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

Statement on the prevention of respiratory syncytial virus (RSV) disease in older adults

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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.

1. What

Respiratory syncytial virus (RSV) is a common respiratory virus, and infants and older adults are at higher risk 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 (including death and admission to hospital or intensive care units [ICU] due to age, medical conditions, setting and other potential factors. Health Canada has recently authorized two vaccines, both based on the prefusion stabilized F protein (preF), to protect adults from RSV:

- RSVPreF3 (Arexvy, GSK) is an AS01$_E$ adjuvanted vaccine authorized with an indication for all adults 60 years of age and over.
- RSVpreF (Abrysvo™, Pfizer) is an unadjuvanted vaccine authorized with an indication for all adults 60 years of age and over. This formulation is also authorized for pregnant women and pregnant people who are 32 to 36 weeks of gestation to protect infants from RSV.

2. Who

NACI recommends RSV 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 recommends that RSV vaccines may be considered as an individual decision by adults 60 to 74 years of age in consultation with their health care provider. 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 deferring vaccination with their health care providers 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.

The RSV vaccine 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 (prior to the COVID-19 pandemic, the RSV season was typically November to April).

3. How

RSVPreF3 is administered intramuscularly using single dose vials of lyophilized powder which is reconstituted at the time of use with the accompanying vial of AS01E adjuvant suspension. A single 0.5mL dose of RSVPreF3 is authorized for administration in adults 60 years of age and older.

RSVpreF is administered intramuscularly using single dose vials of lyophilized powder which is reconstituted with sterile water (diluent) in a prefilled syringe. A single 0.5mL dose of RSVpreF is authorized for administration in adults 60 years of age and older.

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. However, according to findings from 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 it is possible 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. Additional research is ongoing to further inform guidance on same-day administration of the RSV vaccine and other adult vaccines, including the COVID-19 vaccine. If possible, RSV vaccine should be given at least 6 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.

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

4. Why

RSV accounts for a significant burden of disease in older adults. RSV disease can have serious complications for older adults, 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. Both RSVpreF and RSVPreF3 may 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 or those living in chronic care facilities, is cost-effective and may promote health equity.

Introduction

Guidance Objective:

The need for NACI guidance for RSV older adult vaccines arose from the development and authorizations of two new products with indications to protect older adults. On August 4, 2023, Health Canada authorized the use of RSVPreF3 (AREXVY, GSK) a novel adjuvanted subunit protein vaccine indicated for the protection of adults 60 years of age and older. On December 21, 2023, Health Canada authorized the use of RSVpreF (ABRYSVO™, Pfizer), a similar novel unadjuvanted subunit protein vaccine indicated for the protection of adults 60 years of age and older.

This is the first NACI statement to provide recommendations for the prevention of RSV in older adults. NACI recently updated recommendations for the prevention of RSV 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 RSV immunization programs in Canada
- describe the ethics, equity, feasibility, and acceptability considerations for RSV immunization programs
- provide recommendations for the use of RSVPreF3 and RSVpreF 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.

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.

Methods

In brief, the broad stages in the preparation of a 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 RSVpreF and RSVPreF3 vaccines, evidence synthesis, including meta-analysis when appropriate and assessment of the quality of the evidence by the NACI Secretariat – summarized in the Summary of findings tables 2 to 5
3. Synthesis of the body of evidence of benefits and harms of RSVpreF and RSVPreF3 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 a systematic review, *de novo* model-based economic evaluation, and a multi-model comparison of RSVpreF and RSVPreF3 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. The full framework and accompanying tools will be available on the NACI webpage in the near future.

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]. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology were prepared [3,4].

An assessment using the Evidence to Decision (EtD) framework was prepared for the main program decision on age and risk were developed [5]. The NACI Vaccine Safety Working Group reviewed and discussed the evidence on the safety of RSVpreF and RSVPreF3 vaccines in adults on January 29 and March 4, 2024. The Working Group chair and PHAC medical specialist

presented the evidence and proposed recommendations to NACI on April 16, 2024. Following thorough review of the evidence and consultation at the NACI meeting of April 16, 2024, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the text.

The policy questions addressed in this statement are:

1. What is the best use of RSV vaccines (i.e., RSVpreF and RSVPreF3) for adults 60 years of age and older (e.g., 60 to 64, 65 to 69, 70 to 74, 75 to 79 and 80 years of age and older)?
2. What is the best use of RSV vaccines (i.e., RSVpreF and RSVPreF3) for adults 60 years of age and older considered at increased risk of severe RSV infection?

I. Epidemiology

RSV is an enveloped RNA virus classified within the *Paramyxoviridae* family. There are two subgroups based on differences in the G surface protein. The F surface protein has more limited variability between RSV A and B subgroups. Humans are the only source of infection and transmission occurs from direct or indirect exposure to respiratory secretions containing the virus.

RSV is a common respiratory virus, with higher risk groups including infants, older adults, and persons with comorbidities including cardiopulmonary disease and immunocompromise [6-8]. Patients who reside in chronic care facilities have a higher likelihood of severe clinical outcomes, including death, compared to patients with other living situations upon hospital admission [7]. Primary infection does not confer protective immunity against reinfections, which recur throughout life and become more serious with advanced age in older adults. A rapid review demonstrated increased risk of severe RSV disease with increasing age and risk factors among older adults, and the rapid review was supplemented with Canadian healthcare administrative data [9]. RSV is not a notifiable disease in Canada and representative national active surveillance data on RSV infection is limited, possibly leading to underestimation of RSV burden of disease in Canada. A detailed publication of these results is available in the Canadian Communicable Disease Report (CCDR) and a summary of this rapid review is presented below [9].

III.1 Medically attended RSV infection

Medically attended RSV infections are common in older adults, and incidence increases with increasing age. A systematic review of high-income countries including Canada found that among adults 60 years of age and older, RSV caused 4.7% of symptomatic respiratory infections in annual studies and 7.8% in seasonal studies [10]. A United States (US) systematic review and meta-analysis found that rates of medically attended RSV infection increased from 934 per 100,000 in adults 18 to 49 years of age to 1,519 per 100,000 in adults 65 years of age and older [11]. In a US community cohort, relative risk of a serious outcome for medically attended RSV was significantly increased in those 75 years and older (compared to 60 to 64 years) [12]. Although evidence is more limited, studies suggest that the incidence of medically attended RSV in younger adults (18 to 59 years) with underlying conditions is in the same range as for older adults [9].

III.2 Hospitalization associated with RSV infection

While incidence of hospitalization varies between studies, risk of hospitalization increases consistently with increasing age [9]. In one prospective Canadian surveillance study of adults 50 years and older hospitalized with respiratory illness, pooled RSV hospitalization rates per 100,000 population were: 13.9 in ages 50 to 59 years, 43.7 in ages 60 to 69 years, 88.6 in ages 70 to 79 years and 282.5 in ages 80 years and older [7]. In a US population-based hospital surveillance system, among older adults with RSV-associated hospitalization, 54% were 75 years of age and older [13]. Hospitalization data from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) similarly demonstrated across 12 seasons an increased risk of hospitalization with increasing age [9,14]. The average rate of hospitalization associated with RSV per 100,000 population by age groups were the following: 4 in adults 50 to 59 years old, 10 in adults 60 to 69 years old, 22 in adults 70 to 79 years old, and 63 in adults 80 years of age and older [9,14].

Depending on age and risk factors, adults 18 years and older with comorbidities were 1.2 to 28 times more likely to be hospitalized due to RSV [11]. A Canadian study found that 26.8% of adults 50 years of age and older who had a hospitalization associated with RSV over the 2012-2015 seasons had immunocompromising conditions and almost all (98.1%) had at least one comorbidity with the most frequent being vascular (71.3%), cardiac (55.5%), pulmonary (48.2%), renal (48.2%) and endocrine (33.2%) conditions [7]. A population-based study from Ontario of RSV-associated adult hospitalizations found that 52.6% resided in long-term care or received home care in the year prior to index date [15]. A US surveillance study found that patients who resided in long-term care or other chronic care facilities had a 4.43 times higher likelihood of severe outcomes, including ICU admission or death, compared to patients with other living situations at admission [16]. Data from the CIHI DAD across 12 seasons demonstrated that of adults 18 years of age and older hospitalized with RSV, 76.4% had at least one risk factor, 34.6% had at least two risk factors, and 9.1% had at least three [9,14].

III.3 Intensive care admission associated with RSV infection

Overall, ICU admission associated with RSV increases with increasing age, with approximately 10% of older adults hospitalized with RSV requiring ICU admission [9]. In one Canadian study, risk of ICU admission and mechanical ventilation was similar to that of influenza [7]. Risk also increases with the presence of comorbidities [9]. A systematic review from high-income countries found a higher proportion of adults 18 years of age and older with high-risk conditions were admitted to the ICU, required oxygen use, and were discharged to care compared to adults 60 years of age and older without high-risk conditions [10]. Data from the CIHI DAD demonstrated across 12 seasons that 10% of hospitalizations due to RSV required ICU admission, with increasing rate of admission with increasing age [9,14].

