

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

Statement on seasonal influenza vaccines for  
2025–2026

**Important notice 1: Update to authorization status for Supemtek™ (Sanofi)**

Supemtek™ quadrivalent recombinant seasonal influenza vaccine (RIV4) has been cancelled post-market and is currently not authorized or available in Canada. Supemtek™ is the first and, to date, the only seasonal influenza vaccine in Canada made with recombinant technology.

**Important notice 2: Update to authorization status for FluMist® Quadrivalent (AstraZeneca)**

FluMist® Quadrivalent live attenuated influenza vaccine (LAIV4) has been cancelled post-market and is currently not authorized or available in Canada. This product has been replaced by the trivalent formulation, FluMist® (LAIV3).

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## Preamble

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

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

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

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

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# Summary of information contained in 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. 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. Each year, there are approximately 3 to 5 million cases of severe influenza illness and 290,000 to 650,000 deaths from influenza worldwide <sup>(1)</sup>.
- Most people will recover from influenza within 7 to 10 days, but some people are at greater risk of severe complications, such as pneumonia. Influenza infection can also worsen certain chronic conditions, such as cardiovascular disease <sup>(2)</sup>.
- Inactivated influenza vaccines (IIV) (which include standard dose [SD], high dose [HD], cell culture-based [cc] or adjuvanted [Adj] vaccines), recombinant influenza vaccine (RIV) and live attenuated influenza vaccine (LAIV) 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 an allergic reaction to a component 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

providers should also be aware that risks of acquiring influenza are higher in some settings and risks from influenza infection are higher in 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); and
- People whose occupational or recreational activities increase their risk of exposure to avian influenza A viruses (e.g., H5N1).
  - In infants less than 6 months of age, evidence is lacking to demonstrate that influenza vaccine would be effective and currently authorized influenza vaccines are not indicated for use in this age group<sup>(3)</sup>. 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 pregnant women and pregnant individuals, breastfeeding women and breastfeeding individuals, 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 all eligible or 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 are available in all jurisdictions and availability of some products as part of publicly funded provincial and territorial programs may be limited or variable year to year.

## 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 2025–2026 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 one 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 contraindication, NACI also recommends that LAIV is contraindicated for:
- People with severe asthma (defined as currently on oral or high-dose inhaled glucocorticosteroids), 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 long-term aspirin or aspirin-containing therapy, because of the association of Reye's syndrome with aspirin and wild-type influenza infection;
- Pregnant women and pregnant individuals, because it is a live attenuated vaccine and there are limited data on safety and effectiveness of LAIV in this population. There has been no identified safety signal regarding the use of LAIV in pregnancy;
- 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; however, children living with stable HIV infection receiving antiretroviral therapy (ART) and with

adequate immune function can receive LAIV.

- 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 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; and
  - When there is administration of antivirals active against influenza (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 vaccine 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

- Influenza is a common vaccine-preventable disease. 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.
- 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 the body's immune response to influenza vaccination may be transient and may not persist beyond a year.

# 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 2025–2026,” 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, refer to the new [Influenza vaccines chapter of the Canadian Immunization Guide](#).

## New or updated information for 2025–2026

### Transition from quadrivalent to trivalent influenza vaccines

NACI recommends that any age-appropriate quadrivalent or trivalent influenza vaccine should be used for individuals 6 months of age and older who do not have contraindications or precautions.

- Both quadrivalent and trivalent formulations are clinically safe and effective.
- 
- B/Yamagata lineage viruses have not been detected globally since March 2020.
- Following this change in epidemiology, expert groups have endorsed the exclusion of the B/Yamagata component from influenza vaccine formulations, in alignment with [WHO's recommendations for the 2024-2025 Northern Hemisphere season](#).

Quadrivalent vaccines were previously preferred for children due to the additional protection conferred by the presence of components from both influenza B lineages. NACI no longer has a preference between quadrivalent and trivalent influenza vaccine formulations for children.

