was the most frequently reported local AE and it was more commonly reported in RSVPreF3 recipients compared to placebo recipients in both the at-increased-risk (AIR) cohort (75.2% vs.13.8%) and the non-at-increased-risk (non-AIR) cohort (76.4% vs. 10.5%). Among those aged 60 years and older, pain was less frequent (61.2%). In the 50 to 59 non-AIR cohort, Grade 3 injection-site pain was higher in the RSVPreF3 group compared to the placebo group (3.2% RSVPreF3 vs. 0.5% placebo) same as Grade 3 erythema and swelling were comparable in the RSVPreF3 and placebo groups (erythema: 1.1% RSVPreF3 vs 0.0%; swelling: 0.3% RSVPreF3 vs 0.0% placebo). Among participants aged 60 years and older, Grade 3 local AEs were reported for erythema (0.8%) and pain (2.1%).

In the ongoing phase II/III trial of mRNA-1345 among adults aged 60 years and older, as of November 30, 2022[15], solicited local AEs including injection-site pain, erythema, swelling and axillary swelling or tenderness, were reported within 7 days post-vaccination in 58.7% of participants in the mRNA-1345 group compared to 16.2% in the placebo group. Injection-site pain was the most frequently reported local AE, occurring in 56.3% of the mRNA-1345 group and 13.7% of the placebo group. As of April 30, 2023[36], Grade 3 injection-site pain, erythema, swelling, and axillary swelling or tenderness were reported in 1.7% vs 1.1%, 0.6% vs 0.3%,

0.9% vs 0.1%, and 0.8% vs 0.6% of mRNA-1345 recipients compared to the placebo group, respectively.

IV.7.2 Systemic adverse events following immunization

In the RSVPreF3 phase III trial among adults aged 50 to 59 years and 60 years and older[25], the rates of systemic adverse events (AEs) within 4 days after immunization. Arthralgia, fatigue, headache, and myalgia were reported more frequently in vaccinated adults aged 50 to 59 years compared to vaccinated older adults aged 60 years and over or placebo. Fatigue and myalgia were the most frequent systemic AEs and were reported more often in RSVPreF3 recipients compared to placebo recipients among those aged 50 to 59. In the 50 to 59 non-AIR cohort, fatigue was reported in 43.8% of RSVPreF3 recipients vs. 17.3% of placebo recipients, and myalgia in 39.0% vs. 5.8%, respectively. In the 50 to 59 AIR cohort, fatigue was reported in 35.9% of RSVPreF3 recipients vs. 19.0% of placebo recipients, and myalgia in 32.2% vs. 13.8%, respectively. Among participants aged 60 years and older receiving the RSVPreF3 vaccine, fatigue (23.7%) and myalgia (21.1%) were reported at lower rates compared to the 50 to 59 participants receiving RSVPreF3 in both cohorts (non-AIR and AIR). However, the rates of Grade 3 events were comparable between groups (Table 5).

In the ongoing phase II/III trial of mRNA-1345 among adults aged 60 years and older, as of November 30, 2022[15], the rate for any systemic AEs was reported as 47.7% of the mRNA-1345 group compared to 32.9% in the placebo group. Most systemic AEs had a median onset of 2 days post-injection and resolved within 1 to 2 days after onset. Fatigue and headache were the most common systemic AEs, reported in 31.0% and 27.0% of participants in the mRNA vaccine group, respectively, compared to 20.0% and 18.9% in the placebo groups. Grade 3 or higher systemic events were reported in 4.0% of mRNA-1345 recipients vs. 2.9% of the placebo group.

IV.7.3 Serious adverse events following immunization

In the phase III trial of RSVPreF3 among adults aged 50 to 59 years, SAEs were reported within 6 months post-vaccination by 0.5% of participants in the non-AIR cohort and 3.6% in the AIR cohort. In comparison, SAEs were reported in 2.1% of placebo recipients in both the non-AIR and AIR cohorts. Among adults aged 60 years and older, SAEs were reported in 2.4% of RSVPreF3 recipients. Potential immune-mediated disorders (pIMDs), including autoimmune diseases and other inflammatory or neurologic disorders such as Guillain-Barré Syndrome (GBS), idiopathic myocarditis and pericarditis[25], were reported at similar frequencies in the various groups (0.0% to 1.0% of participants aged 50 to 59 years, 0.8% in those aged 60 years and older and 0% to 0.5% in the placebo groups (Table 6). No deaths were reported.

In the ongoing phase II/III trial of mRNA-1345 among adults aged 60 years and older[15,18], SAEs reported as of March 8, 2024, occurred in 0.7% of participants in the mRNA-1345 and 0.6% in the placebo group within 28 days of vaccination. Adverse events of special interest (AESI), including thrombocytopenia, neurologic diseases (e.g., GBS), myocarditis, pericarditis, and anaphylaxis, were reported in less than 0.1% of participants in each group within 28 days post-vaccination. Of these, no events were considered related to the mRNA-1345 vaccine, including three reported cases of GBS (one in the vaccine group and two in the placebo group), which occurred more than 500 days post-injection and were determined to be unrelated. No cases of acute myocarditis were reported in vaccine recipients, and no confirmed cases of acute pericarditis with onset within 42 days were observed in vaccine recipients. Fatal events occurred in 0.1% of participants in both the intervention (vaccine) and placebo groups, but none were deemed related to vaccination.

IV.7.4 Post-Marketing safety surveillance data

Preliminary post-market safety surveillance data for the RSVPreF3 and RSVpreF vaccines in U.S. adults aged 60 years and older were derived from several sources, including data from V-safe, the Vaccine Adverse Event Reporting System (VAERS), and the Vaccine Safety Datalink (VSD)[37-39]. Hause et al., 2024[40], summarized V-safe and VAERs data, while additional safety updates were presented by the U.S. Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA) at the June 2024 and October 2024 Advisory Committee on Immunization Practices (ACIP) meetings, to update information presented at the February 2024 meeting. Updated post-market surveillance among individuals aged 60 years and older continues to suggest a potential increased risk of Guillain-Barré Syndrome (GBS) following the administration of either RSVpreF or RSVPreF3 vaccines. However, the available data has limitations and do not provide clear, conclusive evidence of an elevated risk of GBS. Further surveillance and analyses are planned. Preliminary results from the VSD suggest a possible increased risk of ITP following RSVPreF3 administration. Additional analyses are planned to further investigate this new statistical signal. Vaccine safety surveillance in Canada is ongoing, and results will be included in future updates if available.

V-safe data

Between May 3, 2023, and April 14, 2024, 16,220 V-safe participants 60 years of age and older reported receiving RSV vaccines. Among them, 6,402 received RSVPreF3, 3,882 received RSVpreF, and 5,936 were unsure of the specific vaccine received. Around one-third of participants reported concomitant administration of other vaccines, most frequently the influenza and COVID-19 vaccines. In total, 6,328 (39.0%) participants reported symptoms potentially related to the RSV vaccination. The most common symptoms were local reactions, reported by 43.9% of RSVPreF3 recipients and 20.3% of RSVpreF recipients. Systemic reactions, such as fatigue and muscle aches, were reported by 36.6% of RSVPreF3 recipients and 21.6% of RSVpreF recipients. Most reported adverse events (AEs) were mild to moderate in severity[40].

VAERS data

VAERS processed 3,200 reports of adverse events from May 3, 2023, to April 14, 2024, among adults aged 60 and older who received RSV vaccines. Of these reports, 2,193 were for RSVPreF3, 919 for RSVpreF, and 88 had unknown manufacturers. One-third of reports involved concomitant administration with other vaccines, most often the influenza vaccine. A total of 2,919 reports were classified as non-serious, while 281 were serious, including 216 hospitalizations, 81 life-threatening events, 66 cases of permanent disability, and 34 deaths. Serious events included 28 cases of GBS, with 13 occurring after RSVPreF3 administration (1.8 per million doses) and 15 after RSVpreF (4.4 per million doses). Additionally, there were 24 cases of stroke or transient ischemic attack (13 with RSVPreF3, 10 with RSVpreF, and 1 with an unknown manufacturer), 14 cases of atrial fibrillation (8 with RSVPreF3, 3 with RSVpreF, and 3 with an unknown manufacturer), and 11 cases of immune thrombocytopenia (ITP) (5 with RSVPreF3 and 6 with RSVpreF). Among the 18 deaths with sufficient information, causes included acute respiratory distress syndrome, cardiac events, sepsis, and GBS[40]. This is a temporal association and there is no established causal relationship.