III.4 Death associated with RSV infection

There were more limited data on burden of death associated with RSV [9]. Case fatality rate among those admitted to hospital who are older adults or at higher risk varies between studies but is approximately 5 to 10% and increases with increasing age and presence of comorbidities [9]. In a multivariable analysis of a Canadian prospective study among patients hospitalized with acute respiratory illness, adults 75 years of age and older were more likely to succumb to their illness than RSV-negative comparators in the same age group [7]. A US prospective cohort found that death associated with RSV was higher in the group admitted from long-term care facilities (38%) than in the group admitted from the community (3%) [17]. Data from the CIHI DAD

demonstrated an in-hospital case fatality rate of 6%, with the average rate of in-hospital deaths associated with RSV increasing with increasing age [9,14].

II. Vaccine

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

Characteristics of the RSV vaccine(s) currently authorized for use in Canada to prevent RSV disease in older adults are summarized in Table 1.

Table 1. Comparison of vaccines authorized for use in Canada

	AREXVY (RSVPreF3) [18]	ABRYSVO™ (RSVpreF) [19]
Manufacturer	GlaxoSmithKline (GSK)	Pfizer
Date of authorization in Canada	August 4, 2023	December 21, 2023
Type of vaccine	Stabilized subunit vaccine	Stabilized subunit vaccine
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), 22.5 mg mannitol, 0.08 mg polysorbate 80, 1.1 mg sodium chloride, 11.3 mg sucrose, 0.11 mg tromethamine, 1.04 mg trometamol hydrochloride reconstituted with sterile water as the diluent
Schedule	1- dose schedule	1- dose schedule
Route of administration	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	Authorized for the prevention of lower respiratory tract disease caused by RSV in individuals 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

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 women and pregnant people, nor on the excretion of Arexvy in human or animal milk. Arexvy is not recommended for use during pregnancy or in breast-feeding/lactating women.	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.
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.

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

IV.2 Efficacy

The evidence suggests that RSVpreF and RSVPreF3 may result in similar reductions in hospitalizations associated with RSV and medically attended RSV RTI for adults 60 years of age and older. However, there was limited evidence on the effect of these vaccines against death due to RSV and ICU admission associated with RSV. Larger populations may be needed to observe and assess these severe clinical outcomes. As no head-to-head trials currently exist comparing these products, there are important limitations to comparing across RSV vaccine trials for different products due to differences in trial design, including clinical endpoints and follow-up time.

Evidence on the efficacy of RSVpreF, an unadjuvanted bivalent prefusion F protein vaccine administered for the prevention of severe clinical outcomes due to RSV in older adults was derived from two randomized controlled trials (RCTs). One phase I/II RCT [20] was conducted among healthy adults 60 years of age and older, including those with preexisting stable disease (defined as disease not requiring any significant change in therapy or hospitalization in the past six weeks) who received 120µg RSVpreF (n=52) or placebo (n=53).

One phase III RCT (RENOIR) [21,22] was conducted among healthy adults 60 years of age and older, including those with preexisting stable disease (defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the six weeks before enrollment) who received RSVpreF (n=18,058) or placebo (n=18,076). Of these participants, 5,797 were 75 years of age or older (n=2,903 who received placebo and n=2,894 who received RSVpreF). Although participants were eligible for enrollment if they were in assisted living or long-term care facilities that provided minimal assistance, such that the participant is primarily responsible for self-care and activities of daily living, data stratified by type of residence is not available.

Evidence on the efficacy of RSVPreF3, an AS01E adjuvanted prefusion F protein vaccine administered for the prevention of severe clinical outcomes due to RSV in older adults was derived from two RCTs. One phase I/II RCT [23] was conducted among older adults 60 to 80 years of age, including patients with chronic stable conditions with or without specific treatment, such as diabetes, hypertension, or cardiac disease, who received 120µg of AS01E adjuvanted RSVPreF3 (n=100) or placebo (n=101). One phase III RCT (AReSVi-006) [24] was conducted among adults 60 years of age or older, including persons with chronic medical conditions considered stable by the investigators who received RSVPreF3 (n=12,467) or placebo (n=12,499). Of these participants, 5,317 were 75 years of age or older (n=2,646 who received placebo and n=2,671 who received RSVPreF3). Around 300 participants from long-term care facilities were included, although specific efficacy data in this population is not available.

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

IV.2.1 Efficacy of RSVpreF and RSVPreF3 vaccines against death due to RSV

There is no evidence on the efficacy of RSVpreF and RSVPreF3 vaccines for the prevention of death due to RSV infection among adults 60 years of age and older.

There were no deaths due to RSV in the two RCTs evaluating the efficacy of RSVpreF in this population (n=36,238; 18,110 in the RSVpreF group and 18,128 in the placebo group) through to the end of the first RSV season (Table 2) [20,22]. Moreover, there were no deaths due to RSV reported in the two RCTs evaluating the use of RSVPreF3 in this population (n=25,160; 12,566 in the RSVPreF3 group and 12,594 in the placebo group) through the end of the second RSV season (Table 4) [23,25].

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. Therefore, the evidence for both RSVpreF and RSVPreF3 preventing death due to RSV were downgraded due to indirectness (Table 2 and Table 4).

IV.2.2 Efficacy of RSVpreF and RSVPreF3 vaccines against RSV respiratory tract infection with ICU admission

There is limited evidence on the efficacy of RSVpreF and RSVPreF3 vaccines for the prevention RSV RTI with ICU admission among adults 60 years of age and older.

No ICU admissions occurred in the phase III RCT evaluating the efficacy of RSVpreF among older adults (n=36,134; 18,058 in the RSVpreF group and 18,076 in the placebo) [Table 2] [22]. No data were provided on RSV RTI with ICU admission in the RSVpreF vaccine phase I/II RCT [20].

There was one participant in the placebo group admitted to ICU in the phase III RCT evaluating the efficacy of RSVPreF3 in adults 60 years of age and older (n=24,960; 12,466 in the RSVPreF3 group and 12,494 in the placebo group), corresponding to a vaccine efficacy (VE) of 86% (95% confidence interval [CI]: -584 to 100%) [Table 4] [26]. In adults 75 years of age and older, there were no ICU admissions reported (Table 5) [26]. No data were provided on RSV RTI with ICU admission in the RSVPreF3 phase I/II RCT [23].

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. Therefore, the evidence for both RSVpreF and RSVPreF3 preventing RSV RTI with ICU admission were downgraded due to indirectness (Table 2, Table 4 and Table 5).

IV.2.3 Efficacy of RSVpreF and RSVPreF3 vaccines against RSV respiratory tract infection with hospitalization

The available evidence from one season of data 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 is very uncertain. The evidence is limited due to the small number of events reported in each trial.

In adults 60 years of age and older, one phase III RCT evaluating the efficacy of RSVpreF vaccine against RSV RTI with hospitalization reported 2 cases among 36,134 participants, all in placebo recipients (VE: 86%; 95% CI: -117 to 99%) [Table 2] [22]. In adults 75 years of age and older, there were no RSV RTIs with hospitalization reported (Table 3) [27]. No data were provided on RSV RTI with hospitalization in the RSVpreF vaccine phase I/II RCT [20].

One phase III RCT evaluating the efficacy of RSVPreF3 vaccine against RSV RTI with hospitalization reported 3 cases among 12,494 placebo recipients and none in the RSVPreF3 recipients (VE: 86%; 95% CI: -30 to 99%) [Table 4] [28]. In adults 75 years of age and older, there were no RSV RTIs with hospitalization reported (Table 5) [29]. No data were provided on RSV RTI with hospitalization in the RSVPreF3 phase I/II RCT [23].

IV.2.4 Efficacy of RSVpreF and RSVPreF3 vaccines against medically attended RSV respiratory tract infection

The available evidence from one season of data suggests that RSVpreF and RSVPreF3 RSV vaccines likely result in a similar reduction in the risk of medically attended RSV RTI in older adults. However, the evidence is limited due to the small number of events reported for each vaccine. For RSVpreF, the manufacturer outcome of first episode of RSV lower respiratory tract infections with two or more symptoms that prompted any healthcare visit(s) was used to represent cases of medically attended RSV RTI. For RSVPreF3, the manufacturer outcome of medically attended RSV lower respiratory tract disease was used to represent cases of medically attended RSV RTI.

In clinical testing of RSVpreF in adults over 60 years of age, there were 35 cases of medically attended RSV RTI in one phase III RCT including 8 cases in the RSVpreF group (n=18,058) and 27 in placebo recipients (n=18,076), which corresponds to a VE of 66% (95% CI: 34 to 83%) [22]. In adults 75 years of age and older (n=5,797; 2,894 in the RSVpreF group and 2,903 in the placebo group), the VE against medically attended RSV RTI was 78% (95% CI: 11 to 94%) [27]. The evidence in this age group was deemed at moderate certainty due to imprecision (Table 3). No data were provided on medically attended RSV RTI in the RSVpreF vaccine phase I/II RCT [20].

In clinical testing of RSVPreF3 in adults over 60 years of age, one RCT reported 27 cases; 3 in the RSVPreF3 group (n=12,466) and 24 in the placebo (n=12,494), corresponding to a VE of 79% (95% CI: 55 to 90%) [28]. Among adults 75 years of age and older (n=5,317; 2,671 in the RSVPreF3 group and 2,646 in the placebo group), the efficacy of RSVPreF3 at preventing medically attended RSV RTIs was 49% (95% CI: -152 to 90%) [29]. The certainty of evidence in this population was deemed low due to imprecision (Table 5). No data was provided on medically attended RSV RTI in the RSVPreF3 phase I/II RCT [23].

