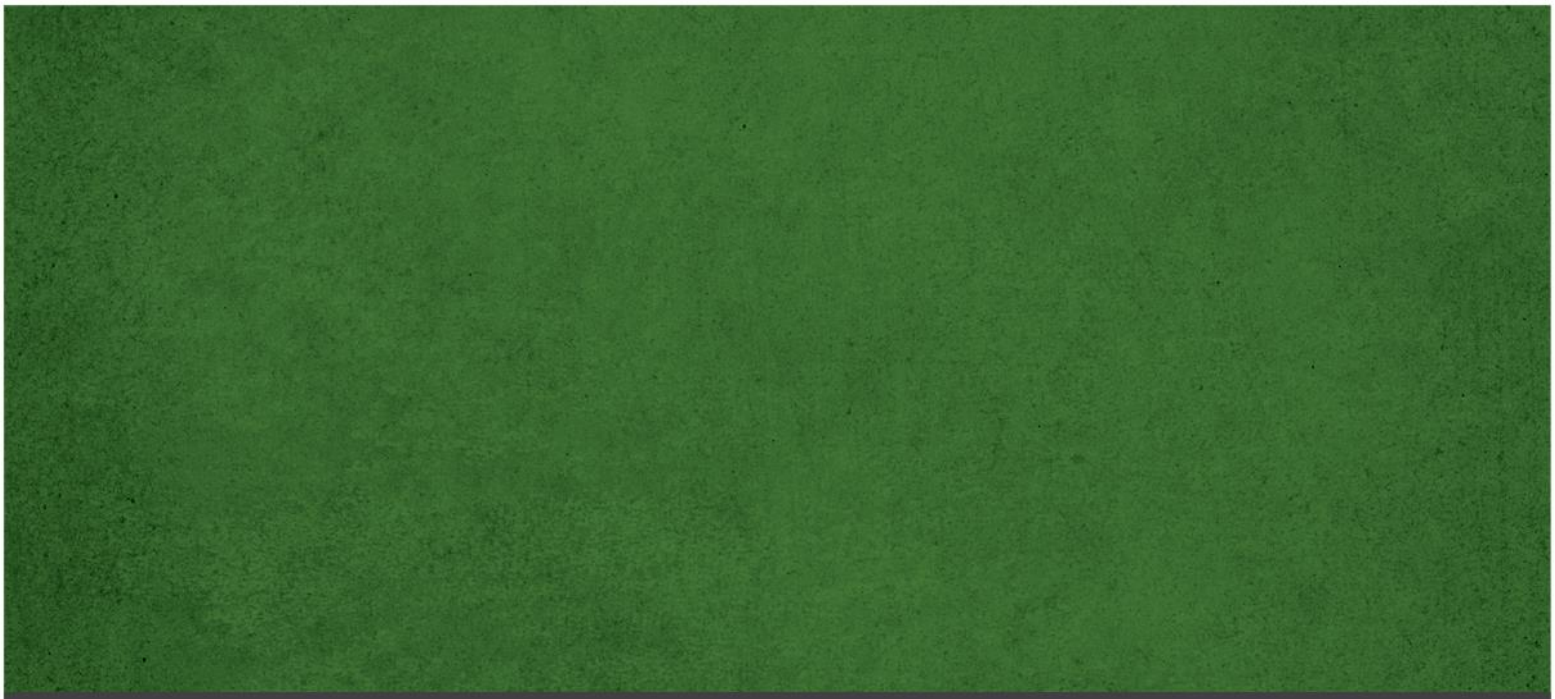
# An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

## Statement on Seasonal Influenza Vaccine for 2024–2025



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# PREAMBLE

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

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

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

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge.

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

# TABLE OF CONTENTS

# SUMMARY OF INFORMATION CONTAINED IN THE NACI STATEMENT

The following highlights key information for immunization providers on seasonal influenza vaccine. Several influenza vaccines are authorized in Canada and the evidence on influenza immunization is continually evolving. NACI will continue to monitor the evidence and update its recommendations as needed. Please refer to the remainder of the statement for details.

## What

- Influenza in humans is a respiratory infection caused primarily by influenza A and B viruses. Seasonal influenza epidemics occur annually in Canada, generally in the late fall and winter months. Prior to the COVID-19 pandemic, influenza had an annual attack rate estimated at 5 to 10% in adults and 20 to 30% in children worldwide [(1)].
- Most people will recover from influenza within a week to 10 days, but some are at greater risk of severe complications, such as pneumonia. Influenza infection can also worsen certain chronic conditions, such as cardiovascular disease [(2)].
- Live attenuated influenza vaccine (LAIV), recombinant influenza vaccine (RIV) and inactivated influenza vaccines (IIV) (which include standard dose [SD], high dose [HD], cell culture-based [cc] or adjuvanted [Adj] vaccines) are all authorized for use in Canada; See Appendix A for a list of abbreviations used in this document for the different influenza vaccines.
- Influenza vaccines are the best protection against influenza and their benefits outweigh the potential risks following immunization. The safety profile of influenza vaccines has been well established. Reactions following immunization are generally benign and of short duration. Very rarely, some individuals may have allergic reactions to some components of the vaccines currently in use. Monitoring of safety signals related to influenza vaccines is ongoing.

## Who

NACI makes the following recommendations for individual-level and public health program-level decision making. Individual-level recommendations are intended for people wishing to protect themselves from influenza and for vaccine providers advising individual patients about preventing influenza. Program-level recommendations are intended for provinces and territories responsible for making decisions on publicly funded immunization programs. Individual-level and program-level recommendations may differ, as the important factors to consider when recommending a vaccine for a population (e.g., population demographics, economic considerations) may be different than for an individual.

### Recommendation for individual-level decision making

- NACI recommends that influenza vaccine should be offered annually to anyone 6 months of age and older who does not have a contraindication to the vaccine. Patients and health care providers should also be aware that risks are higher in some settings and for some individuals than others. Immunization is particularly important for the following groups (see List 1):
    - People at high risk of severe disease, influenza-related complications, or hospitalization
    - People capable of transmitting influenza to those at high risk

    - People who provide essential community services (including health care workers)
    - People in direct contact with poultry infected with avian influenza during culling operations [3].

In infants less than 6 months of age, evidence is lacking to demonstrate that influenza vaccine would be effective [3]. Currently, authorized influenza vaccines are not indicated for use in infants less than 6 months of age. For these reasons, NACI recommends that influenza vaccine should not be offered to these infants. Since infants less than 6 months of age are at high risk of influenza-related illness, the influenza vaccine should be offered to individuals who are pregnant, breastfeeding, and any household contacts and care providers of young infants.

**Recommendation for public health program-level decision-making**

The national goal of the annual influenza immunization programs in Canada is to prevent serious illness caused by influenza and its complications, including death. Programmatic decisions to provide influenza vaccination to target populations as part of publicly funded provincial and territorial programs depend on many factors, such as cost-effectiveness evaluation and other programmatic and operational factors.

- NACI recommends that influenza vaccine should be offered as a priority to the groups for whom influenza vaccination is particularly important.

## How

The benefits and risks of influenza vaccination should be discussed prior to vaccination, including the risks of not being immunized.

**Choice of influenza vaccine**

A variety of influenza vaccines are authorized for use in Canada, some of which are authorized for use only in specific age groups. Furthermore, not all products will necessarily be made available in all jurisdictions and availability of some products as part of publicly funded provincial and territorial programs may be limited.

**Dose and route of administration**

The dose and route of administration vary by influenza vaccine product.

See Appendix B for information on characteristics of all influenza vaccines expected to be available for use in Canada for the 2024–2025 influenza season.

**Schedule**

NACI recommends that:

- Adults and children 9 years of age and older should receive 1 dose of influenza vaccine each year; and
- Children 6 months to less than 9 years of age who have never received the seasonal influenza vaccine in a previous influenza season should be given 2 doses of influenza vaccine in the current season, with a minimum interval of 4 weeks between doses. Children 6 months to less than 9 years of age who have been vaccinated with 1 or more doses of seasonal influenza vaccine in any previous season should receive 1 dose of influenza vaccine per season thereafter.

## Contraindications

For all influenza vaccines (IIV, RIV and LAIV), NACI recommends that influenza vaccination should not be given to:

- People who have had an anaphylactic reaction to a specific influenza vaccine, or to any of the components of a specific influenza vaccine, with the exception of egg

If an individual is found to have an anaphylactic reaction to a component in 1 influenza vaccine, consideration may be given to offering another influenza vaccine that does not contain the implicated component, in consultation with an allergy specialist.

For LAIV, in addition to the above-mentioned contraindications, NACI also recommends that LAIV is contraindicated for:

- People with severe asthma (defined as currently on oral or high-dose inhaled glucocorticosteroids or active wheezing) or medically attended wheezing in the 7 days prior to the proposed date of vaccination, due to increased risk of wheezing following administration of LAIV
  - LAIV is not contraindicated for people with a history of stable asthma or recurrent wheeze which is not active.
- Children less than 24 months of age, due to increased risk of wheezing following administration of LAIV
- Children 2 to 17 years of age currently receiving aspirin or aspirin-containing therapy, because of the association of Reye's syndrome with aspirin and wild-type influenza infection
- Pregnant individuals, because it is a live attenuated vaccine and there is a lack of safety data at this time
  - LAIV is not contraindicated in breastfeeding (lactating) individuals however, there are limited data for the use of LAIV in this population.
  - Refer to the Updated Guidance on Influenza Vaccination During Pregnancy for additional information.
- People who are immunocompromised due to underlying disease and/or therapy, with the exception of children living with stable HIV infection and adequate immune function receiving highly active anti-retroviral therapy [HAART]
  - Refer to the Recommendation on the Use of Live Attenuated Influenza Vaccine (LAIV) in HIV-Infected Individuals for additional information

## Precautions

- Influenza vaccination should usually be postponed in people with serious acute illnesses until their symptoms have abated
  - More information on vaccinating individuals during acute illness can be found in the Canadian Immunization Guide's (CIG) section on Contraindications and precautions associated with specific conditions: Acute Illness.
- NACI generally recommends people who have developed Guillain-Barré Syndrome (GBS) within 6 weeks of a previous influenza vaccination should not receive influenza vaccine unless another cause was found for the GBS.
  - The potential risk for a recurrent episode of GBS associated with influenza vaccination must be balanced against the risk of GBS associated with influenza infection itself and the benefits of influenza vaccination.
- For LAIV, NACI additionally recommends precautions for the following situations:
  - In the presence of significant nasal congestion or discharge that might impede delivery of LAIV to the nasopharyngeal mucosa

    - For close contacts of people with severe immune compromising conditions
    - When there is administration of antivirals active against the influenza virus (e.g., oseltamivir, zanamivir)
- Contraindications or precautions related to LAIV administration should not be used as a reason to withhold or delay immunization with an alternate vaccine. In such cases, a parenteral inactivated or recombinant influenza vaccine can be offered.

More information on contraindications and precautions can be found in Section IV.6: Vaccine Safety and Adverse Events and in the influenza vaccines chapter of the Canadian Immunization Guide's section on Contraindications and precautions.

**Concurrent administration with other vaccines**

Inactivated or recombinant influenza vaccines may be administered concurrently with (i.e., same day) or at any time before or after other inactivated or live attenuated vaccines.

NACI recommends that LAIV can be given together with or at any time before or after the administration of any other live attenuated or inactivated vaccine.

For information on specific concurrent administration of vaccines with influenza vaccines, refer to the Concurrent administration section of the statement.

Different injection sites and separate needles and syringes should always be used for concurrent parenteral injections. If multiple injections in the same limb are required, the injection sites should be separated by at least 2.5 cm (1 inch).

## Why

- Vaccination is the most effective way to prevent influenza and its complications.
- Vaccination can help prevent the spread of influenza from person-to-person.
- Although most people will recover fully from influenza infection in 7 to 10 days, influenza can lead to severe disease, complications, or both, including hospitalization and death. Influenza is a common vaccine preventable disease leading to hospitalization and death in adults.
- Annual vaccination is required because the specific strains in the vaccine are reviewed each year by WHO and are often changed to provide a better match against the viruses expected to circulate in that given year, and because the body's immune response to influenza vaccination may be transient and may not persist beyond a year

# I. INTRODUCTION

The National Advisory Committee on Immunization (NACI) provides PHAC with annual recommendations regarding the use of seasonal influenza vaccines, which reflect identified changes in influenza epidemiology, immunization practices and influenza vaccine products authorized and available for use in Canada. This document, the "National Advisory Committee on Immunization (NACI) Statement on Seasonal Influenza Vaccine for 2024–2025", updates NACI's recommendations regarding the use of seasonal influenza vaccines.

For a summary of clinical information on seasonal influenza vaccine administration for vaccine providers, please refer to the new Influenza vaccine chapter of the Canadian Immunization Guide.

## I.1 New or Updated Information for 2024–2025

### Updated recommendations on the use of influenza vaccines during pregnancy

In November 2023, NACI released Updated Guidance on Influenza Vaccination During Pregnancy. This supplemental statement provides an evidence summary on the safety and effectiveness of influenza vaccination in pregnant individuals, their developing fetus, and infants under 6 months of age. Overall, the evidence supports the safety and effectiveness of influenza vaccines during pregnancy. NACI continues to strongly recommend that inactivated or recombinant influenza vaccines be offered during pregnancy, at any gestational age. NACI also continues to include pregnant individuals among those for whom influenza vaccination is particularly important. Finally, NACI reaffirms its recommendation that influenza vaccination may be given at the same time as, or at any time before or after administration of another vaccine, including the COVID-19 or pertussis vaccine. The vaccine can be given in any trimester.

For additional information on the use of influenza vaccines during pregnancy, please refer to the updated NACI guidance on influenza vaccination during pregnancy.

### Updated recommendations on the use of influenza vaccines in older adults

NACI released supplemental guidance on influenza vaccination in adults 65 years of age and older on May 31, 2024. Adults 65 years of age and older are prioritized to receive influenza vaccines because of the increased risks of severe disease in this population. Therefore, NACI continues to include adults 65 years of age and older among those for whom influenza vaccination is particularly important. This supplemental statement provides an evidence summary on the preferential use of 1 or more of the age-appropriate influenza vaccines in adults 65 years of age and older, over other age-appropriate influenza vaccines. A systematic review of the economic literature was also undertaken to inform public health program decision-making. Overall, the evidence supports high-dose inactivated influenza vaccine (IIV-HD), adjuvanted inactivated influenza vaccine (IIV-Adj) and recombinant influenza vaccine (RIV) as having increased benefits as compared to standard-dose inactivated influenza vaccine (IIV-SD), with no difference in safety. NACI strongly recommends that IIV-HD, IIV-Adj or RIV should be offered, when available, over other influenza vaccines for adults 65 years of age and older. If a preferred product is not available, any of the available age-appropriate influenza vaccines should be used.

For additional information, please refer to the NACI supplemental guidance on influenza vaccination in adults 65 years of age and older.

## I.2 Background

The World Health Organization's (WHO) recommendations on the composition of influenza virus vaccines are typically available in February of each year for the upcoming season in the Northern Hemisphere. The WHO recommends that 3 influenza strains be included in the trivalent seasonal influenza vaccine: 1 influenza A (H1N1), 1 influenza A(H3N2), and 1 influenza B. Quadrivalent seasonal influenza vaccines should contain the 3 strains recommended for the trivalent vaccine, as well as an influenza B virus from the lineage that is not included in the trivalent vaccine.

As of September 2023, due to the absence of confirmed detection of naturally occurring B/Yamagata lineage viruses amongst seasonal strains, the WHO has recommended the removal of B/Yamagata antigen as a component of inactivated and live attenuated influenza vaccines for the Southern Hemisphere 2024 season[(4)]. NACI will continue to monitor the evolving situation and will review the guidance for quadrivalent and trivalent vaccines as additional information becomes available.

Health care providers in Canada should offer the seasonal influenza vaccine as soon as feasible after it becomes available in the fall, since seasonal influenza activity may start as early as October in the Northern Hemisphere. Decisions regarding the precise timing of vaccination in a given setting or geographic area should be made according to local epidemiologic factors (influenza activity, timing, and intensity), opportune moments for vaccination, as well as programmatic considerations. Further advice regarding the timing of influenza vaccination programs may be obtained through consultation with local public health agencies.