Vaccine Safety Datalink (VSD)

From August 2023 to May 2024, a total of 385,729 RSV vaccines were administered in the VSD[37], including 338,290 doses of RSVPreF3 and 47,287 doses of RSVpreF, with 152 unspecified. A statistical signal on ITP was identified in the 1-21 day risk interval versus 22 to 42

day comparison interval following RSVPreF3 without simultaneous vaccination. In the 1 to 21 day risk interval following RSVPreF3 administration, a total of 19 ITP cases (including 4 newly diagnosed) were identified compared to 6 (including 1 newly diagnosed) in the 22 to 42 day comparison interval. Of note, medical record reviews showed that most ITP cases had onset before vaccination. No association between RSVPreF3 vaccination and ITP can be confirmed[41] at this time, investigation is ongoing. No statistical signal was found for GBS or atrial fibrillation. Surveillance for these outcomes will continue through May 2025.

IV.8 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. There are limited data on the use of these vaccines in individuals less than 18 years of age and in immunocompromised individuals. 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[42].

There have been documented administration errors in the United States, where some new RSV vaccines have been administered to populations for which they are not authorized, including young children, pregnant women and pregnant people[43,44]. 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.

IV.9 Vaccination of Specific Populations

IV.9.1 Immunization of immunocompromised persons

Immunocompromised persons are at higher risk of serious outcomes from RSV including RSV-associated death, and some immunocompromised persons (such as those with hematopoietic stem cell transplants and lung transplants) may be at higher risk than others. There are little data at present on the efficacy, effectiveness, or safety of the RSV vaccines in immunocompromised populations. The efficacy and effectiveness of vaccines for those with immunocompromise varies by specific condition and/or use of medication, both of which influence degree of immunosuppression.

V. Ethics, equity, feasibility and acceptability considerations

The ethics, equity and acceptability considerations are similar for these populations and products as they are for currently authorized products and populations. See previous NACI statement on prevention of RSV in older adults for additional information.

V.1 Feasibility considerations

The storage conditions for the protein-subunit based vaccines (from RSVPreF3 and RSVpreF) are different from mRNA-based mRNA-1345 vaccine. The full storage conditions are available in the product monograph, briefly to store between 2°C to 8°C and reconstitute at 25°C[6,7]. However, the storage conditions for Moderna are for frozen storage for up to 18 months at -40°C to -15°C and a 30-day shelf life at 2°C to 8°C. Please see Table 1. Full storage condition available in the product monograph[8].

There may be feasibility challenges for this limited shelf life at refrigerated temperature for protein-subunit based vaccines vs frozen temperature for mRNA-based vaccines. They may increase vaccine wastage as thawed vaccine may not be able to be used in time. In addition, there may be feasibility challenges transporting vaccines at frozen temperature or if more frequent transportation is needed at elevated temperature.

VI. Economics

An environmental scan and additional cost-effectiveness analyses using a previously described Canadian cost-utility model[45] were used to generate economic evidence related to the use of mRNA-1345 and a younger age authorization for RSVPreF3. This economic evidence supplemented that previously used to assess the cost-effectiveness of RSV vaccination programs for adults of different age groups[9,45]. Where applicable, results are presented using vaccination of adults aged 75 years and older as the comparator, to reflect current NACI recommendations. All costs are presented in 2023 Canadian dollars. For the Canadian cost-utility model, results are presented for the health system perspective and a 1.5% discount rate was used.

VI.1 Environmental scan

An environmental scan of national immunization technical advisory group websites was conducted to identify economic evidence related to the use of RSV vaccines in adults published since a recently conducted systematic review[46]. The search was completed on August 9, 2024 and identified three economic evaluations that were presented to the US Advisory Committee on Immunization Practices (ACIP)[47,48]. For clarity, the economic evaluations summarized to ACIP are referred to by the names of the model authors[47,49,50]. All costs were converted from 2023 US to Canadian dollars (exchange rate of 1.3497)[51]. Two of the economic evaluations were industry funded[49,50] and all estimated incremental cost-effectiveness ratios (ICERs) from the societal perspective, with a 3% annual discount rate. Vaccine prices per dose were $378 for RSVPreF3, $391 for mRNA-1345, and $398 for RSVpreF.

Two studies evaluated the cost-effectiveness of mRNA-1345[47,50]. Compared to no vaccination, ICERs for vaccination of adults aged 75 years and older using mRNA-1345 were $75,580[50] and $89,470[47] per QALY. One of these studies estimated the cost-effectiveness of mRNA-1345 and the protein subunit RSV vaccines (RSVpreF and RSVPreF3), each relative to a no vaccination strategy[47]. A key difference in inputs for the mRNA-1345 and the protein subunit vaccines was that mRNA-1345 was assumed to have lower initial VE and more rapid waning than the protein subunit vaccines. Compared to no vaccination, vaccination of adults aged 75 years and older resulted in larger ICERs for mRNA-1345 ($89,470 per QALY) than for the protein subunit vaccines ($63,500 to $79,280)[47].

The two studies that evaluated cost-effectiveness of vaccination for people aged 50 to 74 years with at least one chronic medical condition (CMC) used different comparators and approaches[47,49]. One study estimated that the ICER to extend vaccination to the 50 to 59 year age group with CMCs exceeded $200,000 per QALY gained compared to vaccination of all adults aged 75 years and older plus adults aged 60 to 74 years with at least one CMC[47]. By comparison, vaccination of adults 60 to 74 years with one or more CMCs and all adults aged 75 years and older resulted in ICERs of $82,240 per QALY gained compared to vaccination of all adults aged 75 years and older[47]. Sequential ICERs were lower when vaccine protection was assumed to extend into a third RSV season, compared to the primary results that assumed 24 months of vaccine protection but still exceeded commonly used cost-effectiveness thresholds, at $61,340 per QALY for adults aged 60 to 74 years with CMCs and $152,450 per QALY for adults aged 50 to 59 years with CMCs. Although vaccinating all people with at least one CMC exceeded commonly used cost-effectiveness thresholds, there was a subset of risk conditions (chronic kidney disease, heart failure, lung transplant, allogenic HCT, and autologous HCT) for which inclusion of people aged 50 to 59 years was cost-effective using a $50,000 per QALY threshold compared to vaccination of the population aged 60 years and older[47]. There was an expanded subset of risk conditions (asthma, severe obesity, and COPD) for which vaccination at age 60 to 74 years resulted in ICERs of less than $50,000 per QALY compared to vaccination at age 75 years and older[47]. The other study assessed cost-effectiveness for vaccination of 50 to 59 year olds with specific risk conditions compared to no vaccination in this age group, with results ranging from cost saving (COPD, heart failure, coronary artery disease, and diabetes) to $3,300 per QALY gained (asthma), assuming vaccine protection of three years[49].

The models included in the environmental scan had different assumptions about incidence and costs of medically attended RSV, as well as initial vaccine effectiveness and waning of protection, which may explain some of the differences in results.

VI.2 Cost-effectiveness analysis

A Canadian cost-utility model previously used to estimate the cost-effectiveness of RSVpreF and RSVPreF3 was modified to include a vaccine with the characteristics of mRNA-1345. All other

parameters, including those for the protein subunit vaccines, were unchanged from the previous analysis and all vaccines were assumed to cost $230 per dose in the primary analysis[45].