IV.2.5 Efficacy of RSVpreF and RSVPreF3 vaccines during a second RSV season

Although not included in the GRADE analysis, NACI reviewed the available data on the efficacy of both RSV vaccines through a second RSV season [25,30,31]. While Pfizer continued disease surveillance for outcomes of interest over 16.4 months, GSK continued year-round disease surveillance for a medium follow up time of 18 months. Evidence is limited; however, early data suggests that through two RSV seasons, efficacy against RSV disease may be maintained for both vaccines. However, when considering season 2 efficacy alone, VE was lower than season 1 VE estimates and combined season 1 and season 2 VE estimates for both individuals who received a single dose and those who were revaccinated in advance of their second RSV season.

For RSVpreF, the manufacturer outcome of first episode of RSV lower respiratory tract infections with two or more symptoms was used to assess efficacy in a second RSV season. For RSVPreF3, the manufacturer outcome of RSV lower respiratory tract disease and medically attended RSV lower respiratory tract disease were used to assess efficacy in a second RSV season. VE estimates for both individuals who received a single dose and those who were revaccinated in advance of their second RSV season are included, where available.

Adults 60 years of age and older who received the RSVpreF vaccine had a combined season 1 and season 2 VE of 58.8% (95% CI: 43.0 to 70.6%) against RSV-associated lower respiratory tract disease [30]. However, when considering season 2 alone, VE was 55.7% (95% CI: 34.7 to 70.4%) [30]. Data are not available on the efficacy of RSV vaccines against medically attended RSV lower respiratory tract disease during a second season. Due to a limited number of cases, the VE could not be calculated in a second RSV season for RSV hospitalizations, RSV admissions to ICU, or deaths due to RSV.

Similarly, adults 60 years of age and older who received RSVPreF3 vaccine in advance of season 1 had a combined season 1 and season 2 VE against first occurrence of RSV lower respiratory tract disease of 74.5% (95% CI: 60.0 to 84.5%) [25]. However, when considering season 2 alone, VE was 56.1% (95% CI: 28.2 to 74.4%) [25]. GSK looked simultaneously at VE following revaccination in advance of season 2. For individuals who received a second dose of RSVPreF3 ahead of season 2, season 2 VE against first occurrence of RSV lower respiratory

tract disease was 55.9% (95% CI: 27.9 to 74.3%) [25]. In other words, efficacy was identical in those who did or did not receive a booster dose prior to season 2. The efficacy of RSVPreF3 vaccination against medically attended RSV lower respiratory tract disease over 2 RSV seasons was 73.1% (95% CI: 49.4 to 86.9%) [25]. Due to a limited number of cases, VE could not be calculated in a second RSV season for RSV hospitalizations, RSV admissions to ICU, or deaths due to RSV.

The efficacy of these vaccines beyond season 1 (including for season 2) are not yet clear and NACI will continue to monitor emerging evidence as it becomes available.

IV.3 Immunogenicity

NACI reviewed the available evidence on immunogenicity of RSVpreF and RSVPreF3 in the context of revaccination schedules, although this outcome was not included in the GRADE analysis. Studies for RSVpreF and RSVPreF3 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 [32]. In addition, several trials have studied the immunogenicity of RSVpreF and RSVPreF3 following revaccination, however clarity around the boostability of this immune response remains unclear. Both Pfizer and GSK are exploring longer intervals between doses (e.g., revaccination at 24 months post-dose 1).

In Pfizer's phase I/II RCT described above [20], an additional dose of RSVpreF 12 months after dose one increased neutralizing titre levels, but they remained below increases observed following dose one [33]. Similarly, in a phase III immunogenicity RCT evaluating revaccination with RSVPreF3 at 12-months post-dose one [34], a smaller booster effect was observed. Serum neutralizing titres were slightly boosted, but they were below titres observed one month after the first dose [35,36].

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.4 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 [19].

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 60 years of age and older is 1 dose. Please see the product monograph for more details [18].

There is limited efficacy and immunogenicity data supporting the need for revaccination. Studies for RSVpreF and RSVPreF3 demonstrate waning of immune responses after the first dose and the boostability of this immune response remains unclear (see IV.3 Immunogenicity above). At this time, RSV vaccines are approved and recommended to be administered as a single dose.

IV.5 Storage requirements

RSVpreF should be refrigerated at 2°C to 8°C. Do not freeze; discard if the vaccine has been frozen. Store the vaccine in the original carton to protect it from light. After reconstitution, RSVpreF should be stored between 15°C and 30°C and administered within 4 hours [19].

RSVPreF3 should be refrigerated at 2°C to 8°C. Do not freeze; discard if the vial has been frozen. Store the vaccine in the original package to protect it from light. After reconstitution, RSVPreF3 can be store in the refrigerator (2°C to 8°C) or at room temperature up to 25°C and administered within 4 hours [18].

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. However, according to 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 flu 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. Additional research is ongoing to further inform guidance on same-day administration of the RSV vaccine and other adult vaccines, including COVID-19 vaccines. If possible, RSV vaccine 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.

RSVpreF

RSVpreF is an unadjuvanted recombinant protein subunit vaccine and is not live. Concurrent administration of RSVpreF to adults 60 years of age and older 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 [37].

Concurrent administration of RSVpreF with standard-dose adjuvanted quadrivalent seasonal inactivated influenza vaccine (IIV4-Adj), in healthy participants 65 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-Adj and RSVpreF vaccines. The geometric mean ratios (GMRs) at 1 month after vaccination for concurrent (RSVpreF and IIV4-Adj) to sequential (RSVpreF alone 1 month after IIV4-Adj) were 0.86 (95% CI: 0.77 to 0.96) for A/Victoria/2570/2019 (H1N1), 0.77 (95% CI: 0.68 to 0.87) for A/Darwin/9/2021 (H3N2), 0.90 (95% CI: 0.79 to 1.02) for B/Austria/1359417/2021 (B/Victoria lineage), 0.87 (95% CI: 0.78 to 0.96) for B/Phuket/3073/2013 (B/Yamagata lineage), 0.86 (95% CI, 0.79 to 0.95) for RSV A, and 0.85 (0.77 to 0.94) for RSV B [38,39]. 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-Adj and RSVpreF.

Concurrent administration of RSVpreF with the tetanus, diphtheria, and acellular pertussis vaccine (Tdap) in healthy, non-pregnant women 18 to 49 years of age has been shown to be safe and immunogenicity data demonstrated non-inferiority was met for the tetanus and diphtheria components of the Tdap vaccine, as well as the RSV-A and RSV-B components of

the RSVpreF vaccine. See the NACI Statement on the prevention of respiratory syncytial virus (RSV) disease in infants for more information.

No data are available on concurrent administration of RSVpreF with vaccines other than Tdap and standard dose adjuvanted influenza vaccine in adults.

RSVPreF3

RSVPreF3 is an adjuvanted recombinant protein subunit vaccine and is not live. Concurrent administration of RSVPreF3 to adults 60 years of age and older 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 [37].

Several studies have looked at concurrent administration of RSVPreF3 with various influenza vaccine formulations. Concurrent administration of RSVPreF3 with a quadrivalent inactivated influenza vaccine (IIV4), in adults 60 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 RSVPreF3 vaccines. The GMRs at 1 month after vaccination for concurrent (RSVPreF3 and IIV4) to sequential (RSVPreF3 alone 1 month after IIV4) were 1.17 (95% CI: 1.02 to 1.35) for A/Hong Kong/2671/2019 (H3N2), 1.22 (95% CI:1.03 to 1.44) for A/Victoria/2570/2019 (H1N1), 1.17 (95% CI: 1.04 to 1.32) for B/Phuket/3073/2013 (B/Yamagata lineage), 1.10 (95% CI: 0.95 to 1.26) for B/Washington/02/2019 (B/Victoria lineage), 1.27 (95% CI: 1.12 to 1.44) for RSV A, and 1.27 (95% CI: 1.08 to 1.49) for RSV B [39,40]. Thus, compared with a pre-specified criterion of an upper CI limit of 1.5, non-inferiority was established for all components.

Concurrent administration of RSVPreF3 with an adjuvanted quadrivalent influenza vaccine (IIV4-Adj), in adults 65 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-Adj and RSVPreF3 vaccines. The GMRs at 1 month after vaccination for concurrent (RSVPreF3 and IIV4-Adj) to sequential (RSVPreF3 alone 1 month after IIV4-Adj) were 1.31 (95% CI: 1.13 to 1.52) for A/Darwin/9/2021 (H3N2), 1.03 (95% CI: 0.91 to 1.18) for A/Victoria/2570/2019 (H1N1), 0.97 (95% CI: 0.89 to 1.05) for B/Austria/1359417/2021 (B/Victoria lineage), 1.04 (95% CI: 0.95 to 1.12) for B/Phuket/3073/2013 (B/Yamagata lineage), 0.98 (95% CI: 0.87 to 1.11) for RSV A, and 1.16 (95% CI: 1.03 to 1.31) for RSV B [35,39]. Thus, compared with a pre-specified criterion of an upper CI limit of 1.5, non-inferiority was established for all components except A/Darwin/9/2021 (H3N2).