Although vaccination before the onset of the influenza season is strongly preferred, influenza vaccine may still be administered up until the end of the season. Delayed administration may result in lost opportunities to prevent infection from exposures that occur prior to vaccination; therefore, individuals seeking or considering vaccination should be informed that vaccine administered during an influenza outbreak may not provide optimal protection. Vaccine providers should use every opportunity to administer influenza vaccine to individuals at risk who have not already been vaccinated during the current season, even after influenza activity has been documented in the community.

Every year, individuals with influenza and influenza-related complications increase the pressures on the healthcare system in the fall and winter months. Particularly during times when other respiratory viruses, such as COVID-19 and RSV, are co-circulating, effective prevention of influenza by vaccination is a critical tool to mitigate ongoing health system stress.

# II. METHODS

Details regarding NACI's evidence-based process for developing a statement are outlined in Evidence-based Recommendations for Immunization − Methods of the National Advisory Committee on Immunization.

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

- Knowledge synthesis
- Synthesis of the body of evidence of benefits and harms, considering the quality of the synthesized evidence and magnitude and certainty of effects observed across the studies
- Translation of evidence into recommendations

Annual influenza vaccine recommendations are developed by the Influenza Working Group (IWG) for consideration by NACI. Recommendation development includes review of a variety of issues including the burden of influenza illness and the target populations for vaccination; safety, immunogenicity, efficacy, and effectiveness of influenza vaccines; and vaccine schedules. In addition, PHAC has expanded the mandate of NACI to include the consideration of programmatic factors in developing their recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels. These programmatic factors include consideration of ethics, equity, feasibility, and acceptability (EEFA) and cost-effectiveness. NACI uses a published, peer-reviewed framework and evidence-informed tools to ensure that issues related to EEFA are systematically assessed and integrated into its guidance. The NACI Secretariat applied this framework with accompanying evidence-informed tools (Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, Acceptability Matrix) to systematically consider these programmatic factors for the development of clear, comprehensive, appropriate recommendations for timely, transparent decision-making. For details on the development and application of NACI's EEFA Framework and evidence-informed tools, please see A framework for the systematic consideration of ethics, equity, feasibility, and acceptability in vaccine program recommendations. For details on when and how NACI incorporates economic evidence for vaccine recommendations, please refer to the NACI Process for incorporating economic evidence into federal vaccine recommendations.

The annual update of the NACI Statement on Seasonal Influenza Vaccine led by the NACI Influenza Working Group (IWG) involves a thorough review and evaluation of the literature as well as discussion at the scientific and clinical practice levels. In the preparation of the 2024–2025 seasonal influenza vaccine recommendations, NACI's IWG identified the need for evidence reviews for new topics, and then reviewed and analyzed the available evidence, and proposed new or updated recommendations according to the NACI evidence-based process for developing recommendations.

On September 27, 2023, the available evidence and the new recommendations proposed by the IWG were presented for consideration and approval by NACI. Following a thorough review of the evidence, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and identified knowledge gaps are described in this statement.

# III. EPIDEMIOLOGY

## Disease description

Influenza is a respiratory infection caused by the influenza A and B viruses in humans and can cause mild to severe illness, including hospitalization or death. Certain populations, such as young children, older adults, and those with chronic health conditions, are at higher risk for serious influenza complications such as viral pneumonia, secondary bacterial pneumonia, and worsening of underlying medical conditions.

## Infectious agent

There are 2 main types of influenza virus that cause seasonal epidemics in humans: A and B. Influenza A viruses are classified into subtypes based on 2 surface proteins: hemagglutinin (HA) and neuraminidase (NA). Three (3) subtypes of HA (H1, H2, and H3) and 2 subtypes of NA (N1 and N2) are recognized among influenza A viruses as having caused widespread human disease over the past decades. Immunity to the HA and NA proteins reduces the likelihood of infection and together with immunity to the internal viral proteins, lessens the severity of disease if infection occurs.

Influenza B viruses have evolved into 2 antigenically distinct lineages since the mid-1980s, represented by B/Victoria/2/87-like and B/Yamagata/16/88-like viruses. Viruses from both the B/Victoria and B/Yamagata lineages have contributed variably to influenza illness in previous years. Since the onset of the COVID-19 pandemic, a reduction in seasonal influenza virus diversity has been observed globally [5, 6]. In particular, there have been no confirmed naturally occurring cases of B/Yamagata influenza lineage viruses since March 2020 [5, 7]. This absence may impact global vaccination strategies and lead to shifts in vaccine composition from quadrivalent to trivalent formulations [6, 8].
Over time, antigenic variation (antigenic drift) of strains occurs within an influenza A subtype or a B lineage. The possibility of antigenic drift, which may occur in 1 or more influenza virus strains, requires the formulation of seasonal influenza vaccines be re-evaluated annually, with 1 or more vaccine strains changing in most seasons.

## Transmission

Influenza is primarily transmitted by aerosols and droplets spread through coughing or sneezing, and through direct or indirect contact with respiratory secretions.

The incubation period of seasonal influenza is usually about 2 days but can range from 1 to 4 days [9]. Adults may be able to spread influenza to others from 1 day before symptom onset to approximately 5 days after symptoms start. Children and people with weakened immune systems may be infectious longer.

## Risk factors

The people at greatest risk of influenza-related complications are adults and children with chronic health conditions (see List 1), residents of nursing homes and other chronic care facilities, adults 65 years of age and older, children 0 to 59 months of age, pregnant individuals, and Indigenous Peoples.

## Seasonal and temporal patterns

Influenza activity in Canada is usually low in the late spring and summer, begins to increase over the fall, and peaks in the winter months. Influenza season in Canada usually begins in December and lasts 12 to 16 weeks but can start as early as October or as late as February, and last for as long as 20 weeks. One (1) of more peaks may occur during a season. Although 1 strain often predominates, more than 1 influenza strain typically circulates each season.

## Spectrum of clinical illness

Classically, symptoms of influenza include the sudden onset of fever, cough, and muscle aches. Other common symptoms include headache, chills, loss of appetite, fatigue, and sore throat. Nausea, vomiting, and diarrhea may also occur, especially in children. However, influenza can cause a range of symptoms, from asymptomatic infection through mild acute respiratory illness (a "cold") to severe influenza pneumonia. Most people will recover within a week or 10 days. More rarely, central nervous system manifestations, acute myositis, myocarditis, or pericarditis have been described. In addition, complications including pneumonia, respiratory failure, cardiovascular complications, delirium, or worsening of underlying chronic medical conditions may occur. Influenza is also associated with a significantly increased risk of myocardial infarction and stroke in the 7 to 14 days after infection, and with GBS with onset 1 to 6 weeks after infection[10, 11].

## Disease incidence

### Global

Before the COVID-19 pandemic, worldwide annual epidemics resulted in approximately 1 billion cases of influenza, 3 to 5 million cases of severe illness, and 290,000 to 650,000 deaths. The global annual attack rate is estimated to be 5 to 10% in adults and 20 to 30% in children[12]. Global influenza circulation was at a historical low during the 2020-2021 influenza season, when public health measures (e.g., masking, social distancing) effectively suppressed seasonal influenza activity ([13-15]. During the 2021-2022 season, influenza activity returned to varying degrees in different jurisdictions. During the 2022-2023 season, global influenza activity appeared to return to circulation patterns resembling pre-pandemic seasons, except for the absence of confirmed detection of B/Yamagata lineage viruses among seasonal influenza strains. The WHO has indicated there have been no confirmed detections of B/Yamagata lineage viruses after March 2020, and, in their opinion, future epidemics of B/Yamagata lineage viruses are probably unlikely [4]. However, changes in testing associated with the pandemic make it challenging to draw definitive conclusions at this time[16].

For current international influenza activity information, refer to WHO's Global Influenza Program website.

### National

Together, influenza and pneumonia are ranked among the top 10 leading causes of death in Canada ([17]. Nationally, influenza has been estimated to cause approximately 12,200 hospitalizations and approximately 3,500 deaths annually [18, 19]. The FluWatch program is Canada's national surveillance system, which monitors the spread of influenza and influenza-like illnesses (ILI) continually throughout the year. In the 5 seasons prior to the COVID-19 pandemic (2014–2015 to 2018-2019 season), an average of 40,000 laboratory-confirmed cases of influenza were reported to FluWatch each year. Most influenza infections are not laboratory-confirmed since the illness may be confused with other viral illnesses and many people with ILI do not seek medical care or have viral diagnostic testing done;

therefore, the number of cases reported to FluWatch is a significant underestimate of the true number of infections.

The burden of influenza-associated illness and death varies every year, depending on various factors such as the type of circulating viruses in the season and the populations affected[20]. Notably, Canada did not experience a seasonal epidemic in 2020-2021 due to the public health measures that were implemented to reduce COVID-19 transmission[13-15]. During the 2021-2022 season, Canada experienced a short influenza epidemic that started in April 2022, which is an unusually late start to the influenza season [21]. In the 2022-2023 season, Canada experienced an early, short, and intense influenza epidemic that had a significant impact on infants, children, and adolescents [22]. Although the potential impact of upcoming influenza seasons in the context of COVID-19 is unknown, future influenza outbreaks may be characterized by higher infection rates and severity[14, 15]. Influenza infection susceptibility may have increased due to lower immunity in the population given the extended periods of decreased influenza exposure and infection caused by the implementation of COVID-19-related public health measures [13, 23-25]. Additionally, the resurgence of seasonal influenza may not follow usual seasonal patterns[26, 27]. These 2 occurrences were evident in both the 2021-2022 and 2022-2023 seasons [21, 22]. Moreover, in times of co-circulation of COVID-19 and influenza viruses, disease severity in individuals simultaneously infected with both may be exacerbated [28]. Information about current influenza activity can be found on the FluWatch website.

# IV. SEASONAL INFLUENZA VACCINES

## IV.1 Vaccine Products Authorized for Use in Canada

The following sections describe the influenza vaccine products that are authorized for use in Canada for the 2024–2025 season. All influenza vaccines available in Canada have been authorized by Health Canada. However, not all products authorized for use are available in the marketplace. The vaccine manufacturers determine whether they will make any or all of their products available in each market. Provincial and territorial health authorities then determine which of the products available for purchase will be used in their respective publicly funded influenza immunization programs and for which population groups. Not all products will be made available in all jurisdictions and availability of some products may be limited. Officials in individual provinces and territories should be consulted regarding the products available in individual jurisdictions.

The antigenic characteristics of circulating influenza virus strains provide the basis for selecting the strains included in each year's vaccine. Vaccine selection by the WHO generally occurs in February for the fall's Northern Hemisphere influenza season to allow time for the vaccine manufacturers to produce the required quantity of vaccine. All manufacturers that distribute influenza vaccine products in Canada confirm to Health Canada that the vaccines to be marketed in Canada for the upcoming influenza season contain the WHO's recommended antigenic strains for the Northern Hemisphere. Vaccine producers may use antigenically equivalent strains because of their growth properties. The strains recommended for egg-based products may differ somewhat from the strains chosen for cell-culture based products to account for differences in the production platforms.

As of September 2023, the WHO has recommended the removal of B/Yamagata antigen as a component of inactivated and live attenuated influenza vaccines for the Southern Hemisphere 2024 season and consequent transition from quadrivalent to trivalent influenza vaccine formulations as soon as possible. The main impetus for this change is the absence of confirmed detection of naturally occurring B/Yamagata lineage viruses among seasonal influenza strains and concerns regarding the theoretical risk of reintroducing the potentially extinct virus lineage into the population through reassortment of vaccine virus with wild-type circulating viruses [(4)]. NACI will continue to monitor the evolving situation and is planning to review the guidance for quadrivalent and trivalent vaccines next year, as additional information becomes available regarding potential changes to influenza vaccine formulations for the 2024-2025 Northern Hemisphere season.

There are 3 categories of influenza vaccine authorized for use in Canada: IIV, RIV, and LAIV. Trivalent (3-strain) vaccines contain 1 A (H1N1) strain, 1 A(H3N2) strain, and 1 influenza B strain from 1 of the 2 lineages. Quadrivalent (4-strain) vaccines contain the strains in the trivalent vaccine plus an influenza B strain from the other lineage. Most influenza vaccines currently authorized for use in Canada are made from influenza viruses grown in chicken eggs. However, there are 2 exceptions. The influenza viruses used to produce Flucelvax Quad are propagated in a mammalian cell line (Madin-Darby Canine Kidney [MDCK] cells), while the Supemtek vaccine technology uses recombinant HA produced in a proprietary insect cell line using a baculovirus vector for protein expression.

A summary of the characteristics of influenza vaccines available in Canada during the 2024–2025 influenza season can be found in Appendix B. For complete prescribing information, readers should consult the product monographs available through Health Canada's Drug Product Database.

Should additional vaccine preparations become available for use in Canada after the release of this statement and prior to the 2024-2025 influenza vaccine season, NACI will communicate relevant information regarding the new vaccine preparations if required.

Refer to Contents of Immunizing Agents Available for Use in Canada in Part 1 of the CIG for a list of all vaccines authorized for use in Canada.

**Inactivated influenza vaccine (IIV)**

IIVs contain standardized amounts of the HA protein from representative seed strains of the 2 human influenza A subtypes (H3N2 and H1N1) and either 1 (for trivalent vaccines) or both (for quadrivalent vaccines) of the 2 influenza B lineages (Victoria and Yamagata). IIVs currently authorized for use in Canada are a mix of split virus and subunit vaccines, both consisting of disrupted virus particles. In split virus vaccines, the virus has been disrupted by a detergent. In subunit vaccines, HA and NA have been further purified by removal of other viral components. The amount of neuraminidase (NA) in the vaccines is not standardized and not reported. HA-based serum antibody produced to 1 influenza A subtype provides no protection against strains belonging to another subtype. The potential for trivalent vaccine to stimulate antibody protection across B lineages requires further evaluation and may be dependent upon factors such as age and prior antigenic experience with the 2 B lineages[29-34].

All IIVs currently available in Canada are produced in eggs, except for Flucelvax Quad (IIV4-cc), which is a mammalian cell culture-based quadrivalent inactivated, subunit influenza vaccine that is prepared from viruses propagated in mammalian cell lines [proprietary 33016-PF Madin-Darby Canine Kidney (MDCK) cell lines] adapted to grow freely in suspension in culture medium. The production of IIV4-cc does not depend on egg supply as it does not require egg-grown candidate vaccine viruses.

The IIVs available in Canada are in a standard dose formulation or in a formulation designed to enhance the immune response in specific age groups, using a higher dose of HA antigen or the inclusion of an adjuvant. Refer to Basic Immunology and Vaccinology in Part 1 of the CIG for more information about inactivated vaccines.

Standard-dose IIVs currently available in Canada are quadrivalent formulations (IIV4-SD: Afluria® Tetra, Flulaval® Tetra, Fluzone Quadrivalent, and Influvac Tetra; IIV4-cc: Flucelvax Quad). These vaccines are un-adjuvanted, contain a standard dose of antigen (15 µg HA per strain), and are administered as a 0.5 mL dose by IM injection. Influvac Tetra may be administered by IM or deep subcutaneous injection.

The adjuvanted IIV currently authorized for use in Canada is a trivalent subunit vaccine (IIV3-Adj) that contains the adjuvant MF59, which is an oil-in-water emulsion composed of squalene as the oil phase that is stabilized with the surfactants polysorbate 80 and sorbitan triolate in citrate buffer. IIV3-Adj contains 7.5 µg HA per strain administered as a 0.25 mL dose by IM injection for children 6 to 23 months of age (Fluad Pediatric) or 15 µg HA per strain administered as a 0.5 mL dose by IM injection for adults 65 years of age and older (Fluad). Other IIVs do not contain an adjuvant.

There is 1 high-dose IIV (IIV-HD) currently authorized for use in Canada/: Fluzone® High-Dose Quadrivalent (IIV4-HD), a quadrivalent unadjuvanted, split virus seasonal influenza vaccine containing 60 µg HA per strain and administered as a 0.7 mL dose by IM injection for adults 65 years and older.

**Recombinant influenza vaccine (RIV)**

There is currently 1 RIV authorized for use in Canada/: Supemtek (RIV4), a quadrivalent adjuvanted, baculovirus-expressed seasonal influenza vaccine that contains 45 µg HA per strain and is administered as a 0.5 mL dose by IM injection for adults 18 years of age and older. RIV contains recombinant HAs produced in an insect cell line using genetic sequences from cell-derived influenza viruses. The production of RIV does not depend on egg supply as it does not require egg-grown candidate vaccine viruses.