For more information supporting this recommendation, refer to the [Addendum to the NACI Statement on Seasonal Influenza Vaccine for 2024-2025: Transition from Quadrivalent to Trivalent Influenza Vaccines](#) and the section [Choice of seasonal influenza vaccine](#) of this statement.

See [Appendix B](#) for information on characteristics of all influenza vaccines expected to be authorized and available for use in Canada for the 2025–2026 influenza season.

### Concurrent administration of influenza vaccines

A literature review was conducted in December 2023 to identify new evidence on efficacy, effectiveness, immunogenicity, and safety of concurrent administration of COVID-19 vaccines with other vaccines, including influenza vaccines, in individuals 6 months of age and older. A detailed evidence synthesis was included in [NACI guidance on the use of COVID-19 vaccines during the fall of 2024](#), and a summary of the findings has been integrated in this statement. This update includes new evidence on the effects of concurrent administration of COVID-19 vaccines and influenza vaccines derived from RCTs and observational studies.

Additionally, a rapid review was conducted in May 2024 to retrieve evidence on the impact of concurrent administration of newer (e.g., mRNA COVID-19) or adjuvanted vaccines with enhanced influenza vaccines (i.e., IIV-Adj, IIV-HD, IIV-cc or RIV) on vaccine efficacy/effectiveness, immunogenicity, and safety. Considering the additional evidence identified through this review, NACI has updated this statement to include new information on the safety and immunogenicity of adjuvanted or high dose influenza vaccines when concurrently administered with other adjuvanted or newer vaccines.

There is no change to the recommendation that influenza vaccines may be administered concurrently with (i.e., same day) or at any time before or after other inactivated or live attenuated vaccines.

For more information, refer to the section [Concurrent administration](#) of this statement.

## Protective effects of influenza vaccination on cardiovascular events

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

Considering the emergence of additional recent evidence on the potential benefits of influenza vaccination on CV events, a literature review was conducted in March 2024 to retrieve and summarize the available data from existing systematic reviews (SR) and meta-analyses (MA) on the risk of CV events and CVD in adults after receipt of influenza vaccine. Overall, 24 SR and MA published between 2012 and 2024 assessing the effect of influenza vaccination on the risk of CV events were identified, providing supporting evidence for a protective effect of influenza vaccination against CV events in high-risk populations, such as those with underlying CVD.

For more information, refer to the section [Groups for whom influenza vaccination is particularly important](#) and [Appendix C](#) of this statement.

## Indigenous language and indigenous-related content

NACI engaged with Indigenous Services Canada's Vaccine Preventable Disease Working Group to better understand the experiences of First Nations, Inuit and Métis communities (regardless of residency) with influenza, and how Indigenous Peoples should be referenced and prioritized in this statement. NACI's recommendations aim to address the severe health inequities that exist and prioritize an intervention for people who have historically lived in and continue to live in marginalized conditions <sup>(4)</sup>. First Nations, Inuit, and Métis communities experience a high burden of illness due to social, environmental, and economic factors, rooted in the history of colonization and systemic racism <sup>(5)</sup>. By providing a recommendation acknowledging that individuals in or from First Nations, Inuit, and Métis communities may be at increased risk of severe influenza disease and the contributing intersecting determinants of health, inequity may be reduced. Implementation should prioritize cultural safety given that there have been documented barriers to feasibility and acceptability of some immunization programs in First Nations, Inuit, and Métis community settings.

For more information, refer to the section [Groups for whom influenza vaccination is particularly important](#) and [List 1](#) of this statement.

## Pregnancy language

NACI recognizes that not all people giving birth or breastfeeding will identify as women or mothers. The writing in this statement uses a gender additive approach where the term “woman” is used alongside gender neutral language. This is intended to demonstrate a commitment to redress the historic exclusion of trans and non-binary people, whilst avoiding the risk of marginalizing or erasing the experience of women within the health care environment. Finally, NACI acknowledges the dynamic nature of language. It is likely that language deemed to be suitable or affirming in one context may not translate across others, and over the coming years will likely change and evolve with respect to appropriate representations.