Concurrent administration of RSVPreF3 with a high-dose quadrivalent inactivated influenza vaccine (IIV4-HD) in adults 65 years of age and older has been shown to be safe and immunogenicity data demonstrated non-inferiority for all components of the IIV4-HD and RSVPreF3 vaccines. The GMRs at 1 month after vaccination for concurrent (RSVPreF3 and IIV4-HD) to sequential (RSVPreF3 alone 1 month after IIV4-HD) were 0.98 (95% CI: 0.84 to 1.14) for A/Darwin/9/2021 (H3N2), 0.93 (95% CI: 0.80 to 1.08) for A/Victoria/2570/2019 (H1N1), 0.95 (95% CI: 0.88 to 1.03) for B/Austria/1359417/2021 (B/Victoria lineage), 0.92 (95% CI: 0.84 to 1.02) for B/Phuket/3073/2013 (B/Yamagata lineage), 1.18 (95% CI: 1.04 to 1.35) for RSV A, and 1.02 (95% CI: 0.89 to 1.16) for RSV B [35,39]. Thus, compared with a pre-specified criterion of an upper CI limit of 1.5, non-inferiority was established for all components.

No data are currently available on concurrent administration of RSVPreF3 with vaccines other than seasonal inactivated influenza vaccines.

Not all of these influenza vaccines may be available in Canada.

IV.7 Vaccine safety

Evidence for the safety of RSVpreF [20,21] and RSVPreF3 [23,24] vaccines in adults 60 years of age and older were derived from RCTs previously described and preliminary post-marketing safety surveillance data [41-43]. Age stratified safety data were only available from the phase III RCT of RSVpreF [21,27] and RSVPreF3 [24,29].

Overall, RSVpreF and RSVPreF3 were well-tolerated with an acceptable safety profile among adults 60 years of age and older. In RCTs, most (greater than 95%) of reported adverse events (AEs) were mild to moderate for RSVpreF and RSVPreF3 vaccines. The available evidence suggests that RSVpreF may result in a slight increase in severe local AEs and little to no difference in severe systemic AEs compared to placebo. For RSVPreF3, data suggest that vaccination results in a slight increase in severe local and systemic AEs compared to placebo.

Among adults 60 years of age and older, the proportions of participants reporting at least one serious adverse event (SAE) were similar between RSVpreF or RSVPreF3 and placebo groups. However, a small imbalance in atrial fibrillation events (20 cases in RSV vaccine recipients versus 8 cases in placebo recipients) and 6 cases of inflammatory neurologic events were reported after RSV vaccination in clinical trials. Early post-marketing safety data from the United States also suggest a potential increased rate of Guillain-Barré syndrome (GBS) after administration of RSVpreF or RSVPreF3 vaccines in adults 60 years of age and older [41,42]. However, the current available preliminary data are subject to limitations. Additional analyses are planned to further assess this potential increased risk of GBS. NACI continues to carefully monitor the evidence on the safety of RSVpreF and RSVPreF3 vaccines in adults and will update guidance accordingly. Details are presented below.

IV.7.1 Local adverse events following immunization reported in RCTs

In the phase III RCTs among adults 60 years of age and older, the proportion of participants reporting at least one local AE were relatively similar between RSVpreF and placebo groups (12.2% vs. 6.7%) but were higher among RSVPreF3 (62.2% vs. 10.0%) vaccine recipients compared to placebo recipients [44,45]. Overall, the most frequent local AE reported was pain at the injection site (10.6% in RSVpreF and 6.0% placebo group from Pfizer RCT and 60.9% in RSVPreF3 and 9.3% in placebo group from GSK RCT). However, the majority of local AEs were mild to moderate in intensity (98.2% in RSVpreF and 99.1% in placebo group from Pfizer RCT vs 98.0% RSVPreF3 and 100% in placebo group from GSK RCT) with low incidence of severe local AEs.

In Pfizer's phase III RCT, 8 (0.2%) participants in the RSVpreF group 60 years of age and older reported at least one severe local AE compared to 2 (0.1%) participants in the placebo group [44]. No participants from Pfizer's phase I/II RCT reported a severe local AE [46]. A meta-analysis of these 2 RCTs did not demonstrate a significant increase in the risk of severe local AEs with RSVpreF compared to placebo (pooled odds ratio [OR]: 3.25; 95% CI; 0.94 to 11.24). Among adults 75 years of age and older, there was no severe local AE reported in Pfizer's phase III RCT [27]. The certainty of evidence in this population was deemed moderate due to imprecision related to the small sample size (Table 3).

Overall, 18 (1.8%) severe local AEs were reported among participants in the RSVPreF3 group 60 years of age and older, including 13 (1.5%) from the phase III and 5 (5%) from the phase I/II RCT [45,47]. No participants in the placebo group from either GSK's RCTs reported a severe local AE. A meta-analysis of these 2 RCTs demonstrated a significant increase in severe local AEs associated with RSVPreF3 vaccine when compared to a placebo (pooled OR:7.55; 95% CI: 2.98 to 19.11). Among adults 75 years of age and older, 3 (1.4%) participants in the RSVPreF3 group and none in the placebo group reported a severe local AE [29]. In GSK's phase III RCT, RSVPreF3 was not associated with a significant increased risk of severe local AEs compared to placebo (OR: 7.70; 95% CI: 0.80 to 74.4). The certainty of evidence was deemed moderate due to imprecision (Table 5).

IV.7.2 Systemic adverse events following immunization reported in RCTs

Although similar, there were some nuanced differences between the reported systemic AEs following immunizations with RSVpreF and RSVPreF3. For Pfizer's phase III RCT of RSVpreF for adults 60 years of age and older, the proportions of participants reporting at least one systemic AE were similar between RSVpreF (27.5%) and placebo (25.7%) recipients [48]. In GSK's phase III RCT of RSVPreF3 for adults 60 years of age and older, systemic AEs were reported more frequently among RSVPreF3 (49.4%) participants compared to placebo (23.2%) recipients [47,49]. Overall, the most frequent systemic AEs reported were fatigue (15.5% in RSVpreF and 14.4% in placebo group from Pfizer RCT and 33.6% in RSVPreF3 and 16.1% in placebo group from GSK RCT) and headache (12.8% in RSVpreF and 11.7% in placebo group from Pfizer RCTs and 27.2% in RSVPreF3 and 12.6% in placebo group from GSK RCT). However, the majority of systemic AEs reported in Pfizer's and GSK's RCTs were mild to moderate (97.3% in RSVpreF and 97.7% in placebo group from Pfizer RCT and 96.7% in RSVPreF3 and 99.1% in placebo group from GSK RCT) in intensity with severe systemic AEs being less frequently reported.

In Pfizer's phase III and phase I/II RCTs for adults 60 years of age and older, 28 (0.8%) participants in the RSVpreF groups compared to 23 (0.6%) participants in the placebo groups reported at least one severe systemic AE in Pfizer's phase III and phase I/II RCTs [46,48]. The most frequently reported severe systemic AE was fatigue. A meta-analysis of the 2 RCTs found that there was no difference in the risk of severe systemic AEs with RSVpreF vaccine when compared to placebo (pooled OR: 1.19; 95% CI: 0.69 to 2.07). Among adults 75 years of age and older, 3 (0.5%) participants in RSVpreF group and none in the placebo group reported a severe systemic AE [27]. In Pfizer's phase III RCT among adults 75 years of age and older, RSVpreF was not associated with a significant increase in the risk of severe systemic AEs compared to placebo, (OR: 7.17; 95% CI: 0.74 to 69.06). The certainty of evidence was deemed moderate due to imprecision (Table 3).

In GSK's phase III and phase I/II RCTs for adults 60 years of age and older, 31 (3.2%) participants in the RSVPreF3 groups compared to 9 (0.9%) participants in the placebo groups reported at least one severe systemic AE [47,50]. The most frequently reported severe systemic AEs were fatigue, myalgia, headache, and arthralgia. A meta-analysis of the 2 RCTs demonstrated an increased risk of severe systemic AEs with RSVPreF3 compared to placebo (pooled risk ratio [RR]: 3.42; 95% CI: 1.63 to 7.16). Among adults 75 years of age and older, 5 (2.3%) participants in the RSVPreF3 group and 4 (1.8%) participants in the placebo group reported a severe systemic AE [29]. In GSK's phase III RCT, there was no difference in the risk of severe systemic AEs with RSVPreF3 vaccine when compared to placebo in adults 75 years of

age and older (RR: 1.29; 95% CI, 0.35 to 4.74). The certainty of evidence was deemed low due to imprecision (Table 5).

IV.7.3 Serious adverse events following immunization

Among adults 60 years of age and older, the proportions of participants reporting at least one SAE were similar between RSVpreF (2.3% vs. 2.3%) or RSVPreF3 (4.9% vs. 4.9%) and placebo groups [46,47,51,52]. However, a small imbalance in atrial fibrillation events (10 in vaccine group compared to 4 in placebo group of Pfizer trials and also GSK trials) and six cases of neuroinflammatory events were reported after RSV vaccination in clinical trials. The available data were insufficient to definitively confirm if atrial fibrillation or neuroinflammatory events (e.g., GBS or acute disseminated encephalomyelitis [ADEM]) is associated with RSV vaccination.

In Pfizer's phase III and phase I/II RCTs, the proportion of SAEs reported were similar in the RSVpreF (2.3%) and placebo (2.3%) groups [46,51]. Overall, a higher number of participants in the RSVpreF group (10 events; less than 0.1%) compared to the placebo group (4 events; less than 0.1%) reported atrial fibrillation within 30 days of vaccination, of which 7 were considered SAEs (4 in the RSVpreF group vs 3 in the placebo group) [46,53]. Among those who reported atrial fibrillation, a medical history of atrial fibrillation was reported by 6 (60%) RSVpreF recipients and 2 (50%) placebo recipients.