**Live attenuated influenza vaccine (LAIV)**

LAIV contains standardized quantities of fluorescent focus units (FFU) of live attenuated influenza virus reassortants. As a live replicating whole virus formulation administered intranasally by spray, it elicits mucosal immunity, which may more closely mimic natural infection. The virus strains in LAIV are cold-adapted and temperature sensitive, so they replicate in the nasal mucosa rather than the lower respiratory tract, and they are attenuated, so they do not produce ILI. There have been no reported or documented cases, and no theoretical or scientific basis to suggest transmission of vaccine virus would occur to the individual administering LAIV. In rare instances, shed vaccine viruses can be transmitted from vaccine recipients to unvaccinated persons.

There is currently 1 LAIV authorized for use in Canada for children 2 to 17 years of age and adults 18 to 59 years of age: FluMist® Quadrivalent (LAIV4), a quadrivalent nasal spray influenza vaccine given as a 0.2 mL dose (0.1 mL in each nostril).

## IV.2 Efficacy, Effectiveness, and Immunogenicity

### Efficacy and effectiveness

Influenza vaccine has been shown in randomized controlled clinical trials to be efficacious in providing protection against influenza infection and illness. However, the effectiveness of the vaccine—that is, how it performs in settings that are more reflective of usual health care practice—can vary from season to season and by influenza vaccine strain type and subtype. Influenza vaccine effectiveness (VE) depends on how well the vaccine strains match with circulating influenza viruses, the type and subtype of the circulating virus, as well as the health and age of the individual receiving the vaccine. Even when there is a less-than-ideal match or lower VE against 1 strain, the possibility of lower VE should not preclude vaccination, particularly for people at high risk of influenza-related complications and hospitalization, since vaccinated individuals are still more likely to be protected compared to those who are unvaccinated.

Influenza infection has been associated with increased risk of cardiovascular events, including myocardial infarction, heart failure and stroke, especially among individuals with pre-existing cardiac disorders [35-38]. In addition to the prevention of influenza infection, influenza vaccination may also have a secondary protective effect against the occurrence of cardiovascular disease (CVD) in those who are at high risk of CVD [39-43]. Research is ongoing in this area.

### Immunogenicity

Antibody response after vaccination depends on several factors, including the age of the recipient, prior and subsequent exposure to antigens, and the presence of immune compromising conditions. Protective levels of humoral antibodies, which correlate with protection against influenza infection, are

generally achieved by 2 weeks after vaccination; however, there may be some protection afforded before that time.

### Additional information

Refer to Appendix C for further information on the efficacy and effectiveness, immunogenicity, and safety of influenza vaccines that are authorized for use in Canada by type: IIV, RIV and LAIV.

Because of potential changes in the circulating influenza virus from year to year and waning immunity in vaccine recipients, annual influenza vaccination is recommended. Although some studies suggest vaccine induced protection may be greater in individuals who have no recent vaccine history, overall, the evidence shows no difference in the VE of repeated influenza vaccination compared to vaccination in the current season only. Importantly, optimal protection against influenza is best achieved through annual influenza vaccination, as repeated vaccination including the current season is consistently more effective than no vaccination in the current season [44, 45]. Additional information regarding the effects of repeated influenza vaccination on vaccine effectiveness, efficacy, and immunogenicity can be found in the NACI Recommendation on Repeated Seasonal Influenza Vaccination. NACI will continue to monitor this issue.

NACI acknowledges that evidence related to influenza vaccine performance, particularly with respect to vaccine efficacy and effectiveness, is constantly evolving with advances in research methodology and accumulation of data over many influenza seasons. Therefore, the evidence summarized in Appendix C may not include the latest studies. However, NACI continues to closely monitor the emerging evidence on the efficacy and effectiveness, immunogenicity, and safety of influenza vaccines to update and make recommendations when warranted.

## IV.3 Vaccine Administration

### Dose, route of administration, and schedule

With the variety of influenza vaccines available for use in Canada, it is important for vaccine providers to note the specific differences in age indication, route of administration, dosage, and schedule for the products that they will be using (see Table 1). Key relevant details and differences between vaccine products are also highlighted in Appendix B.

For influenza vaccines given by the IM route, the anterolateral thigh muscle is the recommended site in infants 6 to 12 months of age. The anterolateral thigh or the deltoid muscle can be used for toddlers and older children. The deltoid muscle of the arm is the preferred injection site in adolescents and adults. For more information on vaccine administration, please refer to Vaccine Administration Practices in Part 1 of the CIG.

The first time that children 6 months to less than 9 years of age receive seasonal influenza vaccination, a 2-dose schedule is required to achieve protection[46-48]. Several studies have looked at whether these 2 initial doses need to be given in the same season[31, 32, 49]. Englund et al. reported similar immunogenicity in children 6 to 23 months of age whether 2 doses were given in the same or separate seasons when there was no change, or only minor vaccine strain change, in vaccine formulation between seasons[31, 32]. However, seroprotection rates to the B component were considerably reduced in the group that received only 1 dose in the subsequent season when there was a major B lineage change, suggesting that the major change in B virus lineage reduced the priming benefit of previous vaccination[30, 32]. Issues related to effective prime-boost when there is a major change in influenza B

lineage across sequential seasons require further evaluation[50]. Because children 6 to 23 months of age are less likely to have had prior priming exposure to an influenza virus, special effort is warranted to ensure that a 2-dose schedule is followed for previously unvaccinated children in this age group.

**Table 1: Recommended dose and route of administration, by age, for influenza vaccine types authorized for the 2024-2025 influenza season**

| Age group | Influenza vaccine type (route of administration) | | | | | | Number of doses required |
|---|---|---|---|---|---|---|---|
| | IIV-SD[a] (IM) | IIV-cc[b] (IM) | IIV-Adj[c] (IM) | IIV-HD[d] (IM) | RIV[e] (IM) | LAIV[f] (intranasal) | |
| 6 to 23 months[g] | 0.5 mL[h] | 0.5 mL | 0.25 mL | - | - | - | 1 or 2[i] |
| 2 to 8 years | 0.5 mL | 0.5 mL | - | - | - | 0.2 mL (0.1 mL per nostril) | 1 or 2[i] |
| 9 to 17 years | 0.5 mL | 0.5 mL | - | - | - | 0.2 mL (0.1 mL per nostril) | 1 |
| 18 to 59 years | 0.5 mL | 0.5 mL | - | - | 0.5 mL | 0.2 mL (0.1 mL per nostril) | 1 |
| 60 to 64 years | 0.5 mL | 0.5 mL | - | - | 0.5 mL | - | 1 |
| 65 years and older | 0.5 mL | 0.5 mL | 0.5 mL | 0.7 mL | 0.5 mL | - | 1 |

**Abbreviations:** IIV-Adj: adjuvanted inactivated influenza vaccine; IIV-cc: mammalian cell culture based inactivated influenza vaccine; IIV-HD: high-dose inactivated influenza vaccine; IIV-SD: standard-dose inactivated influenza vaccine; RIV: recombinant influenza vaccine; IM: intramuscular; LAIV: live attenuated influenza vaccine.

[a] Afluria® Tetra (5 years and older), Flulaval® Tetra (6 months and older), Fluzone® Quadrivalent (6 months and older), Influvac® Tetra (6 months and older)
[b] Flucelvax® Quad (6 months and older)
[c] Fluad Pediatric® (6 to 23 months) or Fluad® (65 years and older)
[d] Fluzone® High-Dose Quadrivalent (65 years and older)
[e] Supemtek™(18 years and older)
[f] FluMist® Quadrivalent (2 to 59 years)
[g] There is insufficient evidence for recommending vaccination with Influvac Tetra (IIV4-SD) in children younger than 3 years of age.
[h] Evidence suggests moderate improvement in antibody response in infants, without an increase in reactogenicity, with the use of full vaccine doses (0.5 mL) for unadjuvanted inactivated influenza vaccines [10, 11]. This moderate improvement in antibody response without an increase in reactogenicity is the basis for the full dose recommendation for unadjuvanted inactivated vaccine for all ages. For more information, refer to Statement on Seasonal Influenza Vaccine for 2011–2012.
i Children 6 months to less than 9 years of age receiving seasonal influenza vaccine for the first time in their life should be given 2 doses of influenza vaccine, with a minimum interval of 4 weeks between doses. Children 6 months to less than 9 years of age who have been properly vaccinated with 1 or more doses of seasonal influenza vaccine in the past should receive 1 dose of influenza vaccine per season thereafter.

## Booster doses and revaccination

Booster doses are not required within the same influenza season. However, children 6 months to less than 9 years of age who have not previously received the seasonal influenza vaccine require 2 doses of influenza vaccine, with a minimum of 4 weeks between doses. Only 1 dose of influenza vaccine per season is recommended for everyone else. Two (2) doses of influenza vaccine in the same season do not appear to improve the immune response to the vaccine compared to 1 dose in older adults [51].

### Serological testing

Serologic testing is not necessary or recommended before or after receiving seasonal influenza vaccine.

## IV.4 Storage requirements

Influenza vaccine should be stored at +2°C to +8°C and should not be frozen. Refer to the individual product monographs for further details. Refer to Storage and Handling of Immunizing Agents in Part 1 of the CIG for additional information.

## IV.5 Concurrent administration with other vaccines

All seasonal influenza vaccines, including LAIV, may be given at the same time as, or at any time before or after administration of other vaccines (either live or inactivated), including COVID-19 vaccines for those aged 6 months of age and older.

NACI will continue to monitor the evidence base, including ongoing and anticipated trials investigating influenza vaccines administered at the same time as, or any time before or after, COVID-19 vaccines and update its recommendations as needed.

Refer to the COVID-19 vaccine: CIG chapter and latest NACI COVID-19 vaccine guidance for any additional emerging guidance on concurrent administration with COVID-19 vaccines as new products are authorized or there are COVID-19 age eligibility expansions.

No studies were found on potential immune interference between LAIV and other live attenuated vaccines (oral or parenteral) administered within 4 weeks.

Studies on concurrent administration of LAIV3 with measles, mumps, rubella (MMR); measles, mumps, rubella, varicella (MMRV); or live oral polio vaccines did not find evidence of clinically significant immune interference[52-54]. One (1) study reported a statistically significant but not clinically meaningful decrease in seroresponse rates to rubella antigen when administered concomitantly with LAIV.

In theory, the administration of 2 live vaccines sequentially within less than 4 weeks could reduce the efficacy of the second vaccine. Possible immune mechanisms include: the inhibitory and immunomodulatory effects of systemic and locally produced cytokines on B- and T-cell response and viral replication; immunosuppression induced by certain viruses (such as measles); and direct viral interference as a result of competition for a common niche. Mucosal vaccines may have less impact on a parenteral vaccine and vice versa. The immune response with a mucosal vaccine may be compartmentalized to the mucosa while that to a parenteral vaccine is systemic. It is likely that there is some interaction between the systemic and mucosal compartments; however, the extent to which this interaction occurs is not known.

Given the lack of data for immune interference, and based on expert opinion, NACI recommends that LAIV can be given together with or at any time before or after the administration of any other live attenuated or inactivated vaccine. While some vaccine providers have given LAIV and other live vaccines separated by at least 4 weeks based on the theoretical possibility of immune interference, NACI does not believe that this precaution is necessary for LAIV. The use of a parenteral inactivated or recombinant influenza vaccine would avoid this theoretical concern. Note that the timing rules

related to 2 parenteral live vaccines (e.g., MMR and varicella vaccines) still apply. For more information regarding vaccination administration timing rules, please refer to Timing of Vaccine Administration in Part 1 of the CIG.

The target groups for influenza and pneumococcal polysaccharide vaccines overlap considerably. A recent study showed that compared to administration alone, concurrent administration of IIV4 with PCV15 in adults demonstrated non-inferiority of pneumococcal- and influenza-specific antibody responses[55]. The immune response to many PCV components was decreased, but not influenza virus components. The clinical significance of this interaction is not known precisely. Vaccine providers should take the opportunity to vaccinate eligible people against pneumococcal disease when influenza vaccine is given.

NACI guidance as of December 2022 outlines that administration of COVID-19 vaccines may occur at the same time as, or at any time before or after influenza immunization (including all parenteral or intranasal seasonal influenza vaccines) for those aged 6 months of age and older. Readers should consult the COVID-19 vaccine: CIG chapter for updated NACI guidance and further information on concurrent administration of COVID-19 vaccines with influenza vaccines and across all eligible age groups.

When more than 1 injection is given at a single clinic visit, it is preferable to administer them in different limbs. If it is not possible to do so, injections given in 1 limb should be separated by a distance of at least 2.5 cm (1 inch). A separate needle and syringe should always be used for each injection.

### Concurrent administration with other adjuvanted vaccines

Data are limited regarding concurrent administration of newer adjuvanted influenza vaccines with other adjuvanted or non-adjuvanted vaccines.

RZV is an example of a recombinant adjuvanted subunit herpes zoster vaccine (Shingrix®, GlaxoSmithKline) that is authorized for use in Canada in adults 50 years of age and older, and adults 18 years of age or older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy; therefore, the target age group for herpes zoster vaccine and influenza vaccine overlap. RZV has been shown to be safe and effective when given concurrently with unadjuvanted, standard dose influenza vaccines [56]. However, no studies have been conducted that have assessed the concurrent administration of RZV with adjuvanted or high dose influenza vaccine [57]. It should be noted that RZV and IIV-Adj currently authorized for use in Canada contain the adjuvants $AS01_B$ and MF59, respectively. How these adjuvants may interact when RZV and IIV-Adj are administered concurrently is not known.

NACI will continue to review the evidence and update guidance accordingly.

## IV.6 Vaccine Safety and Adverse Events

Post-marketing surveillance of influenza vaccines in Canada has shown that seasonal influenza vaccines have a safe and stable profile. In addition to routine surveillance, every year during the seasonal influenza vaccination campaigns, PHAC and the Federal/Provincial/Territorial Vaccine Vigilance Working Group (VVWG) of the Canadian Immunization Committee conduct weekly expedited surveillance of adverse events following immunization (AEFI) for current influenza vaccines to identify vaccine safety signals in a timely manner. Refer to the section *Guidance on reporting adverse events following immunization* below for more information on mandatory reporting of AEFIs. Refer to the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) web

page for more information on post-marketing surveillance and AEFIs in Canada. In addition, the Canadian National Vaccine Safety (CANVAS) Network, a national network of sites across Canada for active vaccine safety surveillance, collects and analyzes information on AEFIs after influenza vaccination to provide influenza vaccine safety information to public health authorities during the core weeks of the annual influenza vaccination campaign.

All influenza vaccines currently authorized for use in Canada are considered safe for use in people with latex allergies. The multi-dose vial formulations of inactivated influenza vaccine that are authorized for use in Canada contain minute quantities of thimerosal, which is used as a preservative[58, 59] to keep the product sterile. Large cohort studies of administrative health databases have found no association between childhood vaccination with thimerosal-containing vaccines and neurodevelopmental outcomes, including autistic-spectrum disorders[60]. All single dose formulations of IIV, RIV and LAIV are thimerosal-free. Refer to Vaccine Safety in Part 2 of the CIG for additional information.

## Common adverse events

With IM administered influenza vaccines, injection site reactions are common but are generally classified as mild and transient. IIV-Adj tends to produce more extensive injection site reactions than un-adjuvanted IIV, but these reactions are also generally mild and resolve spontaneously within a few days. IIV-HD tends to induce higher rates of systemic reactions compared to IIV-SD, but most of these reactions are mild and short-lived. Recombinant vaccines appear to have a similar safety profile to IIVs. The most common adverse events (AE) experienced by recipients of LAIV are nasal congestion and runny nose.

## Less common and serious or severe adverse events

Serious adverse events (SAEs) are rare following influenza vaccination, and in most cases, data are insufficient to determine a causal association. Allergic responses to influenza vaccine are a rare consequence of hypersensitivity to some components of the vaccine or its container.

## Other reported adverse events and conditions

### Egg-allergic individuals

After careful review of clinical and post-licensure safety data, NACI has concluded that egg-allergic individuals may be vaccinated against influenza using any influenza vaccine, including egg-based vaccines and LAIV, without prior influenza vaccine skin test and with the full dose, irrespective of a past severe reaction to egg and without any particular consideration, including vaccination setting. The amount of trace ovalbumin allowed in influenza vaccines that are authorized for use in Canada is associated with a low risk of AE, and in addition, 2 of the authorized products (i.e., IIV-cc and RIV) do not contain any ovalbumin. For more guidance on vaccinating egg-allergic individuals, refer to the Statement on Seasonal Influenza Vaccine for 2018–2019 and the egg allergy LAIV addendum for safety data supporting this recommendation for IIV and LAIV.The observation period post-vaccination is as recommended in Vaccine Safety in Part 2 of the CIG. As with all vaccine administration, vaccine providers should be prepared with the necessary equipment, knowledge, and skills to respond to allergic reactions, including anaphylaxis, at all times.