VI.2.1 Cost-effectiveness of mRNA-1345 in adults aged 75 years and older

There are no data directly comparing the VE and safety of all authorized RSV vaccines, making it challenging to compare outcomes and cost-effectiveness across vaccines. Differences in study endpoints and evaluation periods contribute to the challenges of direct comparisons. To address this uncertainty, cost-effectiveness of mRNA-1345 was not directly compared to the other vaccine products in a sequential analysis. Instead, two VE scenarios were conducted for mRNA-1345, to explore results under different VE assumptions. The first scenario assumed equivalent VE values for mRNA-1345 as were used previously for the protein subunit vaccines. The second scenario assumed lower VE for mRNA-1345 based on available RCT data[18,52]. For the second scenario, VE for preventing RSV disease requiring outpatient care was assumed to be 56% for the first RSV season (with 12 months follow-up) and 30% for the second RSV season (with 7 months follow-up)[52]. As there was an insufficient number of hospitalizations during the study period to estimate VE, RSV-LTRD associated shortness of breath was used as a proxy for mRNA-1345 VE for preventing RSV requiring hospitalization; mRNA-1345 VE for preventing RSV disease requiring hospitalization was assumed to be 75% for season 1 (with 9 months follow-up) and 41% for season 2 (with 7 months follow-up)[18]. For both scenarios, vaccine protection was assumed to last for 2 years, with VE by the end of the second year waning to one-third of the VE value at the start of season 2, consistent with the previously described analysis.

Compared to a strategy of no vaccination, ICERs for vaccination of adults aged 75 years and older resulted in ICERs of $25,450 to $28,010 per QALY if VE for mRNA-1345 is similar to the protein subunit vaccines and is considered cost-effective at the commonly used cost-effectiveness threshold of $50,000 per QALY. For the more conservative scenario that assumed lower VE, the ICER for vaccination of adults aged 75 years and old was $53,000 per QALY compared to no vaccination. For this lower VE scenario, vaccine price per dose needed to be reduced by 4% (to $220 per dose) for the ICER to be less than $50,000 per QALY or by approximately 25 to 30% (to $160 to 170 per dose) for the ICER to be similar to the ICER estimated when VE was assumed equivalent to the protein subunit vaccines.

VI.2.2 Cost-effectiveness of RSVPreF3 in adults aged 50 to 74 years with chronic medical conditions

The same cost-utility model was used to estimate the incremental cost-effectiveness of expanding the currently recommended vaccination program to include individuals aged 50 to 74 years with one or more CMCs[53]. Cost-effectiveness was estimated for program expansion from vaccination for all individuals aged 75 years and older to a program that included individuals at high risk of RSV disease aged 60 to 74 years, as well as for further program expansion to include individuals aged 50 to 59 years at high risk of RSV disease. Results are summarized for a vaccine with characteristics similar to RSVPreF3, given its authorization for use in adults aged 50 to 59 years at high risk of RSV disease.

Compared to vaccination for all aged 75 years and older, program expansion to include individuals aged 60 to 74 years with at least one CMC resulted in an ICER of $79,470 per QALY. When vaccine price was reduced by 28% (to $165 per dose), vaccination of individuals aged 60 to 74 years with CMCs was cost-effective using a $50,000 per QALY threshold. Compared to a strategy of vaccinating individuals aged 60 to 74 years with one or more CMCs

and all individuals aged 75 years and older, inclusion of individuals aged 50 to 59 years with CMCs had an ICER of $178,350 per QALY gained. Even with substantial reductions in vaccine price, lowering the age to 50 years for individuals with one or more CMCs was not cost-effective in this analysis. This finding was robust in scenario analyses that used alternate assumptions about disease incidence and vaccine characteristics, including longer duration of protection. The one exception was in a higher RSV disease incidence and higher medical cost setting, which may occur in some remote and isolated communities, where offering vaccine to everyone aged 75 and older and people aged 50 to 74 years with one or more CMCs was expected to be the optimal strategy for a $50,000 per QALY cost-effectiveness threshold.

VI.3 Summary

Using currently available VE data for mRNA-1345[18,52], ICERs for vaccination of adults aged 75 years and older using mRNA-1345 compared to a strategy of no vaccination are higher than estimated under the assumption that VE is equivalent to the authorized protein subunit RSV vaccines. A lower vaccine price for mRNA-1345 would reduce these differences. Comparisons between different vaccines should be interpreted with caution, given the different endpoints and time periods used to evaluate VE for the vaccines being compared. For this reason, the vaccines were not directly compared to each other in a sequential analyses and an analysis assuming similar VE for all authorized vaccines was conducted. Additional head-to-head data on VE and duration of vaccine protection are required to assess differences between vaccine products. Vaccination of people aged 50 to 59 years with at least one CMC using RSVPreF3 is unlikely to be cost-effective at commonly used cost-effectiveness thresholds. However, vaccination of people aged 50 to 74 years with CMCs may be cost-effective in settings experiencing higher RSV disease incidence and higher medical costs. Additionally, a study in the US population showed there are some medical risk conditions for which vaccination at a younger age may be cost-effective[47].

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 9 for a more detailed explanation of strength of NACI recommendations and Table 2 for the grade of the body of evidence.

NACI will continue to carefully monitor the scientific developments related to vaccines to prevent RSV in adults and will update recommendations as evidence evolves.

Recommendations for public health program level decision-making (i.e., Provinces/Territories making decisions for publicly funded immunization programs)

1. NACI continues to recommend RSV immunization programs for adults 75 years of age and older, particularly for older adults 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/m2 and over)

Additional Considerations

- A single dose of RSVPreF3, RSVpreF or mRNA-1345 can be used. Although NACI judged that all vaccines work well from a clinical perspective, there are less available data for the safety and efficacy of mRNA-1345 compared to the protein subunit vaccines.
- 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.

- 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 duration of protection and the need for and timing of any potential booster doses with any of the authorized adult RSV vaccine products

Summary of evidence and rationale:

- Evidence suggests that RSV severe clinical outcomes increase with increasing age and presence of chronic medical conditions.
- RSVPreF3, RSVpreF or mRNA-1345 have demonstrated protection against hospitalization and medically attended RSV in clinical trials. Post-market data have also shown effectiveness of RSVPreF3 and RSVpreF in phase IV studies.
- Although there were small increases in severe local and systemic adverse events for all three vaccines, they were shown to be safe and well tolerated.
- Preliminary data from multiple US post licensure safety platforms indicate that the risk of GBS may be increased following RSVpreF and RSVPreF3 vaccines in older adults. Studies with more robust designs to evaluate further are planned.

2. NACI continues to recommend RSV immunization programs for adults 60 years of age and older who are residents of nursing homes and other chronic care facilities. (Strong NACI recommendation)

Additional considerations:

- A single dose of RSVPreF3, RSVpreF or mRNA-1345 can be used. Although NACI judged that all vaccines work well from a clinical perspective, there are less available data for the safety and efficacy of mRNA-1345 compared to the protein subunit vaccines.
- NACI acknowledges the feasibility concerns of the different storage temperature of mRNA-1345, and supports jurisdictions to weigh this alongside other vaccine characteristics when considering product selection and program design.
- There is still uncertainty about the duration of protection and the need for and timing of any potential booster doses with any of the authorized adult RSV vaccine products

Summary of evidence and rationale:

- Residents of nursing homes and other chronic care facilities have a higher likelihood of RSV severe clinical outcomes compared to those with other living situations
- RSVPreF3, RSVpreF or mRNA-1345 have demonstrated protection against hospitalization and medically attended RSV in clinical trials. Post-market data have also shown effectiveness of RSVPreF3 and RSVpreF in phase IV studies.
- Although there were small increases in severe local and systemic adverse events for all three vaccines, they were shown to be safe and well tolerated.
- Preliminary data from multiple US post licensure safety platforms indicate that the risk of GBS may be increased following RSVpreF and RSVPreF3 vaccines in older adults. Studies with more robust designs to evaluate further are planned

Recommendations for individual level decision-making (i.e., healthcare providers advising individual clients and patients)

1. NACI recommends that RSV vaccines may be considered as an individual decision by adults 50-74 years of age with their health care provider. (Discretionary NACI recommendation)

Additional considerations:

- A single dose of RSVPreF3, RSVpreF or mRNA-1345 can be used in adults 60 to 74 years of age. A single dose of RSVPreF3 can be used in adults 50 to 74 years of age.
- There are more benefits from vaccination for individuals who are at increased risk of severe RSV disease as identified in List 1 (above).
- There is still uncertainty about the duration of protection and the need for and timing of any potential booster doses.