## Updated recommendation for people whose occupational or recreational activities increase their risk of exposure to avian influenza A(H5N1) viruses

In previous statements, poultry handlers were identified as a group for whom influenza vaccination is particularly important. Multiple outbreaks of avian influenza A(H5N1), specifically clade 2.3.4.4b, have occurred in poultry and wild birds in Canada and the United States (US) since late 2021, with spillover events to other mammals, including dairy cattle and swine in the US. In the US, documented transmission from cattle to humans and poultry to humans has been reported. Although there is no evidence that seasonal influenza vaccines protect against avian influenza infection, they may reduce the risk of seasonal human and avian influenza A(H5N1) virus co-infection and possible viral reassortment leading to a human-transmissible virus with pandemic potential. In this context, NACI has expanded [List 1](#) (groups for whom influenza vaccination is particularly important) to include people whose occupational or recreational activities increase their risk of exposure to avian influenza A(H5N1) viruses.

For more information, refer to the section [Groups for whom influenza vaccination is particularly important](#) and [List 1](#) of this statement.

## 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, which allows time for vaccine manufacturers to produce the quantity of vaccine required. Currently, 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 (B/Victoria). 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 (B/Yamagata).

Due to the absence of confirmed detections of naturally occurring B/Yamagata lineage viruses amongst seasonal strains since March 2020, the WHO has recommended the removal of the B/Yamagata antigen as a component of all live and non-live influenza vaccines for both the Southern Hemisphere 2024 season and Northern Hemisphere 2024-2025 season <sup>(6, 7)</sup>. In March

2024, several other regulatory agencies, including the United States Food and Drug Administration Vaccines and Related Biological Products Advisory Committee (US FDA VRBPAC) and European Medicines Agency (EMA) also adopted these recommendations and are anticipating to fully transition to trivalent influenza vaccine products for the 2025-2026 season<sup>(8, 9)</sup>. NACI supports the removal of the B/Yamagata strain from influenza vaccines and the transition to trivalent influenza vaccines, in alignment with public health and regulatory agencies globally, as soon as practically possible. Recognizing the significant logistical implications and potential complexities involved from a regulatory perspective, a gradual transition to trivalent vaccines is anticipated.

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 results in lost opportunities to prevent infection from exposures that occur prior to vaccination. Individuals seeking or considering vaccination should be informed that vaccine administered during an influenza outbreak may not provide optimal protection, as it takes time to develop antibody response to the vaccine. 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 respiratory syncytial virus (RSV), are co-circulating. Effective prevention of influenza by vaccination is a critical tool to mitigate ongoing health system stress.

## 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, 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, 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 2025–2026 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 18th, 2024, the available evidence and updates for this year's seasonal influenza statement proposed by the IWG were presented for consideration and approval by NACI. Following a thorough review of the evidence, the committee approved the changes. The description of relevant considerations, rationale for specific decisions, and identified knowledge gaps are described in this statement.

## Epidemiology

### Disease description

Influenza is a respiratory infection that 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 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, most commonly A(H1N1) and A(H3N2). 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 are classified into two lineages that evolved in the early 1980s: B/Victoria and B/Yamagata. Both influenza A and B viruses can be further classified into clades and sub-clades.

Over time, antigenic variation (i.e., 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.

### B/Yamagata

In the years prior to the emergence of SARS-CoV-2, the B/Yamagata and B/Victoria virus lineages circulated simultaneously globally <sup>(10)</sup>. Historically, B/Yamagata viruses have been more prevalent in adults, while B/Victoria viruses have been more prevalent in children and adolescents <sup>(10, 11)</sup>. Between 2012 and 2017, B/Yamagata viruses were responsible for a larger proportion of influenza B infections than B/Victoria, but in the last two years prior to the COVID-19 pandemic (i.e., after a major outbreak of B/Yamagata in 2017-2018 in most countries, including Canada), the B/Victoria lineage started becoming dominant <sup>(10)</sup>. As of March 2020, there have been no confirmed naturally occurring cases of B/Yamagata influenza lineage viruses worldwide, and any sporadic specimens reported to yield B/Yamagata have either been linked to individuals vaccinated with LAIV or errors in lineage determination upon investigation <sup>(10)</sup>. The extinction of B/Yamagata has not yet been declared, so epidemiological and virological monitoring of influenza viruses continues to be important <sup>(12)</sup>.