### Guillain-Barré syndrome

In a review of studies conducted between 1976 and 2005, the United States Institute of Medicine concluded that the 1976 “swine flu” vaccine was associated with an elevated risk of GBS. However,

evidence was inadequate to accept or to reject a causal relation between GBS in adults and seasonal influenza vaccination[61]. The attributable risk of GBS in the period following seasonal and monovalent 2009 pandemic influenza vaccination is about 1 excess case per million vaccinations[62, 63]. In a self-controlled study that explored the risk of GBS after seasonal influenza vaccination and after influenza health care encounters (a proxy for influenza illness), the attributable risks were 1.03 GBS admissions per million vaccinations compared with 17.2 GBS admissions per million influenza-coded health care encounters [47, 63].

These findings suggest that both influenza vaccination and influenza illness are associated with small attributable risks of GBS, but the risk of GBS associated with influenza illness is notably higher than with influenza vaccination. The self-controlled study also found that the risk of GBS after vaccination was highest during weeks 2 to 4, whereas for influenza illness, the risk was greatest within the first week after a health care encounter and decreased thereafter but remained significantly elevated for up to 4 weeks.

Although the evidence considering influenza vaccination and GBS is inadequate to accept or reject a causal relation between GBS in adults and seasonal influenza vaccination, avoiding subsequent influenza vaccination of individuals known to have had GBS without other known etiology within 6 weeks of a previous influenza vaccination appears prudent at this time. However, the potential risk of GBS recurrence associated with influenza vaccination must be balanced against the risk of GBS associated with influenza infection itself and the other benefits of influenza vaccination [48-51, 64-67].

**Oculorespiratory syndrome**

Oculorespiratory syndrome (ORS), the presence of bilateral red eyes and 1 or more associated respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness, or sore throat) that starts within 24 hours of vaccination, with or without facial oedema, was identified during the 2000–2001 influenza season[68]. Since then, there have been far fewer cases per year reported to CAEFISS[69]. ORS is not an allergic response. People who have an occurrence or recurrence of ORS upon vaccination do not necessarily experience further episodes with future vaccinations.

Individuals who have experienced ORS without lower respiratory tract symptoms may be safely revaccinated with influenza vaccine. Individuals who experienced ORS with lower respiratory tract symptoms should have an expert review. Health care providers who are unsure whether an individual previously experienced ORS versus an immunoglobulin E (IgE) mediated hypersensitivity immune response should seek advice. Data on clinically significant AEs do not support the preference of 1 vaccine product over another when revaccinating those who have previously experienced ORS.

## Allergic reactions to previous vaccine doses

Expert review of the benefits and risks of vaccination should be sought for those who have previously experienced severe lower respiratory symptoms (wheeze, chest tightness, difficulty breathing) within 24 hours of influenza vaccination, an apparent significant allergic reaction to the vaccine, or any other symptoms that could indicate a significant allergic reaction (e.g., throat constriction, difficulty swallowing) that raise concern regarding the safety of revaccination. This advice may be obtained from experts in infectious disease, allergy, and immunology, or public health that can be found in various health settings, including the Special Immunization Clinic (SIC) network.

In view of the considerable morbidity and mortality associated with influenza and rarity of true vaccine allergy, a diagnosis of allergy to an influenza vaccine should not be made without confirmation, which may involve consultation with an allergy or immunology expert.

### Drug interactions

Although influenza vaccine can inhibit the clearance of warfarin and theophylline, clinical studies have not shown any adverse effects attributable to these drugs in people receiving influenza vaccine. Statins have effects on the immune system in addition to their therapeutic cholesterol-lowering actions. Two (2) published studies have found that adults who are regular statin users (at least 65 years of age[70] in 1 study and 45 years and older in the other[71]) had a decreased response to influenza vaccination as measured by reduced geometric mean titres (GMT)[70] or reduced VE against medically attended acute respiratory illness[71]. Statins are widely used in the same adult populations who are also at-risk for influenza-related complications and hospitalizations. Therefore, if these preliminary findings are confirmed in future studies, concurrent statin use in adult populations could have implications for influenza VE and how this use is assessed in the measurement of VE. NACI will continue to monitor the literature related to this issue.

Antiviral agents (e.g., oseltamivir, zanamivir) may inactivate the replicating vaccine virus contained in LAIV. Administration of LAIV should be postponed until 48 hours after the last dose of an antiviral. If these antiviral agents are required for clinical management of an infection within 2 weeks after receiving a dose of LAIV vaccine, re-vaccination should take place either at least 48 hours after the antivirals are stopped or another influenza vaccine (inactivated or recombinant) can be administrated at any time.

### Guidance on reporting adverse events following immunization

To ensure the ongoing safety of influenza vaccines in Canada, reporting of AEFIs by vaccine providers and other clinicians is critical, and in most jurisdictions, reporting is mandatory under the law.

An AEFI is any untoward medical occurrence that follows vaccination whether or not there is a causal relationship with the usage of a vaccine. The AEFI may be any unfavourable or unintended sign, abnormal laboratory finding, symptom, or disease. Any AEFI temporally related to vaccination and for which there is no other clear cause at the time of reporting should be reported. Vaccine providers are asked to report AEFIs through local public health officials and to check for specific AEFI reporting requirements in their province or territory. If there is any doubt as to whether or not an event should be reported, a conservative approach should be taken, and the event should be reported.

For influenza vaccines, the following AEFIs are of particular interest:

- ORS; and
- GBS within 6 weeks following vaccination

Refer to Reporting Adverse Events Following Immunization (AEFI) in Canada for additional information about AEFI reporting and to Vaccine Safety in Part 2 of the CIG for general vaccine safety information, including information on the management of AEs.

# V. RECOMMENDATIONS

NACI makes the following recommendations for individual-level and public health program-level decision making. Individual-level recommendations are intended for people wishing to protect themselves from influenza or for vaccine providers wishing to advise individual patients about preventing influenza. Program-level recommendations are intended for provinces and territories responsible for making decisions on publicly funded immunization programs. Individual-level and program-level recommendations may differ, as the important factors to consider when recommending a vaccine for a population (e.g., population demographics, economic considerations) may be different than for an individual.

**Recommendation for individual-level decision making**

NACI recommends that influenza vaccine should be offered annually to anyone 6 months of age and older who does not have a contraindication to the vaccine. Influenza vaccination is particularly important for the groups indicated in List 1.

**Recommendations for public health program-level decision making**

The national goal of the annual influenza immunization programs in Canada is to prevent serious illness caused by influenza and its complications, including death. Programmatic decisions to provide influenza vaccination to target populations as part of publicly funded provincial and territorial programs depend on many factors, such as cost-effectiveness evaluation and other programmatic and operational factors, such as implementation strategies.

- NACI recommends that influenza vaccine should be prioritized for the groups for whom influenza vaccination is particularly important (see List 1 in the section below).

**List 1: Groups for whom influenza vaccination is particularly important**

**People at high risk of influenza-related complications or hospitalization**

- All children 6 to 59 months of age
- Adults and children with the following chronic health conditions [a]:
    - Cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis, and asthma);
    - Diabetes mellitus and other metabolic diseases;
    - Cancer, immune compromising conditions (due to underlying disease, therapy, or both, such as solid organ transplant or hematopoietic stem cell transplant recipients);
    - Renal disease;
    - Anemia or hemoglobinopathy;
    - Neurologic or neurodevelopmental conditions (includes neuromuscular, neurovascular, neurodegenerative, neurodevelopmental conditions, and seizure disorders [and, for children, includes febrile seizures and isolated developmental delay], but excludes migraines and psychiatric conditions without neurological conditions) [b]
    - Morbid obesity (defined as BMI of 40 $kg/m^2$ and over); and
    - Children 6 months to 18 years of age undergoing treatment for long periods with acetylsalicylic acid, because of the potential increase of Reye's syndrome associated with influenza
- All individuals who are pregnant;
- All individuals of any age who are residents of nursing homes and other chronic care facilities;
- Adults 65 years of age and older; and
- Indigenous Peoples.

**People capable of transmitting influenza to those at high risk**

- Health care and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk
- Household contacts, both adults and children, of individuals at high risk, whether or not the individual at high risk has been vaccinated:
    - household contacts of individuals at high risk
    - household contacts of infants less than 6 months of age, as these infants are at high risk but cannot receive influenza vaccine
    - members of a household expecting a newborn during the influenza season;
- Those providing regular childcare to children 0 to 59 months of age, whether in or out of the home; and
- Those who provide services within closed or relatively closed settings to people at high risk (e.g., crew on a cruise ship).

**Others**

- People who provide essential community services; and
- People who are in direct contact with poultry infected with avian influenza during culling operations

[a] Refer to Immunization of Persons with Chronic Diseases and Immunization of Immunocompromised Persons in Part 3 of the CIG for additional information about vaccination of people with chronic diseases.

[b] Refer to the NACI Statement on Seasonal Influenza Vaccine for 2018–2019 for rationale supporting the decision to include persons with neurologic or neurodevelopment conditions among the groups for whom influenza vaccination is particularly important and the Literature Review on Individuals with Neurologic or Neurodevelopment Conditions and Risk of Serious Influenza-Related Complications for additional details of the evidence reviews that were conducted.

## V.1 Choice of Seasonal Influenza Vaccine

With the recent availability of a number of new influenza vaccines, some of which are designed to enhance immunogenicity in specific age groups, the choice of product is now more complex.

Table 2 provides age group-specific recommendations for the age-appropriate influenza vaccine types authorized and available for use in Canada for individual and public health program-level decision making. Additional information for these recommendations are provided in the section below.

**Table 2: Recommendations on choice of influenza vaccine type for individual- and public health program-level decision making by age group**

| Recipient by age group | Vaccine types authorized and available for use | Recommendations on choice of influenza vaccine |
|---|---|---|
| 6 to 23 months | • IIV-Adj<br>• IIV-SD<br>• IIV-cc | • A quadrivalent influenza vaccine authorized for this age group should be used in infants and young children without contraindications, given the burden of influenza B disease in this age group and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine.<br>- Currently, there is insufficient evidence for recommending vaccination with Influvac Tetra (IIV4-SD) in children younger than 3 years of age.<br>• If a quadrivalent vaccine is not available, a trivalent vaccine licensed for this age group should be used. |
| 2 to 17 years [a] | • IIV-SD<br>• IIV-cc<br>• LAIV | • An age-appropriate quadrivalent influenza vaccine (IIV4-SD, LAIV4, or IIV4-cc) should be used in children without contraindications or precautions (see text below applicable to LAIV), including those with chronic health conditions, given the burden of influenza B disease in this age group and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine. If a quadrivalent vaccine is not available, a trivalent vaccine licensed for this age group should be used.<br>o Currently, there is insufficient evidence for recommending vaccination with Influvac Tetra (IIV4-SD) in children younger than 3 years of age.<br>• LAIV4 may be given to children with:<br>o stable, non-severe asthma;<br>o cystic fibrosis who are not being treated with immunosuppressive drugs (e.g., prolonged systemic corticosteroids); and<br>o stable HIV infection, i.e., if the child is currently being treated with ART (i.e., HAART) for at least 4 months and has adequate immune function.<br>• LAIV should not be used in children or adolescents for whom it is contraindicated or for whom there are warnings and precautions such as those with:<br>o severe asthma (defined as currently on oral or high-dose inhaled glucocorticosteroids or active wheezing);<br>o medically attended wheezing in the 7 days prior to vaccination;<br>o current receipt of aspirin or aspirin-containing therapy;<br>o immune compromising conditions, with the exception of stable HIV infection, i.e., if the child is currently being treated with HAART for at least 4 months and has adequate immune function; |

| Recipient by age group | Vaccine types authorized and available for use | Recommendations on choice of influenza vaccine |
|---|---|---|
| | | ○ pregnancy<br>▪ in pregnancy, IIV4-SD or IIV4-cc should be used instead. |
| 18 to 59 years | • IIV-SD<br>• IIV-cc<br>• RIV<br>• LAIV | • Any of the available influenza vaccines authorized for this age group should be used in adults 18-59 years without contraindications or precautions, noting the following consideration and exceptions:<br>○ There is some evidence that IIV may provide better efficacy than LAIV in healthy adults; and<br><br>• LAIV is not recommended for:<br>○ Pregnant individuals<br>▪ in pregnancy, IIV4-SD, IIV4-cc or RIV4 should be used instead.<br>○ adults with any of the chronic health conditions identified in List 1, including immune compromising conditions; and<br>○ health care workers |
| 60 to 64 years | • IIV-SD<br>• IIV-cc<br>• RIV | • Any of the available influenza vaccines authorized for this age group should be used in adults 60 to 64 years without contraindications. |
| 65 years and older [b,c] | • IIV-Adj<br>• IIV-SD<br>• IIV-HD<br>• IIV-cc<br>• RIV | • IIV-HD, IIV-Adj, or RIV should preferentially be offered, when available, over other influenza vaccines for adults 65 years of age and older. If a preferred product is not available, any of the available age-appropriate influenza vaccine should be used. |

**Abbreviations:** ART: antiretroviral therapy; HAART: highly active antiretroviral therapy; IIV: inactivated influenza vaccine; IIV-Adj: adjuvanted inactivated influenza vaccine; IIV-SD: standard-dose inactivated influenza vaccine; IIV-cc: mammalian cell–culture-based inactivated influenza vaccine; IIV4-HD: high-dose quadrivalent inactivated influenza vaccine; IIV4-SD: standard-dose quadrivalent inactivated influenza vaccine; RIV4: recombinant influenza vaccine; LAIV: live attenuated influenza vaccine

[a] Refer to Table 3 for a summary of vaccine characteristics of LAIV compared with IIV in children 2 to 17 years of age.

[b] Refer to Table 4 for a comparison of the vaccine characteristics of influenza vaccine types available for use in adults 65 years of age and older.

[c] Refer to the NACI Supplemental statement on influenza vaccination in adults 65 years of age and older for rationale, supporting evidence appraisal and additional details on the evidence reviews that were conducted to support this recommendation

## V.2 Children

### Burden of disease in children

Children experience a higher burden of disease due to influenza B infection compared to other age groups. Although children less than 24 months of age comprise approximately 2% of the Canadian population [(72)], children 0 to 23 months of age averaged 10.8% of reported influenza B cases (range: 8.3 to 13.7%), using case-based laboratory data from 2001–2012 (excluding 2009). With respect to severe outcomes (e.g., hospitalization, intensive care unit admission, and death), influenza B was confirmed in 15.5 to 58.3% (median: 38.4%) of pediatric influenza-associated hospitalizations (children 16 years of age and younger) reported by the Canadian Immunization Monitoring Program Active (IMPACT) surveillance network between 2004–2005 and 2012–2013 (excluding the 2009–2010 pandemic season) [(73)]. From 2010-2011 to 2020-2021, inclusively, 32% of IMPACT influenza admissions were for influenza B[(74)].

The IMPACT study also found that the proportion of deaths attributable to influenza (any strain) was significantly greater for children admitted to hospital with influenza B (1.1%) than for those admitted

with influenza A (0.4%). The proportion of hospitalizations due to influenza B relative to all influenza hospitalizations has been generally similar to the proportion of influenza B detections relative to all influenza infections in the general population during the same time period. Additional information can be found in the Statement on Seasonal Influenza Vaccine for 2014–2015.

In the NACI Literature Review on Quadrivalent Influenza Vaccines, a review of B lineage antigens included in the Canadian influenza vaccines and the circulating strains each season indicates a match in 5 of the 12 seasons from 2001–2002 through to 2012–2013, a moderate match (about 50% from each lineage) in 1 season, and a mismatch in remaining 6 influenza seasons (i.e., 70% or more of the characterized B strains were of the opposite lineage to the antigen in that season's vaccine).

### Children 6 to 23 months of age

Three (3) types of influenza vaccine are authorized and available for use in children 6 to 23 months of age: IIV-Adj, IIV-SD, and IIV-cc.

Given the burden of influenza B disease in children and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine, NACI recommends that a quadrivalent influenza vaccine should be used. If a quadrivalent vaccine is not available, an available age-appropriate trivalent vaccine should be used.