Summary of evidence and rationale:

- Evidence suggests that RSV severe clinical outcomes increase with increasing age and presence of chronic medical conditions
- RSVPreF3, RSVpreF or mRNA-1345 have demonstrated protection against hospitalization and medically attended RSV in clinical trials among adults 60 years of age and older. Post-market data have also shown effectiveness of RSVPreF3 and RSVpreF in phase IV studies.
- For adults 50 to 59 years of age, there are no efficacy data for RSVPreF3 and efficacy data from clinical trials are not anticipated for this population. Immunogenicity findings show that RSVPreF3 elicits a non-inferior immune response in adults 50 to 59 years of age compared to adults 60 years of age and over.
- Although there were small increases in severe local and systemic adverse events for all three vaccines, they were shown to be safe and well tolerated.
- Preliminary data from multiple US post licensure safety platforms indicate that the risk of GBS may be increased following RSVpreF and RSVPreF3 vaccines in older adults. Additional studies with robust designs are planned.

Research Priorities

Research to address the following outstanding questions is encouraged:

New and emerging research priorities

- Clarify any similarities and differences between RSV vaccines using different vaccine platforms (i.e.: protein subunit vs mRNA)
- Describe the burden of RSV disease and vaccine efficacy in adults 18 years of age and older with medical conditions

Standing research priorities

- Further clarify the burden of RSV disease including further exploration of risk factors for severe disease such as immunocompromise, and include previously underrepresented populations
- The 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
- Duration of protection for RSV vaccines for older adults
- Long term implications of RSV vaccines for older adults, including whether or not boosting can be achieved and if so, learn the optimal interval between doses
- Safety of RSV vaccines outside of the RCT setting
- Whether or not there is an association between GBS and RSV vaccination and RSV vaccination for patients with a history of GBS
- Safety, efficacy and effectiveness of concurrent administration of RSV vaccines for older adults with other vaccines for older adults
- Impacts on equity due to programs for RSV vaccines for older adults or lack thereof
- Acceptability and uptake of RSV vaccines for older adults

Tables

Table 2. 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.

Table 3. Summary of findings comparing mRNA-1345 to placebo in adults 60 years of age and older

Outcome	No. of studies (study design)	Summary of findings				Certainty
		No. of events/No. of participants		Effect		
		mRNA-1345	Placebo	Relative (95% CI)	Absolute (95% CI)	
Death due to RSV (follow up: median 8.6 months)	1 (RCT)	0/18,112 (0.0%)	0/18,045 (0.0%)	Not estimable		Moderate [a]
RSV RTI with ICU admission (follow up: median 8.6 months)	1 (RCT)	0/18,112 (0.0%)	0/18,045 (0.0%)	Not estimable		Moderate [a]

RSV RTI with hospitalization (follow up: median 8.6 months)	1 (RCT)	0/18,112 (0.0%)	2/18,045 (0.0%) 0.1% [b]	Peto OR 0.14 (0.01 to 2.16) VE 86% (-116 to 99)	10 fewer per 100,000 (from 11 fewer to 13 more) 87 fewer per 100,000 (from 99 fewer to 115 more)	Moderate [a,c]
Medically attended RSV RTI (follow up:median8.6 months)	1 (RCT)	5/18,112 (0.0%)	13/18,045 (0.1%)	Peto OR 0.41 (0.16 to 1.03)	42 fewer per 100,000 (from 61 fewer to 2 more)	Moderate [a]
Severe (Grade 3 and 4) systemic AEs (follow up: 4 days)	1 (RCT)	719/18,171 (4.0%)	513/18,101 (2.8%)	RR 1.40 (1.25 to 1.56)	1,134 per 100,000 (from 709 more to 1,587 more)	Moderate [a]
Severe (Grade 3 and 4) local AEs (follow up: 4 days)	1 (RCT)	561/18,171 (3.1%)	310/18,097 (1.7%)	RR 1.80 (1.57 to 2.07)	1,370 more per 100,000 (from 976 more to 1,833 more)	Moderate [a]

[a] Downrating by 1 for indirectness due to underrepresentation of adults 80 years of age and older (only 5.6% of study population).

[b] Seasonal incidence rate (baseline risk) of 145.5 RSV hospitalizations per 100,000 adults aged 60 years of age and older. This estimate is derived from ElSherif 2023[54].

[c] Certainty of evidence was assessed using the absolute effect calculate using baseline risk and not the placebo arm of the trial.

Table 4. Summary of findings comparing mRNA-1345 to placebo in adults 75 years of age and older

Outcome	**No. of studies (study design)**	**Summary of findings**				**Certainty**
		No. of events/No. of participants		**Effect**		
		mRNA-1345	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
Death due to RSV (follow up:	1 (RCT)	0/3,282 (0.0%)	0/3,280 (0.0%)	Not estimable		High

median 8.6 months)						
RSV RTI with ICU admission (follow up: median 8.6 months)	1 (RCT)	0/3,282 (0.0%)	0/3,280 (0.0%)	Not estimable		High
RSV RTI with hospitalization (follow up: median 8.6 months)	1 (RCT)	0/3,282 (0.0%)	1/3,280 (0.0%)	Peto OR 0.14 (0.00 to 6.82) VE 86% (-582 to 100)	26 fewer per 100,000 (from 30 fewer to 177 more)	High
Medically attended RSV RTI (follow up: median 8.6 months)	1 (RCT)	3/3,282 (0.1%)	2/3,280 (0.1%)	Peto OR 1.49 (0.26 to 8.61)	30 more per 100,000 (from 45 fewer to 462 more)	Low [b,c]
			2.5% [a]		1.180 more per 100,000 (from 1,838 fewer to 15,584 more)	
Severe (grade 3 and 4) systemic AEs (follow up: 4 days)	1 (RCT)	122/3,289 (3.7%)	114/3,289 (3.5%)	RR 1.07 (0.83 to 1.38)	243 more per 100,000 (from 589 fewer to 1,317 more)	Low [c]
Severe (grade 3 and 4) local AEs (follow up: 4 days)	1 (RCT)	87/3,289 (2.6%)	80/3,288 (2.4%)	RR 1.09 (0.81 to 1.47)	219 more per 100,000 (from 462 fewer to 1,144 more)	Low [c]

[a] Seasonal incidence rate (baseline risk) of 2,487.1 medically attended RSV RTIs requiring outpatient healthcare provider visit per 100,000 adults aged 80 years of age and older. This estimate is derived from ElSherif 2023[54], McLaughlin 2022[55], and data from RVDSS (average of 9 seasons, 2010/2011 to 2018/2019).

[b] Certainty of evidence was assessed using the absolute effect calculate using baseline risk and not the placebo arm of the trial.

[c] Downrating by 2 for imprecision as the width of the CI of the absolute effect contains estimates that differ in effect size interpretation from the point estimate.