### 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 <sup>(13)</sup>. 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.

## People at risk

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 (particularly frail older adults), children 0 to 59 months of age, pregnant women and pregnant individuals, and individuals in or from First Nations, Inuit, or Métis communities.

## 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 mid to late-November and lasts an average of 27 weeks, although seasons can start as early as October or as late as February <sup>(14)</sup>. One or more peaks may occur during a season. Although 1 strain often predominates, more than 1 influenza strain typically circulates each season. There are differences in the timing of influenza activity observed across regions in Canada.

Seasonal and temporal patterns over the past 3 seasons (2021-2022, 2022-2023, and 2023-2024) have differed from pre-pandemic seasons with respect to variations in season start and end dates, season length, and temporal patterns across Canada.

## 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 bacterial 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 first 15 days after infection, and with GBS with onset 1 to 6 weeks after infection <sup>(15, 16)</sup>.

## Burden of disease in children

Influenza poses a significant disease burden on children. Infants, especially those under 6 months old, are disproportionately vulnerable to influenza infection and its complications due to their lack of prior immunity and ineligibility for the influenza vaccine. Across 7 influenza seasons (2012-2013 to 2018-2019) in Quebec, infants under 6 months old had a 3- and 5-fold higher risk of hospitalization compared to children aged 6 to 23 months and 2 to 4 years, respectively <sup>(17)</sup>. For additional information regarding the impact of influenza on infants, refer to the [NACI statement: Updated guidance on influenza vaccination during pregnancy](#).

In recent seasons of B/Victoria predominance in Canada, individuals under 19 years of age accounted for approximately half (48 to 54%) of influenza B cases <sup>(18)</sup>. Between the 2004 and 2013 (excluding the 2009-2010 H1N1 pandemic) seasons, influenza B was associated with 15.5 to 58.3% of influenza-related hospitalizations and higher mortality rates than influenza A (1.1% and 0.4%, respectively) among children admitted to Canadian Immunization Monitoring Program Active (IMPACT) centres <sup>(19)</sup>. During the 2023-2024 season in Canada, most (46%) influenza B hospitalizations occurred among children and adolescents under 19 years of age <sup>(20)</sup>. Moreover, children under 5 years of age had the second-highest cumulative influenza-associated hospitalization rate (139 per 100,000 population) overall <sup>(20)</sup>.

## Burden of disease in adults

Adults aged 65 years and older have a disproportionately greater risk of severe influenza disease, hospitalization, intensive care unit admission, and death, compared to younger adults <sup>(21)</sup>. Specifically, older adults face a higher burden of influenza A infection than other age groups <sup>(21, 20)</sup>. During the 2023-2024 season in Canada, adults aged 65 years and older accounted for most influenza-associated hospitalizations (45%) and deaths (71%) and had the highest cumulative hospitalization rate (199 per 100,000 population) overall <sup>(18)</sup>. For additional information regarding influenza in older adults, refer to the [Supplemental guidance on influenza vaccination in adults 65 years of age and older](#).