Also, in Pfizer's phase III and phase I/II RCTs, 3 neuroinflammatory events were reported within 42 days of vaccination among 18,622 participants in the RSVpreF group [54,55]. Conversely, none were reported in the placebo group (n=18,335). The events included one case of GBS with onset at 14 days following vaccination in a 66 years old participant from the United States, one case of Miller Fisher syndrome with onset at 10 days following vaccination in a 66 years old participant from Japan, and one case of undifferentiated motor-sensory axonal polyneuropathy with worsening of preexisting symptoms 21 days after vaccination in a 68 years old participant from Argentina [54,55].

In GSK's phase III and phase I/II RCTs, the proportion of SAEs reported were similar in the RSVPreF3 (4.9%) and placebo (4.9%) groups [47,52]. Within 30 days of vaccination, a higher number of participants in the RSVPreF3 (10 events; 0.1%) group reported atrial fibrillation compared to the placebo group (4 events; less than 0.1%); of those 8 were SAEs (7 in the RSVPreF3 group vs 1 in the placebo group) [56]. All atrial fibrillation SAEs occurred in participants with relevant predisposing medical conditions and risk factors.

Across all GSK's phase III and phase I/II RCTs, 3 neuroinflammatory events were reported within 42 days of vaccination among 17,922 RSVPreF3 recipients [57,58]. The events occurred in two phase III RCTs but neither had a placebo arm as a comparator [34,59]. One case of GBS with onset at 9 days following vaccination occurred in a 78 year old participant from Japan from an open label RCT evaluating the safety and immunogenicity of one dose compared to revaccination with RSVPreF3 vaccine at 12 and/or 24 months following the first dose [34,60]. Two unconfirmed cases of ADEM occurred in a co-administration study with standard dose inactivated influenza vaccine (IIV), both were based on clinical findings and symptoms leading to uncertainty in the diagnoses [59,60]. One case with onset at 7 days following co-administration of RSVPreF3 and IIV was in a 71 year old participant from South Africa who died 22 days after the co-administration of the study vaccines. The other case was in a 71 year old participant from

South Africa with onset at 22 days following the co-administration of the study vaccines. Of note, the diagnoses were later updated by the investigator to hypoglycemia and dementia for the fatal case and stroke for the non-fatal case rather than ADEM [57].

IV.7.4 Post-marketing safety surveillance data

In February 2024, the US Centers for Disease Control and Prevention (CDC) and US Food and Drug Administration (FDA) shared preliminary post-licensure data on the safety of RSV vaccines derived from multiple vaccine safety surveillance platforms [41,42]. As of February 3, 2024, a total of 9,651,744 doses of RSVpreF (n=3,063,832) and RSVPreF3 (n=6,587,912) had been administered. Local and systemic symptoms (e.g., fatigue) were the most reported AEs following RSV vaccination in adults 60 years of age and older [41]. Data from the Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Datalink (VSD) and FDA suggest a potential increased rate of GBS after administration of RSVpreF or RSVPreF3 vaccines in adults 60 years of age and older. However, these estimates are based on preliminary post-marketing safety surveillance data subject to limitations. Additional analyses are planned to further assess this potential increased risk.

As of February 16, 2024, there were 23 verified reports of GBS within 42 days of RSV vaccination observed through VAERS [41]. Of those, 15 were following RSVpreF vaccination, including 4 reports which had respiratory symptoms within 4 weeks prior to GBS onset, and 8 were following RSVPreF3 vaccination. Other vaccines (i.e., influenza, mRNA COVID-19, rabies, pneumococcal, Tdap or Zoster vaccines) were given during the same visit in 14 of the 23 GBS reports (9 involving RSVpreF and 5 involving RSVPreF3 vaccinations) [41]. Data from VAERS and FDA suggest a potential increased rate of GBS after administration of either RSV vaccine. Current estimates in both surveillance systems suggest that the risk following RSVpreF may be higher than the risk following RSVPreF3 vaccination. However, additional analyses with more reported cases are needed to better assess the product-specific risks. Early estimates from VSD also suggest a potential increased rate for GBS following RSVPreF3 vaccination [41]. The risk following RSVpreF could not be efficiently assessed as insufficient doses of RSVpreF vaccine were administered in VSD.

The benefit and risk assessment of RSV vaccines based on the latest available data may indicate that, from a population perspective, the estimated benefits of RSV vaccination continue to outweigh the potential risk of GBS in adults 60 years of age and older [43]. The benefits of RSV vaccination likely vary by age group and individual-level risk of severe RSV disease with increasing benefits observed among older individuals and those with underlying medical condition placing them at higher risk of complications. However, there are limitations (e.g., inconsistent data quality and completeness, small number of reported cases, concurrent administration of other vaccines, reporting bias) to the current data leading to substantial uncertainty in the estimates of both benefits and risks of RSV vaccination. Additional analyses are planned to further assess this potential increased risk of GBS following RSV vaccination in adults 60 years of age and older.

NACI continues to carefully monitor the evidence on the use of RSVpreF and RSVPreF3 vaccines in adults as more data become available and will update guidance accordingly.

IV.8 Contraindications and precautions

RSVpreF and RSVPreF3 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 has 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 [61].

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 [62,63]. 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 individuals previously infected with RSV

Most individuals are infected with RSV by the time they are 2 years of age. RSV immunization should be administered regardless of previous infection status. For guidance on the immunization of individuals with acute illness, please refer to the Canadian Immunization Guide chapter on Contraindications and precautions.

III. Ethics, equity, feasibility and acceptability considerations

V.1 Ethics considerations

NACI evaluated the following ethical considerations when making its recommendations: promoting well-being and minimizing risk of harm; maintaining trust; respect for people and fostering autonomy; and promoting justice and equity. In developing these recommendations, no significant ethical issues were identified by NACI other than the equity considerations discussed below.

V.2 Equity considerations

NACI considered age-based as well as medical and social risk-based RSV vaccine recommendations for older adults. Equity could be increased with an age-based recommendation, given that there are fewer barriers to access with an age-based recommendation, such as, for example, an increased diversity of settings for vaccination and increased ease of determining eligibility. Furthermore, an age-based recommendation would capture those individuals with medical conditions placing them at increased risk of severe RSV disease who have not been diagnosed. However, equity could also potentially be increased through a risk-based recommendation, given that older adults at greater risk of severe illness would be prioritized.

NACI also evaluated equity considerations when interpreting the epidemiological, clinical, and economic evidence, including intersecting factors leading to higher incidence of severe RSV disease, longer RSV season, and decreased access to health care for some populations. Equity considerations were used as a lens to identify trends in the data that are useful for recommendation synthesis, particularly where gaps in the data exist. Biases in available data were acknowledged, for example those due to systemic limitations in available data for racialized groups. Recommendations were synthesized based on equity-informed trends in available data extended to similar contexts where gaps in the data exist. In particular, there are limited data on the risk of RSV for First Nations, Métis and Inuit populations. The more robust data on the risk of severe disease for other respiratory viruses such as influenza and COVID-19 in these populations were applied to these recommendations.

NACI consulted with Indigenous Services Canada (ISC)'s Vaccine Preventable Disease Working Group (VPD WG) to better understand the experiences of First Nations, Métis and Inuit populations (regardless of residency) with adult RSV disease, and if and how Indigenous Peoples should be referenced and prioritized in this statement. NACI's recommendations aim to address the severe health inequities that exist and prioritize an intervention for people who have historically been and continue to be marginalized [64]. First Nations, Métis and Inuit populations experience a high burden of illness due to social, environmental, and economic factors, rooted in the history of colonization and systemic racism [64,65]. By providing a recommendation acknowledging that First Nations, Métis and Inuit populations may be at increased risk of severe RSV disease, inequity may be reduced. Implementation should be culturally safe given documented barriers to feasibility and acceptability of other RSV immunization programs in similar settings [66]. Finally, autonomous decisions should be made by Indigenous Peoples with the support of healthcare and public health partners in accordance with the United Nations Declaration on the Rights of Indigenous Peoples [67].

V.3 Feasibility considerations

NACI consulted with the Canadian Immunization Committee (CIC) regarding feasibility of implementing programs for RSV vaccines for older adults. In general, although risk factors and cost-effectiveness were seen as important elements to consider for an immunization program, CIC and NACI both expressed that an age-based recommendation would be much more feasible to implement, particularly in contrast to a risk-based program for advanced-age older adults. With a risk-based program, there were concerns regarding achieving adequate uptake, estimating doses required, and determining and communicating eligibility. A risk-based program based on setting (e.g., nursing homes) was seen as more feasible to implement than a program based on individual medical risks. Where possible, alignment with influenza vaccine programs for seasonal timing or age was seen as ideal, particularly in the context of possible concurrent administration. The ability to concurrently administer the RSV vaccine with other vaccines may increase the feasibility and uptake of the RSV vaccine and other vaccines (see IV.6 Concurrent administration with other vaccines).

V.4 Acceptability considerations

In general, acceptability of RSV vaccines may be increased for older adults at higher risk of severe RSV disease due to increased perceived benefits. Reducing the burden of disease in older adults may increase acceptability from the perspectives of providers and policymakers. However, the vaccines are novel and there are ongoing investigations into the public's awareness of RSV disease and the perceived burden of illness in older adults. Acceptability may

be reduced if there is little understanding of possible illness severity. The numerical imbalance in inflammatory neurological events observed between vaccine and placebo groups in clinical trials may also reduce acceptability.