The current evidence is insufficient for recommending vaccination with Influvac Tetra (IIV4-SD) in children younger than 3 years of age.

### Children 2 to 17 years of age

Three (3) types of influenza vaccine are authorized and available for use in children 2 to 17 years of age: IIV-SD, IIV-cc, and LAIV.

The current evidence does not support a recommendation for the preferential use of LAIV in children and adolescents 2 to 17 years of age. Refer to the NACI Statement on Seasonal Influenza Vaccine for 2018–2019 for information supporting this recommendation.

The current evidence is insufficient for recommending vaccination with Influvac Tetra (IIV4-SD) in children younger than 3 years of age.

**Children 2 to 17 years of age with chronic health conditions**

NACI recommends that any age-appropriate influenza vaccine (IIV or LAIV) may be considered for children 2 to 17 years of age with chronic health conditions; however, LAIV should not be used for children with severe asthma (as defined as currently on oral or high-dose inhaled glucocorticosteroids or with active wheezing), those with medically attended wheezing in the 7 days prior to vaccination, those currently receiving aspirin or aspirin-containing therapy, and those with immune compromising conditions, excluding those with stable HIV infection on HAART and with adequate immune function. LAIV is also contraindicated in adolescents who are pregnant. Children and adolescents for whom LAIV is contraindicated should receive IIV. If IIV is used, NACI recommends that a quadrivalent vaccine should be used. If a quadrivalent vaccine is not available, an age-appropriate trivalent vaccine should be used.

NACI recommends that LAIV may be given to children with stable, non-severe asthma, children with cystic fibrosis who are not treated with immunosuppressive drugs, such as prolonged systemic corticosteroids, and children with stable HIV infection on HAART and with adequate immune function.

Refer to the NACI Recommendations on the Use of Live, Attenuated Influenza Vaccine (FluMist®): Supplemental Statement on Seasonal Influenza Vaccine for 2011–2012 for additional information supporting these recommendations.

**Summary of vaccine characteristics for decision making**

IIV-SD, IIV-cc, and LAIV are authorized for use in Canada for children 2 to 17 years of age. The comparison of the vaccine characteristics of IIV and LAIV, in Table 3 below, may be considered in deciding on the preferred vaccine option(s) for use by an individual or a public health program. Note that although data comparing LAIV to IIV-cc are not available, IIV-cc is comparable to egg-based IIV.

**Table 3: Vaccine characteristics of live attenuated influenza vaccine (LAIV) compared with inactivated influenza vaccine (IIV) in children 2 to 17 years of age**

| Considerations[a] | LAIV[b] compared with IIV[c] |
|---|---|
| Efficacy and effectiveness | There was early evidence of superior efficacy of LAIV3 compared with IIV3-SD in children less than 6 years of age from randomized controlled trials, with weaker evidence of superior efficacy in older children. However, later post-marketing and surveillance studies across multiple influenza seasons found comparable protection against influenza for LAIV and IIV, with findings of reduced effectiveness for LAIV against A (H1N1) in some studies. |
| Immunogenicity | LAIV has been shown to be as immunogenic as IIV-SD, depending on age. |
| Safety | Rhinitis (runny nose) and nasal congestion are more common with LAIV. Clinical studies and post-marketing studies showed a similar safety profile to IIV. |
| Contraindications | There are vaccine contraindications specific to LAIV. LAIV is contraindicated for children with severe asthma, medically attended wheezing in the 7 days prior to vaccination, and immune compromising conditions (with the exception of children with stable HIV infection on HAART and with adequate immune function), as well as those currently receiving aspirin or aspirin-containing therapy. LAIV is also contraindicated for pregnant adolescents. |
| Acceptability | Delivery of LAIV as a nasal spray may be preferable for children who are averse to receiving the vaccine by needle injection. |

**Abbreviations:** HAART: highly active antiretroviral therapy; IIV: inactivated influenza vaccine; IIV-SD: standard-dose inactivated influenza vaccine; IIV-SD: standard-dose inactivated influenza vaccine; LAIV: live attenuated influenza vaccine; LAIV: live attenuated influenza vaccine; LAIV4: quadrivalent live attenuated influenza vaccine.

[a] NACI has not assessed the comparative cost-effectiveness of authorized influenza vaccine types for children 2 to 17 years of age.

[b]The trivalent formulation of LAIV (LAIV3) received a Notice of Compliance from Health Canada in June 2010 and was first used in publicly funded immunization programs in Canada for the 2012–2013 influenza season. The quadrivalent formulation (LAIV4) was approved for use in Canada for the 2014–2015 season and has been in use since that time.

[c]Data comparing LAIV to IIV-cc are not available, however IIV-cc is comparable to egg-based IIV.

## V.3 Adults

### Burden of disease in adults

A study focusing on estimates of deaths associated with influenza in the United States has established that the average annual rate of influenza-associated deaths for adults aged 65 years of age and older was 17.0 deaths per 100,000 (range: 2.4 to 36.7) [(75)]. The study also states that of deaths coded as being influenza- or pneumonia-related, persons 65 years of age and older accounted for 87.9% of the overall estimated annual average number of deaths. When influenza-related deaths among adults 65 years of age and older were estimated using codes for underlying respiratory and circulatory causes

of death, these estimates increased to 66.1 deaths per 100,000 (range: 8.0 to 121.1) and 89.4%, respectively. This study described a wide variation in the estimated number of deaths from season to season, which was closely related to the influenza virus types and subtypes in circulation. Estimates presented in the study of yearly influenza-associated deaths with underlying pneumonia and influenza causes (1976 to 2007) reveal a large difference between influenza type A and B with a calculated median of greater than 6,000 deaths associated with influenza type A and half of that number for influenza type B (approximately 3,360) for persons 65 years of age and older. During the 22 seasons in which influenza A(H3N2) was the prominent strain, the average influenza-associated mortality rates were 2.7 times higher than for the 9 seasons that it was not (all age groups combined), and on average, there were about 37% more annual influenza-associated deaths, regardless of the primary medical cause of death. A higher risk of hospitalization and death was also reported by Cromer et al. in adults 65 years of age and older, compared to younger adults in their assessment of the burden of influenza in England by age and clinical risk group[76].

Canadian surveillance data show that hospitalization rates among adults 65 years of age and older were higher during the A(H3N2)-predominant 2014–2015 season compared to the previous 5 influenza seasons and also compared to the 2012–2013 season when A(H3N2) also predominated; 2014–2015 was a season in which there was a vaccine mismatch with the circulating A(H3N2) strain. Similar to the hospitalization rates, death rates among older adults were highest in the 2014–2015 season compared to the previous 5 seasons and compared to the previous A(H3N2) season in 2012–2013. Mortality rates among other age groups were similar to or lower than the previous 5 influenza seasons. Laboratory detections over this same time period showed that influenza seasons in which influenza subtype A(H3N2) predominated, disproportionally affected adults 65 years of age and older, while seasons with greater A (H1N1) detections resulted in a higher proportion of positive cases in younger age groups.

### Adults 18 to 59 years of age

Four (4) types of influenza vaccine are authorized and available for use in adults 18 to 59 years of age: IIV-SD, IIV-cc, RIV, and LAIV.

NACI recommends that any of the available influenza vaccines should be used in adults without contraindications to the vaccine. NACI previously found insufficient evidence to recommend the use of LAIV in adults with chronic health conditions due to the potentially better immune response following IIV compared to LAIV in healthy adults in some studies. As such, IIV or RIV should be used for adults with chronic health conditions identified in List 1, HCWs or individuals who are pregnant (noting that limited published clinical data pertaining to safety of vaccination with RIV4 during pregnancy is currently available to inform vaccine-associated risks for this population). For further information, refer to Recommendations on the use of live, attenuated influenza vaccine (FluMist®) Supplemental Statement on Seasonal Influenza Vaccine for 2011-2012.

### Adults 60 to 64 years of age

Three (3) types of influenza vaccine are authorized and available for use in adults 60 to 64 years of age: IIV-SD, IIV-cc, and RIV.

NACI recommends that any of the available age-appropriate influenza vaccines should be used.

## Adults 65 years of age and older

Five (5) types of influenza vaccine are authorized and available for use in adults 65 years of age and older: IIV-Adj, IIV-SD, IIV-cc, IIV-HD, and RIV.

### Recommendation for individual-level and public health program-level decision making

NACI recommends that IIV-HD, IIV-Adj, or RIV should be offered, when available, over other influenza vaccine for adults 65 years of age and older. If a preferred product is not available, any of the available age-appropriate influenza vaccine should be used (Strong NACI Recommendation). Where supply of IIV-HD, IIV-Adj, or RIV is limited, consideration can be given to prioritizing groups at highest risk of severe outcomes from influenza among adults 65 years of age and older, such as advanced-age older adults (e.g., 75 years of age and older), those with 1 or more comorbidities, older frail adults, and residents of nursing homes and other chronic care facilities. Based on a review of the evidence to determine whether any age-appropriate influenza vaccines should be preferentially used in adults 65 years of age and older, the evidence supports IIV-HD, IIV-Adj, and RIV as having increased benefit as compared to IIV-SD, with no difference in safety. No study included in the review of the evidence compared IIV-cc to other influenza vaccines against critical outcomes for decision-making. Consequently, it was not possible to make a recommendation on the preferential use of IIV-cc in adults 65 years of age and older.

Refer to the NACI Supplemental Statement on Influenza Vaccination in Adults 65 Years of Age and Older for additional information supporting these recommendations.

### Summary of vaccine characteristics for decision making

There are 4 types of inactivated influenza vaccines (IIV-Adj, IIV-SD, IIV-cc, and IIV-HD) and 1 type of recombinant influenza vaccine (RIV) authorized for use in Canada for adults 65 years of age and older. The comparison of vaccine characteristics of IIV-HD, IIV-Adj and RIV compared to IIV-SD in adults 65 years of age and older, in Table 4 below, may be considered when deciding on the preferred vaccine option(s) for use by an individual or a public health program. Data directly comparing IIV-cc and IIV4-HD to IIV-SD are not available.

**Table 4. Comparison of the vaccine characteristics of influenza vaccine types available for use in adults 65 years of age and older**

| Considerations[a] | IIV-HD, IIV-Adj and RIV compared to IIV-SD |
|---|---|
| **Efficacy and effectiveness** | IIV-HD, IIV-Adj, and RIV appear to have increased vaccine efficacy and effectiveness as compared to IIV-SD.<br><br>Notably, IIV-HD has the most substantial body of supporting evidence, followed by IIV-Adj, and then RIV. The magnitude of relative benefit varied and was not seen in all studies and all seasons.<br><br>There are few RCTs comparing IIV-HD, IIV-Adj, and RIV to IIV-SD and to 1 another. No RCT compared IIV-Adj with IIV-SD for the outcome of LCI.<br><br>No definitive conclusion can be reached regarding the superiority of any of these vaccines over 1 another as there is limited evidence directly comparing IIV-HD, IIV-Adj, and RIV against each other.<br>There is limited evidence on newer vaccine technologies (e.g., IIV-cc and RIV).<br><br>Further evidence is needed on the efficacy and effectiveness of influenza vaccines in subpopulations of adults 65 years of age and older at higher risk of severe influenza-related outcomes and complications, such as advanced-age older adults, individuals living with 1 or more chronic medical conditions, and frail individuals. |
| **Safety** | IIV-HD, IIV-Adj, and RIV appear to be well-tolerated and safe alternatives to IIV-SD in adults 65 years of age and older.<br><br>Evidence suggests that there is no difference in safety between IIV-HD, IIV-Adj, and RIV based on direct evidence among adults 65 years of age and older.<br>Only a few studies reported data for certain vaccine comparisons (e.g., IIV-Adj vs RIV4).<br>Limited data were available for Guillain-Barré Syndrome. |
| **Economics** | IIV-HD and IIV-Adj may be considered cost-effective when compared to IIV-SD under commonly used cost-effectiveness thresholds [77].<br>There is no economic evidence directly comparing IIV-HD, IIV-Adj, and RIV against each other [78]. |
| **EEFA** | Equity could potentially be increased for older adults at greater risk of severe illness and influenza-related complications if they are given vaccines with higher efficacy. Feasibility from a provider and policymaker perspective may be decreased as enhanced vaccines have higher costs and the level of increased efficacy is uncertain.<br><br>Acceptability may be increased for high-risk groups due to increased perceived benefits of preferred vaccines in adults 65 years of age and older.<br>Reducing the burden of disease may increase acceptability from the providers' and policymakers' perspectives. However, due to a lack of data supporting higher efficacy and potential increased costs, the use of a preferred vaccine may not be as acceptable. |

**Abbreviations:** IIV-Adj: adjuvanted inactivated influenza vaccine; IIV-HD: high-dose inactivated influenza vaccine; IIV-SD: standard-dose inactivated influenza vaccine; LCI: laboratory-confirmed influenza; RCT: randomized controlled trial; RIV: recombinant influenza vaccine.

[a] For additional information, please refer to the NACI supplemental guidance on influenza vaccination in adults 65 years of age and older.

### Adults with chronic health conditions

NACI recommends that any age-appropriate IIV or RIV, but not LAIV, should be offered to adults with chronic health conditions identified in List 1, including those with immune compromising conditions.

### Pregnant individuals

NACI recommends that any age-appropriate IIV or RIV, but not LAIV, should be offered to pregnant individuals (noting that limited published clinical data pertaining to safety of vaccination with RIV4 during pregnancy is currently available to inform vaccine-associated risks).

Due to a lack of safety data at this time, LAIV should not be administered to pregnant individuals due to the theoretical risk to the fetus from administering a live virus vaccine. LAIV can be administered to breastfeeding individuals.

### Health care workers

NACI recommends that any age-appropriate IIV or RIV, but not LAIV, should be offered to HCWs.

Comparative studies in healthy adults have found IIV to be similarly or more efficacious or effective compared with LAIV[79]. In addition, as a precautionary measure, LAIV recipients should avoid close association with people with severe immune compromising conditions (e.g., bone marrow transplant recipients requiring isolation) for at least 2 weeks following vaccination, because of the theoretical risk for transmitting a vaccine virus and causing infection.

### Travellers

Influenza occurs year-round in the tropics. In temperate northern and southern countries, influenza activity generally peaks during the winter season (November to March in the Northern Hemisphere and April to October in the Southern Hemisphere).

- NACI recommends that influenza vaccine should be offered annually to anyone 6 months of age and older, including travellers, who does not have a contraindication to the vaccine, with focus on the groups for whom influenza vaccination is particularly important (see List 1).

Vaccines prepared specifically for use in the Southern Hemisphere are not available in Canada, and the extent to which recommended vaccine components for the Southern Hemisphere may overlap with those in available Canadian formulations will vary. A decision for or against revaccination (i.e., boosting) of travellers to the Southern Hemisphere between April and October, if they had already been vaccinated in the preceding fall or winter with the Northern Hemisphere's vaccine, depends on individual risk assessment, the similarity between the Northern and Southern Hemisphere vaccines, the similarity between the Northern Hemisphere vaccine strains and currently circulating strains in the Southern Hemisphere, and the availability of a reliable and safe vaccine at the traveller's destination. Refer to Immunization of Travellers in Part 3 of the CIG for additional general information.

## V.4 Particularly Important Vaccine Recipients

The groups for whom influenza vaccination is particularly important are presented in List 1. Additional information regarding recipients for whom influenza vaccination is particularly important is provided below.

### All children 6 to 59 months of age

On the basis of existing data, NACI recommends the inclusion of all children 6 to 59 months of age among those for whom influenza vaccine is particularly important.

Refer to the Statement on Seasonal Influenza Vaccine for 2011–2012 for additional details on children 6 to 23 months of age and to the Statement on Seasonal Influenza Vaccine for 2012–2013 for children 24 to 59 months of age.

### Adults and children with chronic health conditions

As noted in List 1, a number of chronic health conditions are associated with increased risk of influenza-related complications and can be exacerbated by a flu infection. Influenza vaccination can induce protective antibody levels in a substantial proportion of adults and children with immune-compromising conditions, including transplant recipients, those with proliferative diseases of the hematopoietic and lymphatic systems, and HIV-infected people. Vaccine effectiveness may be lower in people with immune compromising conditions than in healthy adults.