Table 5. Solicited adverse events within 4 days after RSVPreF3 or placebo administration

Adverse Event	**50–59-non-AIR-RSV (N=377) n (%)**	**50–59-non-AIR-placebo (N=191) n (%)**	**50–59-AIR-RSV (N=379) n (%)**	**50–59-AIR-placebo (N=188)[a] n (%)**	60 years and older–RSV **(N=379) n (%)**
Administration-site adverse events					
Erythema					
Any	45 (11.9%)	1 (0.5%)	55 (14.5%)	1 (0.5%)	46 (12.1%)
Grade 3	0 (0.0%)	0 (0.0%)	4 (1.1%)	0 (0.0%)	3 (0.8%)
Pain					
Any	288 (76.4%)	20 (10.5%)	285 (75.2%)	26 (13.8%)	232 (61.2%)
Grade 3	12 (3.2%)	1 (0.5%)	14 (3.7%)	0 (0.0%)	8 (2.1%)
Swelling					
Any	35 (9.3%)	2 (1.0%)	44 (11.6%)	1 (0.5%)	29 (7.7%)
Grade 3	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Systemic adverse events					
Arthralgia					

Any	98 (26.0%)	11 (5.8%)	79 (20.8%)	19 (10.1%)	49 (12.9%)
Grade 3	6 (1.6%)	0 (0.0%)	7 (1.8%)	3 (1.6%)	4 (1.1%)
Fatigue					
Any	165 (43.8%)	33 (17.3%)	136 (35.9%)	36 (19.0%)	90 (23.7%)
Grade 3	13 (3.4%)	1 (0.5%)	8 (2.1%)	2 (1.1%)	7 (1.8%)
Fever					
Any	14 (3.7%)	2 (1.0%)	10 (2.6%)	2 (1.1%)	6 (1.6%)
Grade 3	1 (0.3%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
Headache					
Any	135 (35.8%)	32 (16.8%)	105 (27.7%)	32 (16.9%)	80 (21.1%)
Grade 3	13 (3.4%)	2 (1.0%)	7 (1.8%)	2 (1.1%)	3 (0.8%)
Myalgia					
Any	147 (39.0%)	11 (5.8%)	122 (32.2%)	26 (13.8%)	80 (21.1%)
Grade 3	10 (2.7%)	0 (0.0%)	9 (2.4%)	2 (1.1%)	3 (0.8%)

[a] N=189 for systemic adverse events.

Abbreviations: AIR, at-increased-risk; N, number of participants with available results; n (%), number (percentage) of participants in the indicated category; 50–59-non-AIR-RSV/placebo, group of 50–59-year-old participants without increased risk for respiratory syncytial virus (RSV) disease who received RSV prefusion F protein-based vaccine (RSVPreF3)/placebo; 50–59-AIR-RSV/placebo, group of 50–59-year-old participants at increased risk for RSV disease who received RSVPreF3/placebo; 60 years and older–RSV, group of participants aged 60 years and older who received RSVPreF3.

Source: Table adapted from Supplementary Table 2 by Ferguson et al. 2024[25]

Table 6. Serious Adverse Events, and Potential Immune-Mediated Diseases (pIMDs) After RSVPreF3 or Placebo Administration (Exposed Population)

Adverse Event	50–59-non-AIR-RSV (N=383) n (%)	50–59-non-AIR-placebo (N=192) n (%)	50–59-AIR-RSV (N=386) n (%)	50–59-AIR-placebo (N=191) n (%)	60 years and older–RSV (N=381) n (%)
SAEs and pIMDs within 6 months					
Any SAE	2 (0.5%)	4 (2.1%)	14 (3.6%)	4 (2.1%)	9 (2.4%)
Any pIMDs[a]	0 (0.0%)	0 (0.0%)	4 (1.0%)	1 (0.5%)	3 (0.8%)
Related or fatal SAEs and related pIMDs until data lock point					
Related SAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Fatal SAE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Related pIMDs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)

[a] Reported pIMDs were new-onset pericarditis, new-onset spondylitis, worsening of pre-existing gouty arthritis, and worsening of pre-existing gout in the 50–59-AIR-RSV group, pericarditis in the 50–59-AIR-placebo group, and new-onset cold-type hemolytic anemia, new-onset polymyalgia rheumatica, and worsening of pre-existing psoriasis in the 60 years and older–RSV group.

Abbreviations: AIR, at-increased-risk; N, number of participants in the exposed population; n (%), number (percentage) of participants in the indicated category; pIMD, potential immune-mediated disease; SAE, serious adverse event; 50–59-AIR-RSV, group of 50–59-year-old participants at increased risk for respiratory syncytial virus (RSV) disease who received RSV prefusion F protein–based vaccine (RSVPreF3); 50–59-non-AIR-RSV, group of 50–59-year-old participants without increased risk for RSV disease who received RSVPreF3; 60 years and older–RSV, group of participants aged 60 years and older who received RSVPreF3.

Source: Table adapted from Table 3 by Ferguson et al. 2024[25]

Table 7. Summary of Participants with Solicited Adverse Reactions within 7 Days after Vaccination by Grade (Solicited Safety Set).

Solicited Adverse Reaction Category	mRNA-1345, 50 µg (N=17,665) n (%)	Placebo (N=17,598) n (%)
Solicited adverse reactions – N1[a]	17,665	17,598
Any	-	-
Grade 3	1069 (6.1)	685 (3.9)
Grade 4	35 (0.2)	29 (0.2)

Solicited local adverse reactions – N1 [a]	17,662	17,593
Any	-	-
Grade 3	558 (3.2)	305 (1.7)
Grade 4	0	0
Pain – N1 [a]	17,661	17,593
Any	9942 (56.3)	2407 (13.7)
Grade 3 [b]	307 (1.7)	192 (1.1)
Grade 4	0	0
Erythema (Redness) – N1 [a]	17,659	17,592
Any	357 (2.0)	101 (0.6)
Grade 3 [b]	105 (0.6)	57 (0.3)
Grade 4	0	0
Swelling (Hardness) – N1 [a]	17,660	17,592
Any	662 (3.7)	59 (0.3)
Grade 3 [b]	154 (0.9)	17 (<0.1)
Grade 4	0	0
Axillary (underarm) swelling or tenderness – N1 [a]	17,659	17,592
Any	2711 (15.4)	1091 (6.2)
Grade 3 [b]	138 (0.8)	115 (0.7)
Grade 4	0	0
Solicited systemic adverse reactions – N1 [a]	17,662	17,597
Any	-	-
Grade 3	675 (3.8)	479 (2.7)
Grade 4	35 (0.2)	29 (0.2)
Fever – N1 [a]	17,651	17,593
Any	501 (2.8)	234 (1.3)
Grade 3 [b]	77 (0.4)	41 (0.2)
Grade 4 [b]	35 (0.2)	29 (0.2)

Headache – N1 [a]	17,658	17,592
Any	4764 (27.0)	3332 (18.9)
Grade 3	276 (1.6)	210 (1.2)
Grade 4	0	0
Fatigue – N1 [a]	17,658	17,592
Any	5470 (31.0)	3518 (20.0)
Grade 3 [b]	310 (1.8)	215 (1.2)
Grade 4	0	0
Myalgia – N1 [a]	17,658	17,592
Any	4574 (25.9)	2542 (14.4)
Grade 3 [b]	255 (1.4)	153 (0.9)
Grade 4	0	0
Arthralgia – N1 [a]	17,658	17,591
Any	3867 (21.9)	2477 (14.1)
Grade 3 [b]	197 (1.1)	136 (0.8)
Grade 4	0	0
Nausea/vomiting – N1 [a]	17,658	17,591
Any	1248 (7.1)	933 (5.3)
Grade 3 [b]	80 (0.5)	75 (0.4)
Grade 4	0	0
Chills – N1 [a]	17,658	17,591
Any	2045 (11.6)	1181 (6.7)
Grade 3 [b]	108 (0.6)	79 (0.4)
Grade 4	0	0

[a] N1, number of exposed participants who submitted any data for the event. Any refers to Grade 1 or above. Percentages were based on the number of exposed participants who submitted any data for the event (N1). The only solicited systemic adverse reaction reported in any participant at Grade 4 was fever, which was defined as oral temperature >40.0°C/>104.0°F. Grade 4 fever was reported for 35 participants in the mRNA-1345 group versus 29 participants in the placebo group (0.2% of participants in each group)
[b] The data presented in the table is as of the cutoff date of November 30, 2022. However, updated information was received from Moderna through personal communication[36] regarding severe local and systemic adverse events within seven days of injection.

Abbreviations: N, number of participants in the exposed population; n (%), number (percentage) of participants in the indicated category.