## Disease frequency

### Global

Each year, there are approximately 3 to 5 million cases of severe influenza illness and 290,000 to 650,000 deaths from influenza worldwide <sup>(1)</sup>. Global influenza circulation was at a historical low during the COVID-19 pandemic (2020-2021 and 2021-2022 seasons) due in part to the implementation of public health measures such as physical distancing and the use of face masks <sup>(22, 23)</sup>. By the 2022-2023 season, global influenza activity returned to circulation patterns resembling pre-pandemic seasons, except for the absence of B/Yamagata lineage virus detections after March 2020. During the most recent 2023-2024 Northern Hemisphere influenza season, influenza activity peaked in late December 2023, with influenza A outnumbering influenza B detections until March 2024 <sup>(24)</sup>. 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 <sup>(25)</sup>. Prior to the COVID-19 pandemic (2010-2011 to 2018-2019 seasons), influenza caused an estimated 15,000 hospitalizations annually, more than any other seasonal respiratory virus <sup>(26)</sup>. 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 2023-2024 season, a total of 103,173 laboratory-confirmed influenza (LCI) detections were reported from 1,358,268 tests <sup>(18)</sup>. However, a large proportion of influenza infections are not laboratory-confirmed; therefore, the number of detections 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 <sup>(27)</sup>. Aligning with global trends, seasonal influenza circulation in Canada was suppressed during the 2020-2021 season but returned to pre-pandemic levels by 2022-2023. The 2023-2024 influenza season in Canada began in November 2023, with influenza activity peaking in late December 2023. Influenza A accounted for most detections overall (77%) and circulated earlier in the season, particularly among older populations, with influenza A(H1N1)pdm09 as the predominant strain <sup>(18)</sup>. Conversely, Influenza B (Victoria) activity circulated later in the season, mainly among younger age groups. There were no detections of B/Yamagata <sup>(20)</sup>. For details on current national influenza activity, refer to the [FluWatch website](#).

## Seasonal influenza vaccines

### Vaccine products authorized for use in Canada

The following sections describe the influenza vaccine products that are authorized for use in Canada for the 2025–2026 season. Given the global transition to trivalent influenza vaccines, the availability of various influenza vaccine preparations in Canada is evolving. 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. 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.

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® and 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 currently authorized for use in Canada and available for the 2025-2026 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](#).

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 <sup>(28-33)</sup>.

All IIVs currently available in Canada are produced in eggs, except for Flucelvax® (IIV3-cc), which is a mammalian cell culture-based 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 IIV3-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.

There are 4 standard dose IIVs currently authorized and available for use in Canada: IIV3-SD: Fluviral, Fluzone®, and Influvac® ; and IIV3-cc: Flucelvax® . 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® 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. Although authorized, Fluad® Pediatric has not been available in Canada since 2019.

There is 1 high-dose IIV (IIV-HD) currently authorized and available for use in Canada: Fluzone® High-Dose Trivalent (IIV3-HD), a trivalent unadjuvanted, split virus seasonal influenza vaccine containing 60 µg HA per strain and administered as a 0.5 mL dose by IM injection for adults 65 years of age and older.

## Recombinant influenza vaccine (RIV)

There is currently 1 RIV authorized for use in Canada: Supemtek® (RIV4), a quadrivalent, 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. Although authorized, RIV is not available in Canada.

## 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 and available for use in Canada for children 2 to 17 years of age and adults 18 to 59 years of age: FluMist® (LAIV3), a trivalent nasal spray influenza vaccine given as a 0.2 mL dose (0.1 mL in each nostril).

## 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.

The Canadian Sentinel Practitioner Surveillance Network (SPSN) provides VE estimates against medically-attended LCI in Canada, using data from British Columbia, Alberta, Ontario and Quebec. Between October 29, 2023 and May 4, 2024, VE against any medically-attended LCI was 46% (95% CI: 37 to 54). VE against influenza A overall was 48% (95% CI: 38 to 56), with 50% (95% CI: 39 to 59) against A(H1N1)pdm09 and 32% (95% CI: 10 to 49) against A(H3N2). VE against influenza B was higher at 63% (95% CI: 48 to 74). Paradoxically, VE against A(H1N1)pdm09 was lower for vaccine-matched clade 5a.2a.1 (43%, 95% CI: 24 to 57) than clade 5a.2a (57%, 95% CI: 41 to 63). VE estimates for A(H1N1)pdm09 were higher in children and adolescents under 20 years (61%, 95% CI: 40 to 75) and adults 65 years and older (61%, 95% CI: 38 to 75), compared to adults aged 20-64 years of age (41%, 95% CI: 24 to 54)<sup>(18)</sup>.