### All individuals who are pregnant

Pregnant individuals along with infants under 6 months of age are particularly at risk of severe illness from influenza infection [12, 80, 81]. A significant number of studies have been published on influenza vaccination during pregnancy. Overall, the evidence supports the safety and effectiveness of influenza vaccines during pregnancy [82]. Vaccination reduces the morbidity and mortality associated with influenza infection in pregnant persons[83]. Since influenza-related outcomes experienced during pregnancy can negatively impact the development of the fetus, vaccination of the pregnant person also helps protect the fetus [83]. Furthermore, passive transfer of antibodies from vaccination during pregnancy protects newborns during their first months of life when they are at high risk of complications from influenza infection, and too young to be immunized.
NACI continues to strongly recommend that inactivated or recombinant influenza vaccines be offered during pregnancy, at any gestational age. NACI also continues to include pregnant individuals among those for whom influenza vaccination is particularly important. Finally, NACI reaffirms its recommendation that influenza vaccination may be given at the same time as, or at any time before or after administration of another vaccine, including the COVID-19 or pertussis vaccine.

For further details, refer to the Supplemental Statement on Updated guidance on influenza vaccination during pregnancy.

### People of any age who are residents of nursing homes and other chronic care facilities

Residents of nursing homes and other chronic care facilities often have 1 or more chronic health condition and live in institutional environments that may facilitate the spread of influenza.

### Adults 65 years of age and older

Hospitalization attributable to influenza in this age group is estimated at 125 to 228 per 100,000 healthy people[84], and influenza-attributed mortality rates increase with increased age[85].

### Indigenous Peoples

Based on a body of evidence indicating a higher rate of influenza-associated hospitalization and death among Indigenous peoples [86], NACI recommends the inclusion of this population among those for whom the influenza vaccine is particularly important.

It has been proposed that the increased risk of severe influenza outcomes in the Indigenous populations is a consequence of many factors, including high prevalence of chronic health conditions (e.g., diabetes, chronic lung disease, end-stage kidney disease, cardiovascular disease, obesity) ([87]), delayed access to health care, and increased susceptibility to disease because of poor housing and overcrowding [88-90]. A review of the available evidence and update to the recommendations for Indigenous peoples as a group at high-risk of influenza-related complications is planned, with inclusion and consideration of key stakeholder engagement.

## V.5 People Capable of Transmitting Influenza to Those at High Risk of Influenza-Related Complications or Hospitalization

People who are potentially capable of transmitting influenza to those at high risk should receive annual vaccination, regardless of whether the high-risk individual has been vaccinated. Vaccination of Health Care Workers (HCWs) decreases their own risk of illness[91, 92], as well as the risk of death and other serious outcomes among the individuals for whom they provide care [93-96]. Vaccination of HCWs and residents of nursing homes is associated with decreased risk of ILI outbreaks[97].

People who are more likely to transmit influenza to those at high risk of influenza-related complications or hospitalization include:

- HCWs and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk; and
- Contacts, both adults and children, of individuals at high risk, whether or not the individual at high risk has been vaccinated

### Health care workers and other care providers in facilities and community settings

**Vaccination of health care workers and other care providers**

For the purposes of this statement, HCWs and other care providers in facilities and community settings refers to HCWs, essential care providers, emergency response workers, those who work in continuing care or long-term care facilities or residences, those who provide home care for people at high risk, and students of related health care services. HCWs include any person, paid or unpaid, who provides services, works, volunteers, or trains in a hospital, clinic, or other health care facility.

Transmission of influenza to patients at high risk of influenza-associated complications results in significant morbidity and mortality. Four (4) cluster randomized controlled trials (RCTs) conducted in geriatric long-term care settings have demonstrated that vaccination of HCWs is associated with substantial decreases in influenza-like illness [94-96] and all-cause mortality [93-96] in the residents. In addition, due to their occupation and close contact with people who may be infected with influenza, HCWs are themselves at increased risk of infection[98].

As previously stated, children 0 to 59 months of age, adults and children with chronic health conditions, pregnant individuals, people of any age who are residents of nursing homes and other chronic care facilities, and adults 65 years of age and older are at greater risk of more severe complications from influenza or worsening of their underlying condition. Given the potential for HCWs and other care providers to transmit influenza to individuals at high risk and knowing that vaccination is the most effective way to prevent influenza, NACI recommends that, in the absence of contraindications, HCWs and other care providers in facilities and community settings should be vaccinated against influenza annually. NACI considers the receipt of influenza vaccination to be an essential component of the standard of care for all HCWs and other care providers for their own protection and that of their

patients. This group should consider annual influenza vaccination as part of their responsibilities to provide the highest standard of care.

Although the current influenza vaccine coverage rate for HCWs is higher than for the general public[99, 100], it remains below the national goal of 80% coverage for HCWs in Canada[101]. Comprehensive vaccination programs should be adopted that address HCWs' acceptance of the vaccine and facilitate the process of vaccinating HCWs to improve uptake of the influenza vaccine beyond the current level. HCW influenza vaccination programs that have successfully increased vaccine coverage of HCWs have included a combination of education, increased awareness, accessible on-site vaccination delivery options for all HCWs, visible support from senior staff and other leaders, and regular review and improvement of vaccination strategies [102-107].

**Outbreak management in health care facilities**

As noted in PHAC's Guidance: Infection Prevention and Control Measures for Healthcare Workers in Acute Care and Long-term Care Settings for seasonal influenza, all health care organizations should have a written plan for managing an influenza outbreak in their facilities. Inherent in such plans should be policies and programs to optimize HCW's influenza vaccination [108]. As part of outbreak management, the above-mentioned PHAC guidance suggests consideration of chemoprophylaxis for all unvaccinated HCWs, unless contraindications exist. Refer to the Association of Medical Microbiology and Infectious Disease Canada (AMMI Canada) website for guidelines regarding the use of antiviral medications for prophylaxis.

### Contacts of individuals at high risk of influenza complications

Vaccination is recommended for contacts, both adults and children, of individuals at high risk of influenza-related complications or hospitalization (see List 1), whether or not the individual at high risk has been vaccinated. These contacts include: household contacts and care providers of individuals at high risk, household contacts and care providers of infants less than 6 months of age (as these infants are at high risk of complications from influenza but cannot receive influenza vaccine), members of a household expecting a newborn during the influenza season, household contacts and care providers (whether in or out of the home) of children 0 to 59 months of age, and providers of services within closed or relatively closed settings with people at high risk of influenza-related complications (e.g., crew on a passenger or cruise ship).

## V.6 Others

### People who provide essential community services

Vaccination for these individuals should be encouraged to minimize the disruption of services and routine activities during annual influenza epidemics. People who provide essential community services, including healthy working adults, should consider annual influenza vaccination, as this intervention has been shown to decrease work absenteeism due to respiratory and related illnesses[91, 92, 109-111].

## People in direct contact with farm animals

### Poultry handlers

Although seasonal influenza vaccination will not prevent avian influenza infection, some countries [112] and provinces have recommended influenza vaccination on a yearly basis for those working with poultry, based on the rationale that preventing infection with human influenza strains may reduce the theoretical potential for human-avian reassortment of genes, should such workers become co-infected with human and avian influenza viruses [113].

NACI recommends seasonal influenza vaccination for people who may be in direct contact with poultry infected with avian influenza during culling operations, as these individuals may be at increased risk of avian influenza infection because of exposure during the culling operation[114-117]. Refer to the Statement on Seasonal Influenza Vaccine for 2013–2014 for further information supporting this recommendation.

Direct contact may be defined as sufficient contact with infected poultry to allow transmission of an avian virus to the exposed person. The relevant individuals include those performing the cull, as well as others who may be directly exposed to the avian virus, such as supervising veterinarians and inspectors. It is recommended that biosecurity measures such as personal protective equipment and antivirals be used. Refer to Human Health Issues Related to Avian Influenza in Canada for PHAC recommendations on the management of domestic avian influenza outbreaks.

### Swine workers

NACI has concluded that there is insufficient evidence at this time to recommend routine influenza vaccination specifically for swine workers; however, NACI recommends that influenza vaccination should be offered to anyone 6 months of age and older who does not have contraindications to the vaccine.

Refer to the Statement on Seasonal Influenza Vaccine for 2013–2014 for further information supporting this recommendation.

# LIST OF ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| Adj | Adjuvanted |
| AE | Adverse event |
| AEFI | Adverse event following immunization |
| ART | Antiretroviral therapy |
| CAEFISS | Canadian Adverse Events Following Immunization Surveillance System |
| Cc | Cell cultured |
| CI | Confidence interval |
| CIG | Canadian Immunization Guide |
| DIN | Drug Identification Number |
| FFU | Fluorescent focus units |
| GBS | Guillain-Barré syndrome |
| GMT | Geometric mean titre |
| GMTR | Geometric mean titre ratio |
| HA | Hemagglutinin |
| HAART | Highly active antiretroviral therapy |
| HCW | Health care worker |
| HD | High dose |
| HIV | Human immunodeficiency virus |
| Ig | Immunoglobulin |
| IIV | Inactivated influenza vaccine |
| IIV3 | Trivalent inactivated influenza vaccine |
| IIV3-Adj | Adjuvanted trivalent inactivated influenza vaccine (egg-based) |
| IIV3-HD | High-dose trivalent inactivated influenza vaccine (egg-based) |
| IIV3-SD | Standard-dose trivalent inactivated influenza vaccine (egg-based) |
| IIV4 | Quadrivalent inactivated influenza vaccine |
| IIV4-cc | Mammalian cell culture-based quadrivalent inactivated influenza vaccine |
| IIV4-HD | High-dose quadrivalent inactivated influenza vaccine (egg-based) |

| | |
|---|---|
| IIV4-SD | Standard-dose quadrivalent inactivated influenza vaccine (egg-based) |
| ILI | Influenza-like illness |
| IM | Intramuscular |
| IMPACT | Immunization Monitoring Program Active |
| LAIV | Live attenuated influenza vaccine (egg based) |
| LAIV3 | Trivalent live attenuated influenza vaccine (egg based) |
| LAIV4 | Quadrivalent live attenuated influenza vaccine (egg based) |
| LCI | Laboratory-confirmed influenza |
| MDCK | Madin-Darby Canine Kidney |
| MMR | Measles, mumps, and rubella |
| NA | Neuraminidase |
| NACI | National Advisory Committee on Immunization |
| ORS | Oculorespiratory syndrome |
| PHAC | Public Health Agency of Canada |
| RCT | Randomized controlled trial |
| RIV | Recombinant influenza vaccine |
| RIV4 | Recombinant quadrivalent influenza vaccine |
| RNA | Ribonucleic acid |
| rVE | Relative vaccine efficacy |
| RZV | Recombinant zoster vaccine |
| SAE | Serious adverse event |
| VE | Vaccine effectiveness |
| WHO | World Health Organization |

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**Ex-officio representatives:** V Beswick-Escanlar (National Defence and the Canadian Armed Forces), E Henry (Centre for Immunization and Respiratory Infectious Diseases [CIRID], Public Health Agency of Canada [PHAC]), M Lacroix (Public Health Ethics Consultative Group, PHAC), P Fandja (Marketed Health Products Directorate, Health Canada), M Su (COVID-19 Epidemiology and Surveillance, PHAC), S Ogunnaike-Cooke (CIRID, PHAC), C Pham (Biologic and Radiopharmaceutical Drugs Directorate, Health Canada), M Routledge (National Microbiology Laboratory, PHAC) and T Wong (First Nations and Inuit Health Branch, Indigenous Services Canada).

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# APPENDIX A: ABBREVIATIONS FOR INFLUENZA VACCINES

| Influenza vaccine category | Valency | Type | Current NACI abbreviation[a] |
|---|---|---|---|
| Inactivated influenza vaccine (IIV) | Trivalent (IIV3) | Standard dose[b], unadjuvanted, IM administered, egg-based | IIV3-SD |
| | | Adjuvanted[c], IM administered, egg-based | IIV3-Adj |
| | | High dose[d], unadjuvanted, IM administered, egg-based | IIV3-HD |
| | Quadrivalent (IIV4) | Standard dose[b], unadjuvanted, IM administered, egg-based | IIV4-SD |
| | | Standard dose[b], unadjuvanted, IM administered, mammalian cell culture-based | IIV4-cc |
| | | High dose[d], unadjuvanted, IM administered, egg-based | IIV4-HD |
| Recombinant influenza vaccine (RIV) | Quadrivalent (RIV4) | Recombinant[e], unadjuvanted, IM administered | RIV4 |
| Live attenuated influenza vaccine (LAIV) | Trivalent (LAIV3) | Unadjuvanted, Nasal spray, egg-based | LAIV3 |
| | Quadrivalent (LAIV4) | Unadjuvanted, Nasal spray, egg-based | LAIV4 |

**Abbreviations:** IIV: inactivated influenza vaccine; IIV3: trivalent inactivated influenza vaccine; IIV3-Adj: adjuvanted egg-based trivalent inactivated influenza vaccine; IIV3-HD: high-dose egg-based trivalent inactivated influenza vaccine; IIV3-SD: standard-dose egg-based trivalent inactivated influenza vaccine; IIV4: quadrivalent inactivated influenza vaccine; IIV4-cc: standard-dose cell culture-based quadrivalent inactivated influenza vaccine; IIV4-HD: high-dose egg-based quadrivalent inactivated influenza vaccine; IIV4-SD: standard-dose egg-based quadrivalent inactivated influenza vaccine; IM: intramuscular; RIV: recombinant influenza vaccine; RIV4: recombinant quadrivalent influenza vaccine; LAIV: live attenuated influenza vaccine; LAIV3: egg-based trivalent live attenuated influenza vaccine; LAIV4: egg-based quadrivalent live attenuated influenza vaccine.

[a] The numeric suffix denotes the number of antigens contained in the vaccine ("3" refers to the trivalent formulation and "4" refers to the quadrivalent formulation). The hyphenated suffix "-SD" (where "SD" is used to denote "standard dose" for an IIV) is used when referring to IIV products that do not have an adjuvant, contain 15 µg hemagglutinin (HA) per strain and are administered as a 0.5 mL dose by intramuscular injection; "-cc" (where "cc" denotes "cell culture") refers to an IIV product that is made from influenza virus grown in cell cultures instead of chicken eggs (Flucelvax® Quad); "-Adj" (where "Adj" is used to abbreviate "adjuvanted") refers to an IIV with an adjuvant (IIV3-Adj for Fluad® or Fluad Pediatric®); and "-HD" refers to an IIV that contains higher antigen content than 15 µg HA per strain standard IIV dose (IIV3-HD for Fluzone® High-Dose or IIV4-HD for Fluzone® High-Dose Quadrivalent).
[b] 15 µg HA per strain.
[c] 7.5 µg (in 0.25 mL) or 15 µg (in 0.5 mL) HA per strain.
[d] 60 µg HA per strain.
[e] 45 µg HA per strain