There are a few studies that may inform the knowledge and acceptability of RSV disease and RSV vaccines in older adults. In November 2023, the Health, Attitudes, and Behavioural Insights Tracker (HABIT) study [68] conducted in Canada (n=2049) found that 57% of respondents had heard of RSV; 19% of total respondents knew what it was and 38% of total respondents did not know much about it. People 55 years of age and older were more likely to have heard of RSV (63%), compared to those 35 to 54 years of age (54%) and 18 to 34 years of age (52%). Women were more likely to have heard of RSV (63%) than men (51%). When respondents 55 years of age and older (n=845) were informed that older adults are at a higher risk for developing more severe illness from RSV, 56% of respondents said they would get vaccinated, 17% said they would not get vaccinated and 27% said "don't know". Among this group, men (60%) were more likely to say they would get vaccinated than women (52%). Moreover, intentions to get an RSV vaccine was linked to familiarity with RSV. 64% of those who had heard of RSV and understood what it was, and 60% of those who had heard of RSV but did not know much about it, said they would get an RSV vaccine, compared to 46% of those who had not heard of it.

On September 1, 2023, in the United States, the CDC released its State of Vaccine Confidence Insights Report: RSV Vaccination in Older Adults Special Report [69]. The study found that although respondents reported knowing few people affected by RSV infection, concern about the virus and interest in the vaccine were high among older adults. Many respondents had limited knowledge and high uncertainty about RSV and RSV related illness, including its ability for asymptomatic spread, frequency of severe infections, and the likelihood of reinfection. Low consumer trust in the regulator, public health authorities, pharmaceutical companies, and vaccines may negatively impact RSV vaccine uptake. As of end of December 2023 in the United States, 20.0% (95% CI: 19.1 to 20.9%) of adults 60 years of age and older reported having received an RSV vaccine. Vaccination was highest among adults 75 to 79 years of age and white non-Hispanic adults. Adults 60 years of age and older with at least one chronic medical condition had significantly higher RSV vaccination coverage (25.1%) than those with no chronic conditions (17.8%). Furthermore, RSV vaccination coverage was higher among those who had received influenza or updated 2023-24 COVID-19 vaccine [70].

IV. Economics

A systematic review, *de novo* model-based economic evaluation, and multi-model comparison (MMC) were used to support decision-making for the use of vaccines for the prevention of RSV in adults.

The systematic review showed that, in general, without a substantial reduction in vaccine price the use of RSV vaccines in all adults aged 60 years and older or 65 years and older was unlikely to be cost-effective at commonly used cost-effectiveness thresholds. The model-based economic analysis showed that medical risk-based vaccination strategies could be cost-effective, with the age cutoff for such a policy dependent on model assumptions. Age-based strategies may also provide a positive net health benefit compared to no vaccination but are not an efficient use of resources compared to medical risk-based strategies. The results of the MMC were consistent with the *de novo* model-based economic evaluation. Below is a summary of the economic evidence, with additional details provided in separate publications [71-73]. All costs are in 2023 Canadian dollars.

VI.1 Systematic review

A systematic review of economic evaluations of vaccines for the prevention of RSV-related outcomes in adults was conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) [71]. In general, without a substantial reduction in vaccine price the use of RSV vaccines in adults aged 60 years and older or 65 years and older was unlikely to be cost-effective at commonly used cost-effectiveness thresholds.

The review included five economic evaluations comparing age-based vaccination using RSVpreF and/or RSVPreF3 to no intervention among individuals 60 years and older, 60 to 64 years, or 65 years and older [74-77]. Four economic evaluations were conducted in the United States from the societal perspective [74-76] and one was conducted in Hong Kong from the health system perspective [77].

Four economic evaluations included comparisons at a fixed price per dose. In the two evaluations that were not industry funded, incremental cost-effectiveness ratios (ICERs) exceeded $100,000 per quality-adjusted life year (QALY) gained for both vaccines [74,76,77]. ICERs from the industry-funded economic evaluations were lower compared to the non-industry funded evaluations and ranged from $24,741 to $81,288 per QALY gained depending on the vaccine [76]. In the studies that considered multiple age cutoffs, ICERs were lower for strategies in adults 65 years and older compared to adults 60 years and older [74,76].

Two economic evaluations included threshold analyses on price [75,77]; that is, the studies identified the price at which an intervention would be cost-effective at a given cost-effectiveness threshold. Overall, studies found that age-based vaccination required lower prices per dose than the prices considered in the primary analyses (e.g., between 50 to 75% lower) [77] to achieve cost-effectiveness at commonly used thresholds (e.g., $50,000 per QALY gained) [74,76].

After the systematic review was conducted, an additional economic evaluation containing threshold analyses on price in the Canadian context was identified [78]. The evaluation, which examined vaccinating residents of long-term care homes only or in conjunction with age-based strategies for community-dwelling adults from the health system perspective, found vaccine would need to be priced between $68 and $177 per dose for a $50,000 per QALY threshold, with higher vaccine prices acceptable for strategies restricted to residents of LTCHs [78].

VI.2 *De novo* model-based economic evaluation

A static individual-based model of medically attended RSV disease was used to evaluate the cost-utility of alternate age-, medical risk-, and age- plus medical risk-based vaccination policies. Based on feedback from CIC regarding feasibility considerations for implementation of medical risk-based programs, a pre-planned analysis that only considered age-based strategies was also conducted. Medical risk was defined as the presence of at least one chronic medical condition (CMC) [72]. The model followed a multi-age cohort of 100,000 people aged 50 years and older over a three-year period. The base case analysis assumed the vaccines were priced at $230 per dose, based on Canadian list prices. Sequential ICERs were calculated for the health system and societal perspectives, discounted to present value at 1.5% [79]. Results below are provided for the health system perspective. Similar trends were observed for the societal perspective, but ICERs were lower.

Vaccines with characteristics based on RSVPreF3 and RSVpreF were modelled and analyzed separately, but results were similar for both vaccines. Although all vaccination strategies averted medically attended RSV infections compared to no vaccination, medical risk-based strategies were more likely to be cost-effective than age-based strategies, with the age cutoff for such a policy dependent on model assumptions. A program focused on vaccinating adults aged 70 years and older with one or more CMC was cost-effective compared to vaccinating adults aged 80 years and older with one or more CMC at a cost-effectiveness threshold of $50,000 per QALY. Compared to a medical risk-based policy for adults 70 years and older, lowering the age recommendation to people with at least one CMC aged 60 years and older resulted in ICERs of approximately $100,000 CAD per QALY gained. ICERs for age- plus risk-based strategies that used different age cutoffs depending on the presence or absence of CMCs exceeded commonly used cost-effectiveness thresholds [80,81]. A no vaccination strategy was never preferred and was always dominated (no vaccination being more costly and less effective) by other vaccination strategies.

Results were sensitive to assumptions about vaccine costs, but medical risk-based approaches remained optimal compared to age-based strategies even when vaccine prices were lower than the $230 per dose assumed in the primary analysis. Findings were robust to a range of alternate assumptions, including that vaccine protection extends into a third RSV season or a lower proportion of people with CMCs among people hospitalized with RSV.

For a scenario of higher disease incidence and higher healthcare costs, as may occur in remote and isolated communities, an age- plus risk-based program that included adults with CMCs in age groups authorized to receive RSV vaccinations plus all adults aged 80 years and older without CMCs was cost-effective.

Age-only strategies were never identified as cost-effective options regardless of the cost-effectiveness threshold used, when considered alongside strategies based on medical risk factors. When medical risk-based strategies were excluded and age-based strategies were considered, vaccinating adults aged 80 years and older resulted in sequential ICERs of $3,261-5,391 per QALY gained compared to no vaccination. When only considering age-based strategies, lowering the age threshold for all adults from 80 years and older to 75 years and older required a cost-effectiveness threshold of $79,922-83,958 per QALY; a 30% reduction in vaccine price was required for vaccination of all adults aged 75 years and older to be cost-effective at a threshold of $50,000 per QALY compared to vaccination of adults aged 80 years and older.

In addition to this pre-specified analysis that only considered age-based strategies due to feasibility considerations associated with medical-risk based programs, an additional, not previously planned analysis was conducted to compare age-based strategies at either age 75 or age 80 years and older to an age-plus risk-based strategy with vaccine offered to people with CMCs aged 75 to 79 years and all adults aged 80 and older. This post-hoc analysis showed that most of the benefit of vaccination of the 75 to 79 year old age group is gained from vaccinating people with CMCs. In this analysis, sequential ICERs for expanding programs to include all adults aged 75 and older compared to the age- plus risk-strategy was well in excess of commonly used cost-effectiveness thresholds.

Based on available data and depending on the vaccination strategy used, RSV vaccination programs in older Canadian adults may be cost-effective. Programs that focus on people with CMCs that place them at increased risk of RSV disease are expected to provide the greatest value for money. Age-based strategies are not cost-effective compared to medical-risk based

strategies. If only considering age-based strategies, a reduction in vaccine price or an older age cutoff (relative to the age threshold identified when evaluating medical-risk based approaches) would be required for age-based approaches to be considered cost-effective.