## 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 D](#) 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<sup>34, 35</sup>. 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 D](#) 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.

## 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 intramuscular (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, 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<sup>(36-38)</sup>. Several studies have looked at whether these 2 initial doses need to be given in the same season<sup>(30, 31, 39)</sup>. Similar immunogenicity was reported 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<sup>(30, 31)</sup>. 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<sup>(29, 31)</sup>. Issues related to effective prime-boost when there is a major change in influenza B lineage across sequential seasons require further evaluation<sup>(40)</sup>. 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 2025–2026 influenza season**

Age group	Influenza vaccine type (route of administration)						Number of doses required
	IIV-SD <sup>a</sup> (IM)	IIV-cc <sup>b</sup> (IM)	IIV-Adj <sup>c</sup> (IM)	IIV-HD <sup>d</sup> (IM)	RIV <sup>e</sup> (IM)	LAIV <sup>f</sup> (intranasal)	
6 to 23 months	0.5 mL <sup>g</sup>	0.5 mL	0.25 mL	-	-	-	1 or 2 <sup>h</sup>
2 to 8 years	0.5 mL	0.5 mL	-	-	-	0.2 mL (0.1 mL per nostril)	1 or 2 <sup>h</sup>
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	0.5 mL	0.5 mL	-	1
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**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.

<sup>a</sup> Fluviral (6 months and older), Fluzone<sup>®</sup> (6 months and older), Influvac<sup>®</sup> (3 years and older)

<sup>b</sup> Flucelvax<sup>®</sup> (6 months and older)

<sup>c</sup> Fluad Pediatric<sup>™</sup> (6 to 23 months) or Fluad<sup>®</sup> (65 years and older). Although authorized, Fluad<sup>®</sup> Pediatric has not been available in Canada since 2019.

<sup>d</sup> Fluzone<sup>®</sup> High-Dose (65 years and older)

<sup>e</sup> Supemtek<sup>®</sup> (18 years and older). Although authorized, Supemtek<sup>®</sup> is not available in Canada.

<sup>f</sup> FluMist<sup>®</sup> (2 to 59 years)

<sup>g</sup> 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. 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](#).

<sup>h</sup> 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 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 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 <sup>(41)</sup>.

## Serological testing

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

## Storage requirements

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

## 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 non-live), 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.

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<sup>(42-44)</sup>. One study reported a statistically significant but not clinically meaningful decrease in seroresponse rates to rubella antigen when administered concurrently 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 non-live 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, refer to [Timing of vaccine administration](#) in Part 1 of the CIG.

The target groups for influenza and pneumococcal vaccines overlap considerably. A recent study showed that compared to administration alone, concurrent administration of IIV4 with 15-valent pneumococcal conjugate vaccine (PCV15) in adults demonstrated non-inferiority of pneumococcal- and influenza-specific antibody responses<sup>(45)</sup>. 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 July 2024 indicates that the concurrent administration of an RSV vaccine with another adult vaccine, including seasonal influenza vaccines, is acceptable and supported. Readers should consult the [RSV vaccines chapter](#) in Part 4 Immunizing Agents of the CIG and NACI's [Statement on the prevention of respiratory syncytial virus \(RSV\) disease in older adults](#) for more information.

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 sterile needle and syringe should always be used for each injection. For more information regarding vaccination administration timing rules, refer to

[Timing of vaccine administration](#) in Part 1 of the CIG.