# APPENDIX B: CHARACTERISTICS OF INFLUENZA VACCINES AVAILABLE FOR USE IN CANADA, 2024–2025[a]

| Product name (manufacturer) | Vaccine Characteristic | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Vaccine type | Route of administration | Authorized ages for use | Antigen content for each vaccine strain | Adjuvant | Formats available | Post-puncture shelf life for multi-dose vials | Thimerosal | Antibiotics (traces) | Production medium |
| **Quadrivalent** | | | | | | | | | | |
| **Flulaval® Tetra (GSK)** | IIV4-SD (split virus) | IM | 6 months and older | 15 µg HA /0.5 mL dose | None | 5 mL multi-dose vial<br>Single-dose pre-filled syringe without attached needle | 28 days | Yes (multi-dose vial only) | None | Egg (Avian) |
| **Fluzone® Quadrivalent (Sanofi)** | IIV4-SD (split virus) | IM | 6 months and older | 15 µg HA /0.5 mL dose | None | 5 mL multi-dose vial<br>Single-dose pre-filled syringe without attached needle | Up to expiry date indicated on vial label | Yes multi-dose vial only) | None | Egg (Avian) |
| **Afluria® Tetra (Seqirus)** | IIV4-SD (split virus) | IM | 5 years and older | 15 µg HA /0.5 mL dose | None | 5 mL multi-dose vial<br>Single dose pre-filled syringe without attached needle | Up to expiry date indicated on vial label | Yes (multi-dose vial only) | Neomycin and polymyxin B | Egg (Avian) |
| **Influvac® Tetra (BGP Pharma ULC, operating as Mylan, d.b.a. Viatris Canada)** | IIV4-SD (subunit) | IM or deep subcutaneous injection | 6 months and older | 15 µg HA /0.5 mL dose | None | Single dose pre-filled syringe with or without attached needle | Not applicable | No | Gentamicin or neomycin and polymyxin B[b] | Egg (Avian) |
| **Flucelvax® Quad (Seqirus)** | IIV4-cc (subunit) | IM | 6 months and older | 15 µg HA /0.5 mL dose | None | 5 mL multi-dose vial<br>Single dose pre-filled syringe without attached needle | 28 days | Yes (multi-dose vial only) | None | Cell culture (Mammalian) |
| **Fluzone® High-Dose Quadrivalent (Sanofi)** | IIV4-HD (split virus) | IM | 65 years and older | 60 µg HA /0.7 mL dose | None | Single dose pre-filled syringe without attached needle | Not applicable | No | None | Egg (Avian) |

| Product name (manufacturer) | Vaccine Characteristic | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Vaccine type** | **Route of administration** | **Authorized ages for use** | **Antigen content for each vaccine strain** | **Adjuvant** | **Formats available** | **Post-puncture shelf life for multi-dose vials** | **Thimerosal** | **Antibiotics (traces)** | **Production medium** |
| **Supemtek™ (Sanofi)** | RIV4 (recombinant protein) | IM | 18 years and older | 45 µg HA /0.5 mL dose | None | Single dose pre-filled syringe without attached needle | Not applicable | No | None | Recombinant (Insect vector-expressed) |
| **FluMist® Quadrivalent (AstraZeneca)** | LAIV4 (live attenuated) | Intranasal | 2 to 59 years | $10^{6.5\text{-}7.5}$ FFU of live attenuated reassortants /0.2 mL dose (given as 0.1 mL in each nostril) | None | Single use pre-filled glass sprayer | Not applicable | No | Gentamicin | Egg (Avian) |
| **Trivalent** | | | | | | | | | | |
| **Fluad Pediatric® and Fluad® (Seqirus)** | IIV3-Adj (subunit) | IM | **Pediatric:** 6 to 23 months<br>**Adult:** 65 years and older | **Pediatric:** 7.5 µg HA /0.25 mL dose<br>**Adult:** 15 µg HA /0.5 mL dose | MF59 | Single dose pre-filled syringe without a needle | Not applicable | No | Kanamycin and neomycin | Egg (Avian) |

**Abbreviations:** FFU: fluorescent focus units; HA: hemagglutinin; IIV3-Adj: adjuvanted egg-based trivalent inactivated influenza vaccine; inactivated influenza vaccine; IIV4-cc: standard-dose cell culture-based quadrivalent inactivated influenza vaccine; IIV4-SD: standard-dose egg-based quadrivalent inactivated influenza vaccine; RIV4: quadrivalent recombinant influenza vaccine; IM: intramuscular; LAIV4: quadrivalent live attenuated influenza vaccine; NA: neuraminidase.

[a] Full details of the composition of each vaccine authorized for use in Canada, including other non-medicinal ingredients, and a brief description of its manufacturing process can be found in the product monograph.
[b] Neomycin and polymyxin B are only used if gentamicin cannot be used. No trace amounts of neomycin or polymyxin B are present if gentamicin was used.

# APPENDIX C: ADDITIONAL INFORMATION ON VACCINE EFFICACY, EFFECTIVENESS, IMMUNOGENICITY, AND SAFETY

## Inactivated Influenza Vaccine (IIV)

**Immunological considerations related to children**

Young children have a high burden of illness, and their vaccine-induced immune response is not as robust as older children. However, some studies suggest moderate improvement in antibody response in young children, without an increase in reactogenicity, with the use of a full vaccine dose (0.5 mL) for IIV-SDs[118-120]. Based on this moderate improvement in antibody response without an increase in reactogenicity, NACI recommends the use of a 0.5 mL dose for all recipients of IIV-SDs, including young children.

**Immunological considerations related to older adults and those with immune compromising conditions**

Although the initial antibody response in older adults is lower to some influenza vaccine components [particularly A(H3N2) antigens] when compared to those in other age groups, influenza vaccination still induces protective antibody levels in a significant proportion of this age group. A literature review identified no evidence for a subsequent antibody decline that was any more rapid in older adults than in younger age groups [121].

Influenza vaccination can induce protective antibody levels in a substantial proportion of adults and children with immune compromising conditions, including transplant recipients, those with proliferative diseases of the hematopoietic and lymphatic systems, and HIV-infected patients[122-125].

Most studies have shown that administration of a second dose of influenza vaccine in the same season to older adults or other individuals who may have an altered immune response does not result in a clinically significant antibody boost [52, 126-128].

## Standard-dose, egg-based, trivalent inactivated influenza vaccine (IIV3-SD)

The following trivalent formulations of standard-dose inactivated influenza vaccines have recently been discontinued and are no longer authorized or available for use in Canada:

- Agriflu® (Seqirus)
- Influvac® (BGP Pharma ULC, operating as Mylan, doing business as (d.b.a.) Viatris Canada)

Refer to the Statement on Seasonal Influenza Vaccine for 2022-2023 for more detailed information on the use of IIV3-SD and a summary of efficacy, effectiveness, immunogenicity, and safety evidence across eligible age groups.

## Adjuvanted inactivated influenza vaccine (IIV3-Adj)

Vaccines currently authorized for use:

- Fluad® (Seqirus)
- Fluad Pediatric® (Seqirus)

### 1. Fluad® (adults 65 years of age and older)

#### Efficacy and effectiveness

There is fair evidence that the MF59-adjuvanted Fluad (IIV3-Adj) may be effective at reducing the risk of hospitalization for influenza and influenza complications in older adults compared to unvaccinated individuals. However, there is insufficient evidence that IIV3-Adj is more effective at reducing the risk of hospitalization for influenza and influenza complications in older adults compared to those who received un-adjuvanted subunit IIV3-SD. Refer to the NACI Literature Review Update on the Efficacy and Effectiveness of High-Dose and MF59-Adjuvanted Trivalent Inactivated Influenza Vaccines in Adults 65 Years of Age and Older for more information on the efficacy and effectiveness of IIV3-Adj in adults 65 years of age and older. For more information on the efficacy and effectiveness of IIV3-Adj in adults 65 years of age and older.

#### Immunogenicity

The mechanism of action of MF59 is not fully determined and has primarily been studied using in vitro and mouse models. From these studies, it appears that MF59 may act differently from aluminum-based adjuvants. These studies show that MF59 acts in the muscle fibres to create a local immune-stimulatory environment at the injection site [129]. MF59 allows for an increased influx of phagocytes (e.g., macrophages, monocytes) to the site of injection. The recruited phagocytes are further stimulated by MF59, thereby increasing the production of chemokines to attract more innate immune cells and inducing differentiation of monocytes into dendritic cells[130, 131]. MF59 further facilitates the internalization of antigen by these dendritic cells[129,131]. The overall higher number of cells available locally increases the likelihood of interaction between an antigen presenting cell and the antigen, leading to more efficient transport of antigen to the lymph nodes, with resulting improved T cell priming[130].

There is evidence from RCTs that IIV3-Adj elicits non-inferior immune responses compared to the un-adjuvanted subunit and split virus IIV3-SDs; however, superiority of IIV3-Adj to these vaccines by pre-defined criteria has not been consistently demonstrated. Refer to the Statement on Seasonal Influenza Vaccine for 2018–2019 for more information on the immunogenicity of IIV3-Adj in adults 65 years of age and older. for more information on the immunogenicity of IIV3-Adj in adults 65 years of age and older.

#### Safety

IIV3-Adj produces injection site reactions (pain, erythema, and induration) significantly more frequently than IIV3-SD, but they are classified as mild and transient. Systemic reactions (myalgia, headache, fatigue, and malaise) are comparable or more frequent with IIV3-Adj compared to IIV3-SD and are rated as mild to moderate and transient. SAEs were uncommon and were comparable to IIV3-SD. Refer to the Recommendations on the use of MF59-adjuvanted Trivalent Influenza Vaccine (Fluad®): Supplemental Statement of Seasonal Influenza Vaccine for 2011–2012 for additional information on the safety of IIV3-Adj in adults 65 years of age and older. for additional information on the safety of IIV3-Adj in adults 65 years of age and older.

## 2. Fluad Pediatric® (children 6 to 23 months of age)

### Efficacy and effectiveness

A pre-licensure efficacy trial in children 6 to 71 months of age found a higher relative efficacy for IIV-Adj than the un-adjuvanted IIV3-SD[133]. However, the findings of this study should be interpreted with caution. The comparator un-adjuvanted IIV3 used in this trial was shown, in an unrelated study, to induce a lower immune response compared to another un-adjuvanted IIV3-SD. There were concerns raised by a European Medicines Agency inspection about the quality of diagnostic laboratory testing and validity of ascertainment of influenza cases. The study administered 0.25 mL doses of the comparator un-Adj IIV3-SD for children less than 36 months of age, which is lower than the dose of 0.5 mL of un-Adj IIV3-SD or IIV4-SD that is recommended for this age group in Canada. Refer to the NACI Literature Review on Pediatric Fluad Influenza Vaccine Use in Children 6 to 72 Months of Age for more information on the efficacy and effectiveness of IIV3-Adj in children. for more information on the efficacy and effectiveness of IIV3-Adj in children.

### Immunogenicity

In children, there is limited but consistent evidence that IIV3-Adj is more immunogenic than IIV3-SD against both influenza A and B[133-138]. In particular, a single dose of IIV3-Adj is more immunogenic than a single dose of IIV3-SD and has been shown in 1 study to produce greater GMTs than 2 doses of IIV3-SD against influenza A[138]. However, similar to IIV3-SD, IIV3-Adj generally induced a weaker hemagglutination-inhibition antibody response against B strains compared to A strains and therefore 2 doses of IIV3-Adj are still necessary for first-time recipients to achieve a satisfactory immune response against influenza B.

Almost all of the pre-licensure pediatric studies used vaccine formulations of 0.25 mL in children 6 to 35 months of age, both for IIV3-Adj and the comparator un-adjuvanted influenza vaccine (NACI recommends 0.5 mL dosage of IIV3-SD or IIV4-SD for all age groups). There is limited immunogenicity evidence comparing IIV3-Adj at 0.25 mL dose to IIV3-SD or IIV4-SD at 0.5 mL dose in the 6 to 23 month age group. Refer to the NACI Literature Review on Pediatric Fluad Influenza Vaccine Use in Children 6 to 72 Months of Age for more information on the immunogenicity of IIV3-Adj in children. for more information on the immunogenicity of IIV3-Adj in children.

### Safety

The safety data in children are consistent with what is known about IIV3-Adj's safety profile in adults. In pediatric trials, IIV3-Adj was more reactogenic than IIV3-SD, with recipients experiencing 10 to 15% more solicited local and systemic reactions. However, most reactions were mild and resolved quickly. A dose-ranging study of MF59-Adj and un-Adj IIV3 and IIV4 did not find an increased risk of AEs associated with increased MF59 dose, antigen dose, or the addition of a second B strain; however, the reactogenicity of 15 µg formulations were slightly higher for both Adj and un-Adj vaccines compared to the corresponding 7.5 µg formulations [136].

There are currently no data on the effects of long-term or repeated administration of Adj influenza vaccines in children. The most significant experience with an Adj influenza vaccine in children was the AS03-Adj A (H1N1) pandemic vaccine that has been associated with an increased risk of narcolepsy. A study comparing 2 AS03-Adj A (H1N1) vaccine products (Pandemrix and

Arepanrix) has suggested that the underlying immune mediated mechanism associated with the increased narcolepsy risk may not be initiated by the adjuvant, but by the A (H1N1) nucleoprotein viral antigen, given that the study found significant antigenic differences between the 2 A (H1N1) pandemic vaccines [139]. However, the pandemic vaccine was a single strain Adj vaccine administered only during 1 season, and it is unknown what effects a multi-strain Adj vaccine or an Adj vaccine administered for more than 1 season may have in young children.

Refer to the NACI Literature Review on Pediatric Fluad Influenza Vaccine Use in Children 6-72 Months of Age for additional information on the safety of IIV3-Adj in children.

## Standard-dose, egg-based, quadrivalent inactivated influenza vaccine (IIV4-SD)

Vaccines currently authorized for use:

- Afluria® Tetra (Seqirus)
- Flulaval® Tetra (GlaxoSmithKline)
- Fluzone® Quadrivalent (Sanofi)
- Influvac® Tetra (BGP Pharma ULC, operating as Mylan, d.b.a. Viatris Canada)

### 1. Literature review on quadrivalent influenza vaccines (IIV4)

In July 2014, NACI published a systematic literature review of the efficacy, effectiveness, immunogenicity, and safety of IIV4 to inform recommendations on immunization against influenza in adults and children 6 months of age and older using quadrivalent influenza vaccines. Refer to the Literature Review on Quadrivalent Influenza Vaccines for additional details.

#### Efficacy and effectiveness

One (1) study assessed the efficacy of IIV4-SD in children 3 to 8 years of age. In this study, efficacy was estimated to be 59%, in comparison to children who received hepatitis A vaccine[140].

#### Immunogenicity

The results of phase II and III trials that compared trivalent formulations to quadrivalent formulations generally showed non-inferiority of the quadrivalent products for the A(H3N2), A (H1N1), and B strain contained in the trivalent formulations. As expected, these studies showed that the immune response to the B strain that was not in the trivalent formulation was better in subjects who received the quadrivalent vaccine, which contained the additional B strain.

#### Safety

Pre-licensure clinical trials (refer to Literature Review on Quadrivalent Influenza Vaccines) and post-marketing surveillance showed that IIV4-SD had a similar safety profile to IIV3-SD[141]..

### 2. Influvac® Tetra (BGP Pharma ULC, operating as Mylan, d.b.a. Viatris Canada)

Following the vaccination recommendations on the use of standard-dose, egg based, quadrivalent inactivated influenza vaccines (IIV4-SD) published in the NACI Statement on Seasonal Influenza Vaccine for 2022–2023, an expanded age indication for the use Influvac Tetra was authorized.

Influvac Tetra was first authorized by Health Canada for use in adults 18 years of age and older on March 1, 2019. Subsequently, an expanded age indication down to children 3 years to 17 years of age was authorized on February 20, 2020, based on a review of the Health Canada assessment of data from phase 3 RCTs conducted in several European countries. One (1) RCT was conducted in adults 18 years of age and older (n= 1,980), and 1 RCT was conducted in children 3 to 17 years of age (n=1,200). Both RCTs compared Influvac Tetra to its trivalent formulation (Influvac; IIV3-SD), which had previously been authorized for use in persons 18 years of age and older. Recommendations on the use of Influvac Tetra in adults and children 3 years of age and older can be found in the NACI Statement on Seasonal Influenza Vaccine for 2021–2022.

A second age indication extension to children 6 to 35 months was authorized on November 30, 2021. NACI reviewed the Health Canada assessment of the efficacy, immunogenicity, and safety of Influvac Tetra compared to non-influenza vaccines (NIVs) in children 6 to 35 months of age (n= 2,007). The RCT was conducted across Europe and Asia over 3 influenza seasons (Southern Hemisphere 2019 and the 2017–2018 and 2018–2019 Northern Hemisphere influenza seasons). Refer to the product monograph for further details and supporting evidence on the use of Influvac Tetra in the various age groups mentioned above.

**Efficacy and effectiveness**

The absolute vaccine efficacy of Influvac Tetra compared with NIV against any seasonal strain in children 6 to 35 months was 54% (VE: 0.54; 95% CI: 0.37 to 0.66%). The estimated vaccine efficacy was higher for antigenically matching strains (VE: 0.68; 95% CI: 0.45 to 0.81%). Vaccine efficacy was estimated to be 21% in children 6 to 11 months of age (VE: 0.21; 95 % CI: -0.70 to 0.64%); however, the study was not powered for subgroup analyses by age group[142].

**Immunogenicity**

Results from the 2 pivotal trials conducted in adults and children 3 years of age and older demonstrated that Influvac Tetra met the non-inferiority criteria for the adjusted GMT ratio for all tested influenza strains when compared to the trivalent formulation. Recipients of the trivalent formulations showed, to a lesser degree, some immune response to the B strain not contained in the trivalent formulation. In the RCT conducted in adults, seroconversion and seroprotection rates for all 4 strains in the Influvac Tetra group were higher than the European Medicines Agency (EMA) and United States Food and Drug Administration (FDA) criteria for influenza vaccines. In the RCT conducted in children 3 to 17 years of age, seroconversion rates were over 60% across all vaccination groups for all 4 strains.