VI.3 Multi-model comparison

A multi-model comparison was conducted to validate the findings of the PHAC-developed cost-effectiveness analysis, described above. The results of the MMC were consistent with the *de novo* model-based economic evaluation [73]. Two industry-funded cost-effectiveness models were developed by Pfizer and GSK. Both are static multi-age cohort models with the ability to model separate risk strata. Input parameters from both models were modified to be consistent with the assumptions of the PHAC-developed model, and age- and medical risk-based policies were sequentially evaluated under the health system perspective using ICERs, as in the cost-utility analysis. Results from each model were compared to test for robustness of conclusions across models.

Despite different model structures and assumptions, results were consistent across models. Age-based strategies were always dominated or extendedly dominated by strategies considering medical risk. Vaccinating adults aged 70 years and older with one or more CMCs was optimal at a threshold of $50,000 per QALY in most scenarios considered. The Pfizer model differed slightly from the PHAC and GSK models, indicating vaccination of adults 65 years or older with CMCs may be optimal at some thresholds, whereas this policy was never cost-effective in other models. The Pfizer model also estimated an ICER for this policy below $50,000 per QALY in the scenario using RSVpreF VE estimates with a three-year waning assumption. In a sub-analysis of age-based strategies, ICERs for an age-based policy for all adults aged 75 and older compared to 80 years and older ranged from $50,000 to $80,000 per QALY across models, using base case model assumptions.

VI.4 Economic evidence summary

Overall, the economic evidence suggests that RSV vaccination programs for older adults may be cost-effective for risk-based programs. Age- plus-risk based vaccination programs may be cost-effective in settings with higher disease incidence and higher healthcare costs. Limitations of the current analyses include limited data on durability of vaccine protection and assumption of a single value of VE regardless of age or medical risk. Estimates of cost-effectiveness of RSV vaccination programs may be conservative because the models did not include indirect effects due to vaccination preventing onward transmission following infection.

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 6 for a more detailed explanation of strength of NACI recommendations and grade of the body of evidence.

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

Recommendations for public health program level decision-making

(i.e., provinces and territories making decisions for publicly funded immunization programs)

In considering these recommendations for the purposes of publicly funded program implementation, provinces and territories may take into account local programmatic factors (e.g., current immunization programs, resources).

Recommendation 1. NACI recommends RSV immunization programs for adults 75 years of age and older, particularly for older adults at increased risk of severe RSV disease (see List 1). (Strong Recommendation)

Considerations:

- A single dose of either RSVPreF3 or RSVpreF can be used.
- The RSV vaccine 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 (prior to the COVID-19 pandemic, the RSV season was typically November to April).
- Indigenous Peoples may experience a disproportionate burden of illness due to social, environmental, and economic factors, rooted in the history of colonization and systemic racism (i.e., structural inequity). In First Nations, Métis, and Inuit communities, autonomous decisions should be made by Indigenous Peoples with the support of healthcare and public health partners in accordance with the *United Nations Declaration on the Rights of Indigenous Peoples Act*.
- Jurisdictions and communities may consider vaccinating individuals who live in or are part of First Nations, Métis, and Inuit communities (regardless of residency) at a younger age given the available evidence on the increased burden of illness due to intersecting structural and social determinants of health.
- Given the expanding product environment for new products and authorized age groups, it is possible that vaccine recommendations for older adults may be revisited for the 2025-2026 RSV season.

- 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 seasonal adult vaccines is acceptable.

Summary of evidence and rationale:

- RSV burden of disease and clinical trials demonstrated that RSV vaccines are efficacious at preventing RSV disease, including in adults 75 years and older, particularly for protection against medically attended RSV RTIs where efficacy ranged from roughly 49 to 78%.
- The duration of protection of the RSV vaccine is not yet known, and it is unclear if the protection offered by vaccination can be boosted by subsequent doses of vaccine. However, those at highest risk who may have severe outcomes from RSV disease (i.e., adults 75 years and older at increased risk, see List 1) should be vaccinated to optimize their near-term protection.
- The currently available evidence indicates that RSV vaccines have a favorable safety profile. NACI will continue to monitor safety data as they become available, particularly in the context of ongoing investigation on the risk of inflammatory neurological events. For adults 75 years of age and older at increased risk of severe RSV disease (see List 1), the benefits of vaccination outweigh the potential harms.
- Economic evidence supports that an RSV immunization program could be considered cost-effective at commonly used thresholds if offered to a subset of the authorized age group. Programs that are focused on older adults at highest risk for severe disease due to chronic medical conditions are expected to be an efficient use of resources; but aged based programs are expected to be more feasible to implement and are expected to improve equity as more is learned about risk factors for severe RSV and as some populations may not be captured in strategies focused only on those with identified medical risk factors.

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)

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

Considerations:

- A single dose of either RSVPreF3 or RSVpreF can be used.
- The RSV vaccine 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 (prior to the COVID-19 pandemic, the RSV season was typically November to April).
- Given the expanding product environment for new products and authorized age groups, it is possible that vaccine recommendations for older adults may be revisited for the 2025-2026 respiratory season.

Summary of Evidence and Rationale:

- RSV burden of disease and clinical trials demonstrated that RSV vaccines are effective at preventing RSV disease, including in adults 60 years of age and older, particularly for protection against medically attended RSV RTIs where efficacy ranged from roughly 66 to 79%.
- The currently available evidence indicates that RSV vaccines have a favorable safety profile. NACI will continue to monitor safety data as they become available, particularly in the context of ongoing investigation on the risk of inflammatory neurological events. For adults 60 years of age and older who are residents of nursing homes and other chronic care facilities, the benefits of vaccination outweigh the potential harms.
- The duration of protection of the RSV vaccine is not yet known, and it is unclear if the protection offered by vaccination can be boosted by subsequent doses of vaccine. However, those at highest risk who may have severe outcomes from RSV disease (e.g., adults 60 years of age and older who are residents of nursing homes and other chronic care facilities) should be vaccinated to optimize their near-term protection.
- A risk-based program based on setting (e.g., nursing homes) was seen as more feasible to implement than a program based on individual medical risks.

Recommendations for individual level decision-making

(i.e., individuals wishing to prevent a vaccine-preventable disease or a clinician wishing to advise individual patients about preventing RSV with vaccines that may not currently be included in public health immunization programs.)

Recommendation 3. NACI recommends that immunization with an RSV vaccine may be considered as an individual decision by adults 60 to 74 years of age with their health care provider. (Discretionary Recommendation)

Considerations:

- A single dose of either RSVPreF3 or RSVpreF can be used.
- NACI strongly recommends vaccination for individuals 75 years of age or older, particularly for those adults at increased risk of severe RSV disease. Benefits are smaller in younger age groups.
- The RSV vaccine 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 (prior to the COVID-19 pandemic, the RSV season was typically November to April).
- Given the expanding product environment for new products and authorized age groups, it is possible that vaccine recommendations for older adults may be revisited for the 2025 - 2026 RSV season.

Summary of evidence and rationale:
- RSV burden of disease and clinical trials demonstrated that RSV vaccines are effective at preventing RSV disease.
- The currently available evidence indicates that RSV vaccines have a favorable safety profile. NACI will continue to monitor safety data as they become available, particularly in the context of ongoing investigation on the risk of inflammatory neurological events. For adults 75 years of age and older at increased risk of severe RSV disease (see List 1), the benefits of vaccination outweigh the potential harms.
- The duration of protection of the RSV vaccine is not yet known, and it is unclear if the protection offered by vaccination can be booster by subsequent doses of vaccine. Therefore, healthy individuals who are less than 75 years of age may want to discuss deferring vaccination with their health care providers to a future time when they may be at greater risk.

Research Priorities

Research to address the following outstanding questions is encouraged:

- Further clarify the burden of RSV disease including further exploration of risk factors for severe disease, and including in 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
- Efficacy and 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, those who are more frail (including lung transplant and hematopoietic stem cell transplant patients), and highest risk patients under 60 years of age.
- Durability of protection for RSV vaccines for older adults
- Long term health consequences of RSV vaccines for older adults, including whether or not boosting can be achieved and if so, 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 and efficacy 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 there of
- Acceptability and uptake of RSV vaccines for older adults

Surveillance limitations

Ongoing and systematic data collection, analysis, interpretation and timely dissemination is fundamental to planning, implementation, evaluation, and evidence-based decision-making. Currently, RSV is neither a reportable disease nationally nor in the majority of provinces and territories. NACI encourages ongoing surveillance and continued expansion of surveillance details in the epidemiology of RSV in Canada. This includes surveillance of changes in the viral evolution of RSV due to potential selection pressures related to the introduction of a novel monoclonal antibody and RSV vaccines.

The Respiratory Virus Detection Surveillance System (RVDSS), Canada's national RSV surveillance system, monitors the spread of RSV by province/territory. Robust enhanced surveillance data on infants, children and pregnant women and pregnant people including health status, and granularity by age group, and RSV-related complications (e.g., hospitalization and ICU admission) is limited. In addition, the impact of RSV on older adults based on underlying health status, sex and other potential confounders is not well documented. Therefore, initiatives are needed to collect data on RSV infection (e.g., non-medically attended-RSV, medically attended-RSV, hospitalization, ICU admission, and death incidence) in older adults to determine the burden of RSV infections in Canada.