## Concurrent administration with COVID-19 vaccines

NACI reviewed the most recent literature on the impact of concurrent administration of seasonal influenza and COVID-19 vaccines on efficacy/effectiveness, safety and immunogenicity outcomes, including the potential safety signal of ischemic stroke. Overall, available evidence supports the concurrent administration of seasonal influenza and COVID-19 vaccines. 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 vaccines chapter](#) in Part 4 Immunizing Agents of the CIG and the latest NACI [COVID-19 vaccine guidance](#) for updated guidance and further information on concurrent administration of COVID-19 vaccines with influenza vaccines and across all eligible age groups.

### Efficacy and effectiveness

Although data are limited, evidence suggests that concurrent administration of influenza and COVID-19 vaccines does not result in a difference in vaccine efficacy/effectiveness against COVID-19 or influenza compared to separate administration of COVID-19 or influenza vaccines <sup>(46, 47)</sup>.

### Safety

Although some studies have reported increased reactogenicity after concurrent administration of COVID-19 vaccines and influenza vaccines compared to influenza vaccination alone, reactogenicity was comparable to COVID-19 vaccination alone <sup>(48, 49, 47, 50)</sup>. Although a large self-controlled case series in the US on adults 65 years of age and older showed that concurrent administration of the bivalent COVID-19 vaccine and a high-dose or adjuvanted influenza vaccine was associated with a higher risk of ischemic stroke, this observation was inconsistent with results from other analyses in the US and other countries <sup>(51-53)</sup>. Most analyses, from several countries, did not show an association between concurrent administration of bivalent mRNA vaccines with influenza vaccines and ischemic stroke <sup>(54, 51-53, 55, 56)</sup>. The totality of data available at this time does not support an association between ischemic stroke and concurrent administration of bivalent mRNA COVID-19 vaccines with influenza vaccines.

### Immunogenicity

Most studies have showed that the concurrent administration of COVID-19 and seasonal influenza vaccines induces non-inferior immune responses against SARS-CoV-2 and HA compared to sequential administration <sup>(57-62)</sup>. Although some studies reported lower immune responses against SARS-CoV-2 following concurrent administration of COVID-19 and influenza vaccines, the clinical significance of these results is unknown <sup>(63, 48, 64, 49)</sup>.

NACI will continue monitoring emerging evidence and update guidance accordingly.

## Concurrent administration with other adjuvanted or newer vaccines

Data are limited regarding concurrent administration of newer or adjuvanted influenza vaccines with other adjuvanted or non-adjuvanted vaccines. Specifically, studies investigating concurrent administration of IIV-cc or RIV with adjuvanted or newer vaccines are scarce.

For example, RZV is a recombinant adjuvanted subunit herpes zoster vaccine (Shingrix<sup>®</sup>, GlaxoSmithKline) that is authorized for use in Canada in adults 50 years of age and older, and adults 18 years of age and 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 <sup>(65)</sup>. However, studies assessing the concurrent administration of RZV with adjuvanted or high-dose influenza vaccines are limited <sup>(66)</sup>. It should be noted that RZV and IIV-Adj currently authorized for use in Canada contain the adjuvants AS01<sub>B</sub> and MF59, respectively. How these adjuvants may interact when RZV and IIV-Adj are administered concurrently is not yet known.

A rapid review was conducted by NACI in May 2024 to retrieve relevant articles on the concurrent administration of enhanced influenza vaccines (i.e., IIV-HD, IIV-Adj, IIV-cc and RIV) with other newer vaccines, adjuvanted vaccines, or vaccines using newer technologies. Few studies were identified through the database search and environmental scanning that evaluated the immunogenicity and/or safety of concurrent administration of IIV-Adj (n=1) or IIV-HD (n=2) with newer vaccines or other adjuvanted vaccines <sup>(67-69)</sup>. A RCT in adults 60 years of age and older demonstrated a good safety profile and no interference in immune response with the concurrent administration of IIV-Adj and another adjuvanted vaccine, the 13-valent pneumococcal conjugate vaccine (Pevnar<sup>®</sup>13, Pfizer), containing the adjuvant AlPO<sub>4</sub> <sup>(67)</sup>. Two recent RCTs evaluated the concurrent administration of IIV-HD with newer RSV vaccines in adults 50 years of age and older <sup>(69, 68)</sup>. No safety concerns were identified with the concurrent administration of IIV-HD and the Respiratory Syncytial Virus prefusion F (RSVpreF) vaccine (Abrysvo<sup>™</sup>, Pfizer) and the AS01<sub>E</sub> adjuvanted RSV prefusion protein F3 (RSVPreF3) vaccine (Arexvy, GlaxoSmithKline). No immune interference was reported with the concurrent administration of IIV-HD and the adjuvanted RSVpreF3 vaccine <sup>(68)</sup>. A reduced immune response to IIV-HD was observed with the concurrent administration of the RSVpreF vaccine; however, the clinical significance of this reduction is currently unknown <sup>(69)</sup>. Additional research is ongoing to further inform guidance on same-day administration of RSV vaccines and other adult vaccines, including influenza vaccines. NACI will continue to review the evidence and update guidance accordingly.