A review of clinical data submitted to Health Canada by the manufacturer was conducted to examine the use of Influvac Tetra in children 6 months to less than 3 years (i.e., 35 months) of age. Specifically, the immunogenicity of Influvac Tetra was assessed in a phase 3 RCT conducted in children 6 to 35 months of age. Participants experienced a substantial increase in hemagglutinin inhibition antibody titres in response to vaccination against influenza type A [A (H1N1) and A(H3N2)], based on GMTs, geometric mean fold increase (GMFI), seroconversion rates and seroprotection rates. However, immunogenicity results for influenza type B (B/Yamagata lineage and B/Victoria lineage) were noted to be low for the 4 immunogenicity outcomes included in the study. Refer to the product monograph for additional details.

**Safety**

The analysis of vaccine safety across all 3 phase 3 clinical trials including adults and children 6 months of age and older demonstrated that Influvac Tetra was well tolerated, and no new safety signals were observed. The incidence of solicited (local and systemic), unsolicited AEs and SAEs were generally comparable between the 2 intervention groups. AEs were mild to moderate in severity. Notably, no deaths were reported across the 3 clinical trials.

## Standard dose mammalian cell culture-based quadrivalent inactivated influenza vaccine (IIV4-cc)

Vaccine currently authorized for use:

- Flucelvax® Quad (Seqirus)

### Methods

Following the IIV4-cc vaccination recommendations published in the NACI Statement on Seasonal Influenza Vaccine for 2022–2023, an expanded age indication for the use of IIV4-cc in children 6 months to 47 months was authorized.

Flucelvax Quad was first authorized for use in adults and children 9 years of age and older on November 22, 2019. In support of this, NACI conducted a systematic review of the literature to examine vaccine efficacy, effectiveness, immunogenicity, and safety data for children in this age group. Refer to the NACI Supplemental Statement on Mammalian Cell Culture-Based Influenza Vaccines and to the Statement on Seasonal Influenza Vaccine for 2022–2023 for further details.

An age indication extension for the use of Flucelvax Quad in adults and children 2 years and older was authorized on March 8, 2021.Recommendations were developed based on a review of the Health Canada assessment of a multi-country phase 3/4 RCT on the efficacy, immunogenicity and safety of Flucelvax Quad in children 2 years to less than18 years of age conducted over 3 influenza seasons (Southern Hemisphere 2017 influenza season and the 2017–2018 and 2018–2019 Northern Hemisphere influenza seasons). Refer to the Statement on Seasonal Influenza Vaccine for 2022–2023 for further details.

A second age indication extension to children 6 months to 47 months was authorized on March 8, 2022. To support this age indication extension, NACI reviewed the Health Canada assessment of a Phase 3 randomized clinical trial of the immunogenicity and safety of IIV4-cc compared to Afluria Tetra (IIV4-SD) in healthy children (N=2402) 6 to 47 months of age submitted by the manufacturer. The clinical trial was conducted in 47 sites across the United States during the 2019-2020 influenza season. The analysis of vaccine immunogenicity and safety in children 6 months to 47 months were consistent with the findings of the previous NACI systematic literature review and the Health Canada clinical assessment.

### Efficacy and effectiveness

Evidence for the effectiveness of IIV4-cc is based on the studies included in the systematic review presented in the NACI Supplemental Statement on Mammalian Cell Culture-Based Influenza Vaccines and the Health Canada assessment of clinical trial evidence supporting the extended age indication for the use of the vaccine in adults and children 2 years of age and older. Evidence related to the efficacy of the trivalent formulation, IIV3-cc, was used to supplement existing evidence for the efficacy of IIV4-cc. For further details refer to the NACI Influenza and Statement on Seasonal Influenza Vaccine for 2022–2023.

### Immunogenicity

In support of extended age indication for the use of the vaccine in adults and children 6 months of age and older, immunogenicity was assessed in a subset of the phase 3/4 RCT study participants 6 months to 47 months of age during the Northern Hemisphere 2019-2020 influenza season. Non-inferiority criteria were met for all tested influenza strains [A (H1N1), A(H3N2), B/Yamagata lineage, B/Victoria lineage], based on GMT ratios and seroconversion rates. Overall, there is fair evidence that IIV4-cc has non-inferior immunogenicity to IIV4-SD.

### Safety

The analysis of vaccine safety in a clinical trial in children 6 to 47 months of age demonstrated that IIV4-cc is well tolerated, and no new safety signals were observed. The majority of solicited (local and systemic) were short in duration. There were no observable differences in the occurrence of AEs between participants who received Flucelvax Quad and versus those who received the comparator vaccine. A small proportion of participants experienced at least 1 SAE in each study arm. No SAE were determined to be related to receipt of the study vaccines. Overall, there is fair evidence that IIV4-cc is a safe and well-tolerated alternative to conventional egg-based influenza vaccines for children and adults.

## High-dose inactivated influenza vaccine (IIV-HD)

Vaccines currently authorized for use:

- Fluzone® High-Dose Quadrivalent (Sanofi)

The trivalent formulations of high-dose inactivated influenza vaccines have been discontinued and are no longer authorized or available for use in Canada.

### Methods

In 2018, NACI published a literature review on the efficacy and effectiveness of high dose trivalent inactivated vaccines (IIV3-HD) in older adults. Refer to NACI's Literature review update on the efficacy and effectiveness of high-dose (Fluzone® High-Dose) and MF59-adjuvanted (Fluad®) trivalent inactivated influenza vaccines in adults 65 years of age and older for further details.

Fluzone High-Dose Quadrivalent (IIV4-HD) builds on the clinical development of its trivalent predecessor Fluzone High-Dose (IIV3-HD) since both vaccines have the same manufacturing process and overlapping compositions. Therefore, data on the efficacy, effectiveness, immunogenicity, and safety of IIV3-HD are relevant and inferred to IIV4-HD.

### Efficacy and effectiveness

There is good evidence that Fluzone High-Dose (IIV3-HD) provides better protection compared with IIV3-SD in adults 65 years of age and older. Two (2) studies found that IIV3-HD may provide greater benefit in adults 75 years of age and older compared to adults 65 to 74 years of age ([143, 144]). The efficacy results for IIV3-HD are inferred to IIV4-HD based on the non-inferior immunogenicity, described in the next section.

### Immunogenicity

There is evidence that immunization with IIV3-HD elicits a higher immune response compared to immunization with IIV3-SD in older adults [145-152]. Across all 3 influenza vaccine strains, rates of seroconversion were found to be about 19% higher (ranging from 8 to 39% higher) for the IIV3-HD group. The post-vaccination GMT ratios (GMTR) of participants' responses to IIV3-HD was about 1.5 to 1.8 times higher than those receiving IIV3-SD. There is good evidence that the immunogenicity for Fluzone High Dose Quadrivalent (IIV4-HD) is non-inferior to IIV3-HD[153, 154]. In a pivotal RCT, IIV4-HD met all non-inferiority criteria set by the US Food and Drug Administration, based on GMTR and seroconversion rates when compared to IIV3-HD [154]. Immunogenicity for IIV4-HD was superior for the influenza B strain not contained within the trivalent high dose vaccine[154].

### Safety

IIV3-HD has been observed to produce a higher rate of some systemic and local reactions than IIV3-SD. Studies have reported higher rates of malaise, myalgia, and moderate to severe fever. Most systemic reactions were mild and resolved within 3 days. SAEs were rare and similar in frequency between standard-dose and high-dose vaccines. When comparing the 2 high dose vaccine products, IIV4-HD has been shown to produce a comparable rate of systemic and local reactions compared to IIV3-HD. A comparable proportion of study participants also experienced unsolicited and serious AEs[154].

## Recombinant quadrivalent influenza vaccine (RIV4)

Vaccines currently authorized for use:

- Supemtek™ (Sanofi)

### Methods

A systematic literature review and meta-analysis was conducted on the vaccine efficacy, effectiveness, immunogenicity, and safety of RIV4 in adults 18 years of age and older. NACI used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework to review the evidence and develop relevant recommendations on the use of RIV4. Further information on this framework can be found in the GRADE handbook.

The complete details of this review, rationale, relevant considerations and additional information supporting this recommendation can be found in the NACI Supplemental Statement – Recombinant Influenza Vaccines and the Statement on Seasonal Influenza Vaccine for 2022-2023.

### Efficacy and effectiveness

One (1) RCT that evaluated the efficacy of RIV4 demonstrated that Supemtek was statistically significantly more efficacious than egg-based IIV4-SD in preventing laboratory confirmed influenza illness in adults 50 years of age and older [155]. Non-inferiority assessments suggested that RIV4 may be more effective than IIV4-SD influenza vaccines against laboratory-confirmed influenza A virus infection, but not laboratory-confirmed influenza B virus infection in older adults. Overall, there is fair evidence (of low certainty) that the efficacy of RIV4 is non-inferior to traditional egg-based comparators, based on data in adults aged 50 years and older.

**Immunogenicity**

Eight (8) RCTs[155-162] assessed the immunogenicity of RIV4. The immunogenicity outcomes reported included seroconversion rates [155-162], seroprotection rates[155-157, 162], and GMTR[155,158,162,163]. Across the 8 studies, Supemtek demonstrated non-inferiority compared to previously authorized IIVs (IIV3-HD, IIV3-Adj, IIV4-SD, and IIV4-cc) against A (H1N1), most strains of A(H3N2), and B/Yamagata lineage. In some studies, RIV4 did not meet non-inferiority criteria against B/Victoria lineage compared to previously authorized IIVs based on seroconversion[155, 158], seroprotection ([155], and GMTR[164].

Pooled seroconversion data from 3[155, 157, 160] of the 8 RCTs conducted in adult participants 50 years of age and older identified that RIV4 induced similar antibody responses compared to IIV4-SD, IIV3-HD, and IIV3-Adj.

Overall, there is fair evidence (of moderate certainty) that the immunogenicity for RIV4 is non-inferior to traditional egg-based comparators, based on data in adults aged 18 years and older.

**Safety**

Six (6) studies[155, 157, 158, 160, 165, 166] assessed the safety of RIV4 in adults, including 5 RCTs and 1 post-marketing surveillance study using data from the United States Vaccine Adverse Event Reporting System (VAERS) ([165]. The 5 RCTs found RIV4 to be safe and well-tolerated compared to conventional egg-based IIVs (noting that no published clinical data pertaining to safety of vaccination with RIV4 during pregnancy were available at the time of the review). Most AE reported to VAERS following RIV4 administration were non-serious. When data from 2 RCTs ([155, 157] conducted among adult participants 50 years of age and older were pooled, no difference in the odds of experiencing a SAE following administration of RIV4 and traditional egg-based IIV3-HD and IIV4-SD vaccine comparators was detected. Overall, there is evidence of moderate certainty that RIV4 is a safe and well-tolerated alternative to conventional egg-based influenza vaccines for adults.

## Live Attenuated Influenza Vaccine (LAIV)

Vaccine currently authorized for use:

- FluMist® Quadrivalent (AstraZeneca)

**Efficacy and effectiveness**

After careful review of the available Canadian and international LAIV VE data over many influenza seasons, NACI concluded that the current evidence is consistent with LAIV providing comparable protection against influenza to that afforded by IIV and does not support a recommendation for the preferential use of LAIV in children 2 to 17 years of age. Additionally, NACI concluded that there is insufficient evidence on the immunogenicity and safety supporting the use of LAIV in adults with immunocompromised conditions and does not support the use of LAIV in this group.

Observational studies from the United States found low effectiveness of LAIV against circulating post-2009 pandemic A (H1N1) [A (H1N1)pdm09], in 2013–2014 and 2015–2016; however, reduced LAIV effectiveness was not observed in Canada or any other countries that have investigated the issue. Manufacturer investigation identified potential reduced replicative fitness of the A (H1N1)pdm09-like LAIV viruses in the nasal mucosa from the 2 affected A (H1N1)-

dominant seasons compared to pre-2009 pandemic influenza A (H1N1) LAIV viruses as contributing to the poor LAIV effectiveness against circulating A (H1N1)[79]. This finding led to the manufacturer replacing the A (H1N1)pdm09 component of LAIV with new strains, with the A/Slovenia/2903/2015 being the strain that has been used since the 2017–2018 season. In adults, studies have found IIV-SD to be similarly or more efficacious or effective compared with LAIV. A recent systematic review and network meta-analysis found that LAIV was more efficacious against laboratory-confirmed influenza (LCI) in adults and older adults compared to placebo or no vaccination. As with other studies, LAIV showed similar efficacy against LCI compared to other influenza vaccines in adults and older adults [167].

Refer to the Statement on Seasonal Influenza Vaccine for 2018–2019 for detailed information supporting this recommendation.

**Immunogenicity**

LAIV, which is administered by the intranasal route, is thought to result in an immune response that mimics that induced by natural infection with wild-type viruses, with the development of both mucosal and systemic immunity. Local mucosal antibodies protect the upper respiratory tract and may be more important for protection than serum antibody.

Studies have demonstrated that the presence of a hemagglutination-inhibition antibody response after the administration of LAIV3 is predictive of protection. However, efficacy studies have shown protection in the absence of a significant antibody response as well [168]. In these studies, LAIV3 has generally been shown to be equally, if not more, immunogenic compared to IIV3-SD for all 3 strains in children, whereas IIV3-SD was typically more immunogenic in adults than LAIV3. Greater rates of seroconversion to LAIV3 occurred in baseline seronegative individuals compared to baseline seropositive individuals in both pediatric and adult populations, because pre-existing immunity may interfere with response to a live vaccine. Refer to the NACI Recommendations on the Use of Live, Attenuated Influenza Vaccine (FluMist®): Supplemental Statement on Seasonal Influenza Vaccine for 2011–2012 for further details regarding the immunogenicity of LAIV3.

LAIV4 has shown non-inferiority based on immunogenicity compared to LAIV3 in both children and adults. The immune response to the B strain found only in the quadrivalent formulation was better in children who received the quadrivalent vaccine [169-171].

**Safety**

The most common AEs experienced by recipients of LAIV3 are nasal congestion and runny nose, which are also reported for LAIV4. In a large efficacy trial, rates of wheezing were statistically higher among children 6 to 23 months of age for LAIV3 compared to IIV3-SD [167]. This finding is expected to be the same for recipients of LAIV4; however, pre-licensure clinical studies for LAIV4 were conducted only in adults and children 2 years of age and older. LAIV4 is not authorized in children less than 2 years of age.

Studies on LAIV3 have shown that vaccine virus can be recovered by nasal swab in children and adults following vaccination (i.e., “shedding”). The frequency of shedding decreases with increasing age and time since vaccination. Shedding is generally below the levels needed to transmit infection, although in rare instances, shed vaccine viruses can be transmitted from vaccine recipients to unvaccinated people. Refer to the NACI Recommendations on the Use of Live, Attenuated Influenza Vaccine (FluMist®): Supplemental Statement on Seasonal Influenza Vaccine for 2011–2012 for more information on LAIV and viral shedding.

**Considerations related to children living with HIV infection**

Following a review of the literature regarding the use of LAIV in individuals living with HIV, NACI concluded that LAIV is immunogenic in children with stable HIV infection on HAART and with adequate immune function. In addition, NACI concluded that LAIV appears to have a similar safety profile as IIV in children on HAART and with stable HIV infection with regard to frequency and severity of AEs [172]. As expected, injection site reactions were seen only with IIV and nasal symptoms were more common with LAIV. However, the evidence base is too small to effectively detect uncommon, rare, and very rare AEs related to the use of LAIV in in this population. Nasal spray may be preferable to IM injection for some individuals who are averse to receiving the vaccine by injection. Therefore, NACI recommends that LAIV may be considered as an option for children 2 to 17 years of age with stable HIV infection on HAART and with adequate immune function. LAIV should be considered only in children with HIV who meet all of the following criteria:

- Receiving HAART for 4 months or longer
- CD4 count equal to or greater than 500/µL if 2 to 5 years of age, or ≥200/µL if 6 to 17 years of age (measured within 100 days before administration of LAIV)
- HIV plasma RNA less than 10,000 copies/mL (measured within 100 days before administration of LAIV)

IM influenza vaccination is still considered the standard for children living with HIV by NACI and the Canadian Pediatric and Perinatal HIV/AIDS Research Group, particularly for those without HIV viral load suppression (i.e., plasma HIV RNA >40 copies/mL). However, if IM vaccination is not accepted by the individual or substitute decision maker, LAIV would be a reasonable option for children meeting the criteria listed above.

Refer to the NACI Statement on the Use of LAIV in HIV-Infected Individuals for more information on the use of LAIV in this population.