Source: Table adapted from Table S12 by Wilson et al. 2023[15].

Table 8. Overall Summary of Unsolicited AEs within 28 Days after Injection (Safety Set).

Adverse event	mRNA-1345, 50 µg (N=17,734) n (%)	Placebo (N=17,679) n (%)
SAEs and fatal AEs up to 28 days after vaccination[a]		
Any SAE	102 (0.6)	93 (0.5)
Fatal	2 (<0.1)	4 (<0.1)
Any pIMDs	Not reported	Not reported
Related SAEs and related fatal AEs up to 28 days after vaccination		
Related SAE	4 (<0.1)	3 (<0.1)
Related Fatal AE	0	0
Related pIMDs	Not reported	Not reported

[a] The data presented in the table is as of the cutoff date of November 30, 2022. However, updated information was presented at the June 26 ACIP meeting[18], regarding unsolicited adverse events after injection regardless of relationship to vaccine/placebo.

Abbreviations: SAE, serious adverse event; AE, adverse event; pIMD, potential immune-mediated disease.

Source: Table adapted from Table S13 by Wilson et al. 2023[15].

Table 9. 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.

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices

AE	Adverse event
AESI	Adverse events of special interest
AIR	At-increased-risk
AReSVi-006	Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults Study
ASC	Advisory Committee Statement
CDC	U.S. Centers for Disease Control and Prevention
CHF	Congestive heart failure
CI	Confidence interval
CIG	Canadian Immunization Guide
CMC	Chronic medical condition
ConquerRSV	Efficacy and Safety of an mRNA-Based RSV PreF Vaccine in Older Adults Study
COPD	Chronic obstructive pulmonary disease
ED	Emergency department
EEFA	Ethics, equity, feasibility, and acceptability
ESRD	End stage renal disease
EtD	Evidence to decision
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
GMR	Geometric mean ratio
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSK	GlaxoSmithKline
HCT	Hematopoietic cell transplantation
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IRR	Incidence rate ratio
ITP	Immune thrombocytopenia
IIV4	Quadrivalent inactivated influenza vaccine
IVY	Influenza and Other Viruses in the Acutely Ill
mRNA-1345	Respiratory Syncytial Virus mRNA Vaccine
N	Number of Participants
NACI	National Advisory Committee on Immunization
NOC	Notice of Compliance
OR	Odds ratio
PHAC	Public Health Agency of Canada
Phase I/II RCT	Phase 2/3 randomized controlled trial
Phase II/III RCT	Phase 1/2 randomized controlled trial
Phase III RCT	Phase 3 randomized controlled trial
pIMDs	Potential immune-mediated disorders
PPV	Positive predictive value
QALY	Quality-adjusted life year
RCT	Randomized controlled trial

RENOIR	RSV Vaccine Efficacy Study in Older Adults Immunized against RSV Disease
RR	Relative risk
RSV	Respiratory syncytial virus
RSVpreF vaccine	Respiratory syncytial virus prefusion F subunit vaccine
RSVPreF3 vaccine	Respiratory syncytial virus prefusion F3 subunit vaccine
RTI	Respiratory tract infection
RVDSS	Respiratory Virus Detection Surveillance System
RZV	Recombinant zoster vaccine
SAE	Serious adverse event
SCCS	Self-control case series
VAERS	Vaccine Adverse Reporting System
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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NACI RSV Working Group

Members: N Brousseau (Chair), M Andrew, A Britton (Centers for Disease Control and Prevention, US), T Bogler, S Buchan,, M Cao, J Jones (Centers for Disease Control and Prevention, US), S McNeil, M Melgar, D Money, D Moore, D Moulia (Centers for Disease Control and Prevention, US), J Papenburg, E Rafferty, J Robinson, and F Schwarz.

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NACI Members: R Harrison (Chair), V Dubey (Vice-Chair), M Andrew, J Bettinger, N Brousseau, A Buchan, H Decaluwe, P De Wals, E Dubé, K Hildebrand, K Klein, M O'Driscoll, J Papenburg, A Pham-Huy, B Sander, and S Wilson.

Liaison Representatives: L Bill/ M Nowgesic (Canadian Indigenous Nurses Association), S Buchan (Canadian Association for Immunization Research, Evaluation and Education) E Castillo (Society of Obstetricians and Gynaecologists of Canada), J Comeau (Association of Medical Microbiology and Infectious Disease Control), M Lavoie (Council of Chief Medical Officers of Health), J MacNeil (Center for Disease control and Prevention), M McIntyre (Canadian Nurses Association), D Moore (Canadian Paediatric Society), M Osmack (Indigenous Physicians Association of Canada), J Potter (College of Family Physicians of Canada), A Pucci (Canadian Public Health Association), D Singh (Canadian Immunization Committee), and E Zannis (Canadian Pharmacists Association).

Ex-Officio Representatives: E Ebert (National Defence and the Canadian Armed Forces), P Fandja (Marketed Health Products Directorate, Health Canada), K Franklin (Centre for Emerging and Respiratory Infections and Pandemic Preparedness (CERIPP), PHAC), E Henry (Centre for Immunization Surveillance and Programs (CISP), PHAC), M Lacroix (Public Health Ethics Consultative Group, PHAC), J Stothart (Vaccine Safety Surveillance, Centre for Immunization Surveillance and Programs (CISP), PHAC), J Kosche (Centre for Vaccines and Therapeutics Readiness (CVTR), PHAC), C Pham (Biologic and Radiopharmaceutical Drugs Directorate, Health Canada), M Routledge (National Microbiology Laboratory, PHAC), and T Wong (First Nations and Inuit Health Branch, Indigenous Services Canada).

References

1. Ismail S, Hardy K, Tunis M, et al. A framework for the systematic consideration of ethics, equity, feasibility, and acceptability in vaccine program recommendations. *Vaccine.* 2020 Aug 10;38(36):5861-5876. http://doi.org/10.1016/j.vaccine.2020.05.051.

2. *Review Manager (RevMan) [Computer program]*. Version Version 5.4. The Cochrane Collaboration; 2020.

3. Alonso-Coello P, Schünemann HJ, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ.* 2016 Jun 28;353http://doi.org/10.1136/bmj.i2016.

4. Public Health Agency of Canada (PHAC). Respiratory syncytial virus (RSV) vaccines: Canadian Immunization Guide [Internet]. Ottawa (ON). Government of Canada; 2024 Nov 19 [cited November 21, 2024]. Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/respiratory-syncytial-virus.html.

5. Abrams EM, Doyon-Plourde P, Davis P, et al. Burden of disease of respiratory syncytial virus in older adults and adults considered at high risk of severe infection. *Canada Communicable Disease Report.* 51-1

6. GlaxoSmithKline Inc. AREXVY (respiratory syncytial virus [RSV] vaccine, recombinant, $AS01_E$ adjuvanted) product monograph [Internet]. Ontario. GlaxoSmithKline Inc.; 2024 Nov 1 [cited 2024 May 30]. Available from: https://pdf.hres.ca/dpd_pm/00077616.PDF.

7. Pfizer Canada ULC. ABRYSVO™ (respiratory syncytial virus stabilized prefusion F subunit vaccine) product monograph [Internet]. Quebec. Pfizer Canada; 2023 Dec 21 [cited 2024 May 30]. Available from: https://pdf.hres.ca/dpd_pm/00073900.PDF.

8. Moderna Biopharma Canada Corporation. mRESVIA (respiratory synticial virus [RSV] mRNA vaccine) product monograph [Internet]. Toronto, ON. Moderna Biopharma Canada Corporation; 2024 Nov 6 [cited November 21, 2024]. Available from: https://pdf.hres.ca/dpd_pm/00077692.PDF.

9. National Advisory Committee on Immunization (NACI). Statement on the prevention of respiratory syncytial virus (RSV) disease in older adults [Internet]. Ottawa (ON). Public Health Agency of Canada; 2024 Jul 12 [cited November 20, 2024]. Available from: https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/national-advisory-committee-immunization-statement-prevention-rsv-disease-older-adults.html.