Tables

Table 2. Summary of findings comparing RSVpreF to placebo for adults 60 years of age and older

Outcome	No. of studies	Summary of findings				Certainty
		No. of events/No. of participants		Effect		
		RSVpreF	Placebo	Relative (95% CI)	Absolute (95% CI)	
Death due to RSV (follow up: 1 season)	2 (RCTs)	0/18,110 (0.0%)	0/18,128 (0.0%)	Not estimable		Moderate [a]
RSV RTI with ICU admission (follow up: 1 season)	1 (RCT)	0/18,058 (0.0%)	0/18,076 (0.0%)	Not estimable		Moderate [a]
RSV RTI with hospitalization (follow up: 1 season)	1 (RCT)	0/18,058 (0.0%)	2/18,076 (0.0%)	OR 0.14 (0.01 to 2.17)	10 fewer per 100,000 (from 11 fewer to 13 more)	Low [a,c,d]
			0.1% [b]	VE 86% (-117 to 99%)	125 fewer per 100,000 (from 144 fewer to 170 more)	
Medically attended RSV RTI (follow up: 1 season)	1 (RCT)	8/18,058 (0.0%)	27/18,076 (0.1%)	OR 0.34 (0.17 to 0.66) VE 66% (34 to 83%)	99 fewer per 100,000 (from 124 fewer to 51 fewer)	Moderate [a]

Severe systemic AEs (follow up: 14 days)	2 (RCTs)	28/3,673 (0.8%)	23/3,591 (0.6%)	OR 1.19 (0.69 to 2.07)	121 more per 100,000 (from 198 fewer to 676 more)	Low [a,d]
Severe local AEs (follow up: 14 days)	2 (RCTs)	8/3,673 (0.2%)	2/3,591 (0.1%)	OR 3.25 (0.94 to 11.24)	125 more per 100,000 (from 3 fewer to 567 more)	Low [a,d]

[a] Downrating by 1 for indirectness due to underrepresentation of adults 80 years of age and older (only 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 [7].
[c] Certainty of evidence was assessed using the absolute effect calculate using baseline risk and not the placebo arm of the trial.
[d] Downrating by 1 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 3. Summary of findings comparing RSVpreF 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		
		RSVpreF	Placebo	Relative (95% CI)	Absolute (95% CI)	
Death due to RSV (follow up: 1 season)	1 (RCT)	0/2,894 (0.0%)	0/2,903 (0.0%)	Not estimable		High
RSV RTI with ICU admission	1 (RCT)	0/2,894 (0.0%)	0/2,903 (0.0%)	Not estimable		High

(follow up: 1 season)						
RSV RTI with hospitalization (follow up: 1 season)	1 (RCT)	0/2,894 (0.0%)	0/2,903 (0.0%)	Not estimable		High
Medically attended RSV RTI (follow up: 1 season)	1 (RCT)	1/2,894 (0.0%)	7/2,903 (0.2%)	OR 0.22 (0.06 to 0.89) VE 78% (11% to 94%)	188 fewer per 100,000 (from 227 fewer to 26 fewer)	Moderate [a,c]
			2.5% [b]		1,939 fewer per 100,000 (from 2,346 fewer to 269 fewer)	
Severe systemic AEs (follow up: 7 days)	1 (RCT)	3/625 (0.5%)	0/604 (0.0%)	OR 7.17 (0.74 to 69.06)	500 more per 100,000 (from 200 fewer to 1,000 more)	Moderate [a]
Severe local AEs (follow up: 7 days)	1 (RCT)	0/625 (0.0%)	0/604 (0.0%)	Not estimable		Moderate [d]

[a] Downrating by 1 for imprecision as the width of the CI of the absolute effect contains estimates that differ in effect size interpretation from the point estimate.

[b] 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 [7], McLaughlin 2022 [11], and data from RVDSS (average of 9 seasons, 2010/2011 to 2018/2019).
[c] Certainty of evidence was assessed using the absolute effect calculate using baseline risk and not the placebo arm of the trial.
[d] Downrating by 1 for imprecision as the review sample size is below the calculated review information size needed to detect a trivial or no effect.

Table 4. Summary of findings comparing RSVPreF3 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		
		RSVPreF3 OA	Placebo	Relative (95% CI)	Absolute (95% CI)	
Death due to RSV (follow up: 1 season)	2 (RCTs)	0/12,566 (0.0%)	0/12,594 (0.0%)	Not estimable		Moderate [a]
RSV RTI with ICU admission (follow up: 1 season)	1 (RCT)	0/12,466 (0.0%)	1/12,494 (0.0%)	OR 0.14 (0.00 to 6.84) VE 86% (-584 to 100%)	7 fewer per 100,000 (from 8 fewer to 47 more)	Moderate [a]
RSV RTI with hospitalization (follow up: 1 season)	1 (RCT)	0/12,466 (0.0%)	3/12,494 (0.0%)	OR 0.14 (0.01 to 1.30) VE 86% (-30 to 99%)	21 fewer per 100,000 (from 24 fewer to 7 more)	Moderate [a]
			0.1% [b]		125 fewer per 100,000 (from 144 fewer to 44 more)	
Medically attended RSV RTI (follow up: 1 season)	1 (RCT)	3/12,466 (0.0%)	24/12,494 (0.2%)	OR 0.21 (0.10 to 0.45) VE 79% (55 to 90%)	152 fewer per 100,000 (from 173 fewer to 106 fewer)	Moderate [a]

Severe systemic AEs (follow up: 4 days)	2 (RCTs)	31/979 (3.2%)	9/978 (0.9%)	RR 3.42 (1.63 to 7.16)	2,227 more per 100,000 (from 580 more to 5,669 more)	Moderate [a]
Severe local AEs (follow up: 4 days)	2 (RCTs)	18/979 (1.8%)	0/978 (0.0%)	OR 7.55 (2.98 to 19.11)	2,470 more per 100,000 (from 630 fewer to 5,580 more) [e]	Very low [a,d]

[a] Downrating by 1 for indirectness due to underrepresentation of adults 80 years of age and older (only 8% 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 [7].

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

[d] 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.

[e] Could not be calculated using standard GRADE methodology owing to no events in the control group. The absolute risk difference between groups has been provided.

Table 5. Summary of findings comparing RSVPreF3 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		
		RSVPreF3 OA	Placebo	Relative (95% CI)	Absolute (95% CI)	
Death due to RSV (follow up: 1 season)	1 (RCT)	0/2,671 (0.0%)	0/2,646 (0.0%)	Not estimable		High
RSV RTI with ICU admission (follow up: 1 season)	1 (RCT)	0/2,671 (0.0%)	0/2,646 (0.0%)	Not estimable		High
RSV RTI with hospitalization (follow up: 1 season)	1 (RCT)	0/2,671 (0.0%)	0/2,646 (0.0%)	Not estimable		High

Medically attended RSV RTI (follow up: 1 season)	1 (RCT)	2/2,671 (0.1%)	4/2,646 (0.0%) 2.5% [a]	OR 0.51 (0.10 to 2.52) VE 49% (-152 to 90%)	74 fewer per 100,000 (from 136 fewer to 229 more) 1,209 fewer per 100,000 (from 2,244 fewer to 3,569 more)	Low [b,c]
Severe systemic AEs (follow up: 4 days)	1 (RCT)	5/220 (2.3%)	4/227 (1.8%)	RR 1.29 (0.35 to 4.74)	511 more per 100,000 (from 1,145 fewer to 6,590 more)	Low [b]
Severe local AEs (follow up: 4 days)	1 (RCT)	3/220 (1.4%)	0/227 (0.0%)	OR 7.70 (0.80 to 74.4)	1,400 more per 100,000 (from 400 fewer to 3,200 more) [d]	Moderate [e]

[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 [7], McLaughlin 2022 [11], 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.

[d] Could not be calculated using standard GRADE methodology owing to no events in the control group. The absolute risk difference between groups has been provided.

[e] Downrating by 1 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 6. GRADE Certainty of evidence for NACI recommendations

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

List of Abbreviations

AE	Adverse event
ADEM	Acute disseminated encephalomyelitis
AReSVi-006	Adult respiratory syncytial virus
CADTH	Canadian Agency for Drugs and Technologies in Health
CCDR	Canadian Communicable Disease Report
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CIC	Canadian Immunization Committee
CIHI	Canadian Institute for Health Information
CMC	Chronic medical condition
DAD	Discharge Abstract Database
DPD	Drug Product Database
EEFA	Ethics, equity, feasibility, and acceptability
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	GlaxoKlineSmith
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IIV	Inactivated influenza vaccine
IIV4	Quadrivalent inactivated influenza vaccine
IIV4-Adj	Adjuvanted quadrivalent inactivated influenza vaccine

IIV4-HD	High-dose quadrivalent inactivated influenza vaccine
ISC	Indigenous Services Canada
LTCH	Long-term care homes
MMC	Multi-model comparison
N	Number of Participants
NACI	National Advisory Committee on Immunization
OR	Odds ratio
PHAC	Public Health Agency of Canada
Phase I/II RCT	Phase 1/2 randomized controlled trial
Phase III RCT	Phase 3 randomized controlled trial
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RENOIR	RSV Vaccine Efficacy Study in Older Adults Immunized against RSV Disease
RR	Risk ratio
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
SAE	Severe adverse event
US	United States
VAERS	Vaccine Adverse Reporting System
VE	Vaccine efficacy
VPD WG	Vaccine Preventable Disease Working Group
VSD	Vaccine Safety Datalink

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