10. Walsh E, Pérez Marc G, Zareba A, et al. Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults. *The New England Journal of Medicine.* 2023 Apr 20;388(16):1465-1477. http://doi.org/10.1056/NEJMoa2213836.

11. Papi A, Ison M, Langley J, et al. Respiratory syncytial virus prefusion F protein vaccine in older adults. *The New England Journal of Medicine.* 2023 Feb 16;388(7):595-608. http://doi.org/10.1056/NEJMoa2209604.

12. Pfizer. Personal communication. RSV adults dossier. 2024 Apr 1.

13. Pfizer. Pfizer announces positive top-line data for full season two efficacy of ABRYSVO for RSV in older adults [Internet]. 2024 Feb 29 [cited 2024 May 30]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-top-line-data-full-season-two.

14. Ison M, Papi A, Athan E, et al. Efficacy and safety of respiratory syncytial virus prefusion F protein vaccine (RSVPreF3 OA) in older adults over 2 RSV seasons. *Clinical Infectious Diseases.* 2024 Jan 22;http://doi.org/10.1093/cid/ciae010.

15. Wilson E, Goswami J, Baqui AH, et al. Efficacy and safety of an mRNA-based RSV PreF vaccine in older adults. *New England Journal of Medicine.* 2023 Dec 14;389(24):2233-2244. http://doi.org/10.1056/nejmoa2307079.

16. Moderna. Personal Communication. Request for age stratified data: Vaccines to protect older adults from RSV. 2024 Jan 15.

17. Moderna. Personal Communication. RSV-NACI Queries_1-11-23. November 11, 2023.

18. Das R. Update on Moderna's RSV vaccine, mRESVIA (mRNA-1345), in adults ≥60 years of age [slides presented at the Advisory Committee on Immunizatino Practices meeting on June 26, 2024] [Internet]. Atlants (GA) CDC; 2024 Jun 26 [cited October 8, 2024.] Available from: https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/04-RSV-Adult-Das-508.pdf.

19. Das R. RSV vaccine (mRESVIA, mRNA-1345) concomitant administration overview [slides presented at the Advisory Committee on Immunization Practices meeting on October 24, 2024] [Internet]. Atlanta (GA): CDC; 2024 Oct 24 [cited December 11, 2024.] Available from: https://www.cdc.gov/acip/downloads/slides-2024-10-23-24/02-RSV-Adult-Das-508.pdf.

20. Ison M, Papi A, Athan E, et al. The efficacy of a single dose of the respiratory syncytial virus prefusion F protein vaccine in adults ≥60 years of age over 3 RSV seasons [poster presentation at CHEST conference on October 6-9, 2024] [Internet]. Boston (MA): 2024 Oct 6-9 [cited October 8, 2024.] Available from: https://assets.gskstatic.com/corporate/Congress/2024/CHEST/DV-010326.pdf.

21. Surie D. Effectiveness of adults respiratory syncytial virus (RSV) vaccines, 2023-2024 [slides presented at the Advisory Committee on Immunization Practices meeting on June 26, 2024] [Internet]. Atlanta (GA): CDC; 2024 Jun 26 [cited October 11, 2024.] Available from: https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/07-RSV-Adult-Surie-508.pdf.

22. Surie D, Self WH, Zhu Y, et al. RSV Vaccine Effectiveness Against Hospitalization Among US Adults 60 Years and Older. *JAMA.* September 4, 2024;332(13):1105-1107. (IVY). http://doi.org/10.1001/jama.2024.15775. https://doi.org/10.1001/jama.2024.15775.

23. Payne A, Watt J, Mitchell P, et al. Respiratory syncytial virus (RSV) vaccine effectiveness against RSV-associated hospitalisations and emergency department encounters among adults aged 60 years and older in the USA, October, 2023, to March, 2024: a test-negative design analysis. *The Lancet.* 2024 Oct 19;404(10462):1547-1559. http://doi.org/10.1016/S0140-6736(24)01738-0.

24. Gerber S. GSK's RSVPreF3 + $AS01_E$ vaccine (AREXVY) [slides presented at the Advisory Committee on Immunization Practices meeting on October 25, 2023] [Internet]. Atlanta (GA): CDC; 2023 Oct 25 [cited November 22, 2024.] Available from: https://www.cdc.gov/acip/downloads/slides-2023-10-25-26/02-gerber-adult-RSV-508.pdf.

25. Ferguson M, Schwarz TF, Núñez SA, et al. Noninferior immunogenicity and consistent safety of respiratory syncytial virus prefusion F protein vaccine in adults 50–59 years compared to ≥60 years of age. *Clinical Infectious Diseases.* 2024 Aug 5;79(4):1074-1084. http://doi.org/10.1093/cid/ciae364.

26. King D, Groves H, Weller C, et al. Realising the potential of correlates of protection for vaccine development, licensure and use: short summary. *NPJ Vaccines.* 2024 Apr 29;9(1):82. http://doi.org/10.1038/s41541-024-00872-6.

27. Falsey A, Walsh E, Scott D, et al. Phase 1/2 randomized study of the immunogenicity, safety, and tolerability of a respiratory syncytial virus prefusion F vaccine in adults with concomitant inactivated influenza vaccine. *The Journal of Infectious Diseases.* 2022 Jun 25;225(12):2056-2066. http://doi.org/10.1093/infdis/jiab611.

28. Pfizer. Respiratory syncytial virus stabilized bivalent prefusion F subunit vaccine (RSVpreF / ABRYSVO) [briefing document provided at the Vaccines and Related Biological Products Advisory Committee meeting on March 1, 2023] [Internet]. FDA; 2023 Mar 1 [cited November 19, 2024.] Available from: https://www.fda.gov/media/165625/download.

29. GlaxoSmithKline. Immunogenicity, safety, reactogenicity and persistence of an investigational respiratory syncytial virus (RSV) vaccine in adults aged 60 years and above [Internet]. ClinicalTrials.gov; 2023 Dec 21 [cited 2024 May 30]. Available from: https://clinicaltrials.gov/study/NCT04732871.

30. Friedland L. GSK's RSVPreF OA vaccine (AREXVY) [slides presented at the Advisory Committee on Immunization Practices meeting on June 21, 2023] [Internet]. Atlanta (GA): CDC; 2023 Jun 21 [cited November 19, 2024.] Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-06-21-23/03-RSV-Adults-Friedland-508.pdf.

31. Schwarz T, Hwang S, Ylisastigui P, et al. Immunogenicity and safety of a second dose of the respiratory syncytial virus (RSV) prefusion F protein vaccine (RSVPreF3 OA), 12 months after the first dose in adults ≥ 60 years. presented at: [presented at the 9th European Scientific Working Group on Influenza (ESWI) Influenza Conference]; 2023 Sep 20 2023 Sep 20; Valencia. https://s3.eu-central-1.amazonaws.com/eswi.org/downloads/ESWI2023_abstractbook.pdf

32. Das R. Overview of Moderna's investigational RSV vaccine (mRNA-1345 in adults ≥60 years of age [slides presented at the Advisory Committee on Immunization Practices meeting on October 24, 2024] [Internet]. Atlanta (GA): CDC; 2024 Feb 29 [cited October 8, 2024.] Available from: https://www.cdc.gov/acip/downloads/slides-2024-02-28-29/02-RSV-Adults-Das-508.pdf.

33. Goswami J, Cardona JF, Hsu DC, et al. Safety and immunogenicity of mRNA-1345 RSV vaccine coadministered with an influenza or COVID-19 vaccine in adults aged 50 years or older: an observer-blinded, placebo-controlled, randomised, phase 3 trial. *The Lancet Infectious Diseases.* November 25, 2024;doi: 10.1016/S1473-3099(24)00589-9. http://doi.org/10.1016/S1473-3099(24)00589-9. https://doi.org/10.1016/S1473-3099(24)00589-9.

34. Dennis P, Roussy J, Gupta A, et al. Co-adminsitration of the adjuvanted respiratory syncytial virus (RSV) prefusion F protein vaccine (RSVPreF3 OA) with the adjuvanted recombinant zoster vaccine (RZV) in adults ≥ 50 years of age [poster presented at EuGMS CONGRESS on September 18-19, 2024] [Internet]. Valencia, Spain: 2024 Sep 18-19 [cited November 20, 2024.] Available from: https://posterit.it/get-posters/PRKZWDTHJGSYANMI/en.

35. Administration USFD. FDA Requires Guillain-Barré Syndrome (GBS) Warning in the Prescribing Information

for RSV Vaccines Abrysvo and Arexvy Internet. U.S. Food & Drug Administration; January 7, 2025 [cited January 16, 2025]. Available from: https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-requires-guillain-barre-syndrome-gbs-warning-prescribing-information-rsv-vaccines-abrysvo-and.

36. Moderna. Personal Communication. RSV - NACI Queries 11212023. November 22, 2023.

37. Donahue J. Update: Rapid cycle analysis of RSV vaccine in older adults [slides presented at the Advisory Committee on Immunization Practices meeting on June 26, 2024] [Internet].

Atlanta (GA): CDC; 2024 Jun 26 [cited November 22, 2024.] Available from: https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/05-RSV-Adult-Donahue-508.pdf.

38. Lloyd P. Evaluation of Guillain-Barré syndrome (GBS) following respiratory syncytial virus (RSV) vaccination among adults 65 years and older [slides presented at the Advisory Committee on Immunization Practices meeting on October 24, 2024] [Internet]. Atlanta (GA): CDC; 2024 Oct 24 [cited November 22, 2024.] Available from: https://www.cdc.gov/acip/downloads/slides-2024-10-23-24/05-RSV-Adult-Lloyd-508.pdf.

39. LLoyd P. Evaluation of Guillain-Barré syndrome (GBS) following respiratory syncytial virus (RSV) vaccination among adults 65 years and older [slides presented at the Advisory Committee on Immunization Practices meeting on June 26, 2024] [Internet]. Atlanta (GA): CDC; 2024 Jun 26 [cited November 22, 2024.] Available from: https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/06-RSV-Adult-Lloyd-508.pdf.

40. Hause AM, Moro PL, Baggs J, et al. Early safety findings among persons aged ≥60 years who received a respiratory syncytial virus vaccine — United States, May 3, 2023–April 14, 2024. *Morbidity and Mortality Weekly Report.* 2024 May 30;73(21):489-494. http://doi.org/10.15585/mmwr.mm7321a3.

41. Britton A, Roper LE, Kotton CN, et al. Use of Respiratory Syncytial Virus Vaccines in Adults Aged ≥60 Years: Updated Recommendations of the Advisory Committee on Immunization Practices - United States, 2024. *MMWR Morb Mortal Wkly Rep.* Aug 15;73(32):696-702. http://doi.org/10.15585/mmwr.mm7332e1. https://www.ncbi.nlm.nih.gov/pubmed/39146277.

42. National Advisory Committee on Immunization (NACI). Statement on the prevention of respiratory syncytial virus (RSV) disease in infants [Internet]. Ottawa (ON). Public Health Agency of Canada; 2024 May 17 [cited 2024 May 30]. Available from: https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/vaccines-immunization/national-advisory-committee-immunization-statement-prevention-respiratory-syncytial-virus-disease-infants/naci-statement-2024-05-17.pdf.

43. Moro P, Gallego R, Scheffey A, et al. Administration of the GSK respiratory syncytial virus vaccine to pregnant persons in error. *Obstetrics and Gynecology.* 2024 May 1;143(5):704-706. http://doi.org/10.1097/AOG.0000000000005551.

44. Moro P, Scheffey A, Gallego R, et al. Incorrect administration of adult RSV vaccines to young children. *Pediatrics.* 2024 May 9;153(6)http://doi.org/10.1542/peds.2024-066174.

45. Tuite AR, Simmons AE, Rudd M, et al. Respiratory syncytial virus vaccination strategies for older Canadian adults: a cost–utility analysis. *Canadian Medical Association Journal.* 2024 Sep 09;196(29):E989-E1005. http://doi.org/10.1503/cmaj.240452.

46. Crawford R, Bailey S, Cornelissen T. CADTH health technology review: Cost-effectiveness of respiratory syncytial virus vaccines for adults. *Canadian Journal of Health Technologies.* 2024 Feb 26;4(2), https://www.cadth.ca/sites/default/files/hta-he/HE0047-RSV-Vaccines-For-PHAC.pdfhttps://www.cadth.ca/sites/default/files/hta-he/HE0047-RSV-Vaccines-For-PHAC.pdf.

47. Hutton D. Economic analysis of RSV vaccination in Adults 50 years and older [slides presented at the Advisory Committee on Immunization Practices meeting on June 26, 2024] [Internet]. Atlanta (GA): CDC; 2024 Jun 26 [cited October 11, 2024.] Available from: https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/08-RSV-Adult-Hutton-508.pdf.

48. Ortega-Sanchez IR. Economics of respiratory syncytial virus (RSV) vaccination in all U.S. adults ≥75 years-old, and adults aged 60-74 and 5059 years at increased risk [slides presented at the Advisory Committee on Immunization Practices meeting on June 26, 2024] [Internet]. Atlanta (GA): CDC; 2024 Jun 26 [cited October 11, 2024.] Available from:

https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/10-RSV-Adult-Ortega-Sanchez-508.pdf.

49. Singer D. et al [GSK]. Presented by: Ortega-Sanchez IR. Economics of respiratory syncytial virus (RSV) vaccination in all U.S. adults ≥75 years-old, and adults aged 60-74 and 5059 years at increased risk [slides presented at the Advisory Committee on Immunization Practices meeting on June 26, 2024] [Internet]. Atlanta (GA): CDC; 2024 Jun 26 [cited October 11, 2024.] Available from: https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/10-RSV-Adult-Ortega-Sanchez-508.pdf.

50. Ghaswalla P. et al. [Moderna]. Presented by: Ortega-Sanchez IR. Economics of respiratory syncytial virus (RSV) vaccination in all U.S. adults ≥75 years-old, and adults aged 60-74 and 5059 years at increased risk [slides presented at the Advisory Committee on Immunization Practices meeting on June 26, 2024] [Internet]. Atlanta (GA): CDC; 2024 Jun 26 [cited October 11, 2024.] Available from: https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/10-RSV-Adult-Ortega-Sanchez-508.pdf.

51. Bank of Canada. Annual exchange rates Internet. Bank of Canada; [cited January 15, 2025]. Available from: https://www.bankofcanada.ca/rates/exchange/annual-average-exchange-rates/.

52. Britton A, Melgar M, Roper L. Evidence to Recommendations Framework (EtR): RSV Vaccination in Adults Aged 50–59 years,

60–74 years, and 75 years and older [slides presented at the Advisory Committee on Immunization Practices meeting on June 26, 2024] Atlanta (GA): CDC; June 26, 2024 [cited January 15, 2025.] Available from: https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/11-RSV-Adult-Melgar-Roper-Britton-508.pdf.

53. Statistics Canada. Number and percentage of adults (aged 18 years and older) in the household population with underlying health conditions, by age and sex (two-year period) Internet. Statistics Canada; [cited January 5, 2025]. Available from: https://www150.statcan.gc.ca/n1/en/catalogue/13100777.

54. ElSherif M, Andrew M, Ye L, et al. Leveraging influenza virus surveillance from 2012 to 2015 to characterize the burden of respiratory syncytial virus disease in Canadian adults ≥50 years of age hospitalized with acute respiratory illness. *Open Forum Infectious Diseases.* 2023 Jun 13;10(7)http://doi.org/10.1093/ofid/ofad315.

55. McLaughlin J, Khan F, Begier E, et al. Rates of medically attended RSV among US adults: A systematic review and meta-analysis. *Open Forum Infectious Diseases.* 2022 Jun 17;9(7)http://doi.org/10.1093/ofid/ofac300.