## 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 (VWVG) 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 to keep the product sterile <sup>(70)</sup>. 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 <sup>(71)</sup>. 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 a component 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 allergic 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 <sup>(72)</sup>. The attributable risk of GBS in the period following seasonal and monovalent 2009 pandemic influenza vaccination is about 1 excess case per million vaccinations <sup>(73, 74)</sup>. 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 <sup>(74)</sup>. Another cohort study found a risk of approximately 2 GBS cases per 1 million doses in the 4 weeks following administration of the 2009 influenza A(H1N1) influenza vaccine; moreover, there was no indication of an excess risk in persons younger than 50 years of age <sup>(75)</sup>.

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 <sup>(74)</sup>.

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 <sup>(76-79)</sup>.

## 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 edema, was identified during the 2000–2001 influenza season <sup>(80)</sup>. Since then, there have been far fewer cases per year reported to CAEFISS <sup>(81)</sup>. 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, allergy to an influenza vaccine should be confirmed with diagnostic testing, 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 published studies have found that adults who are regular statin users (at least 65 years of age in 1 study and 45 years and older in the other) had a decreased response to influenza vaccination as measured by reduced geometric mean titres (GMT) or reduced VE against medically attended acute respiratory illness<sup>(82, 83)</sup>. 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. Influenza antiviral agents (e.g., oseltamivir, zanamivir) may inactivate the replicating vaccine virus contained in LAIV and therefore reduce the vaccine effectiveness. 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 administered 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.

# 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<sup>a</sup>:
  - 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)
  - Class 3 obesity (defined as body mass index of 40 kg/m<sup>2</sup> and over); and
  - 
  - Children 6 months to 18 years of age undergoing long-term treatment with

acetylsalicylic acid, because of the potential increase of Reye's syndrome associated with influenza

- All pregnant women and pregnant individuals;
- All individuals of any age who are residents of nursing homes and other chronic care facilities;
- Adults 65 years of age and older; and
- Individuals in or from First Nations, Inuit, or Métis communities as a result of intersecting determinants of health rooted in historic and ongoing colonization and systemic racism.

#### **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 whose occupational or recreational activities increase their risk of exposure to avian influenza A(H5N1) viruses.

<sup>a</sup> 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.

## Choice of seasonal influenza vaccine

Due to the evolving influenza vaccine landscape, including the introduction of new influenza vaccines, some of which are designed to enhance immunogenicity in specific age groups, the choice of product is now more complex. NACI recommends that any age-appropriate quadrivalent or trivalent influenza vaccine should be used for individuals 6 months of age and older who do not have contraindications or precautions.

[Table 2](#) provides age group-specific recommendations for the age-appropriate influenza vaccine types authorized for use in Canada for individual and public health program-level decision making. Additional information for these recommendations and considerations on choice of influenza vaccine 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 for use	Recommendations on choice of influenza vaccine
<b>6 to 23 months</b>	<ul style="list-style-type: none"> <li>▪ IIV-Adj</li> <li>▪ IIV-SD</li> <li>▪ IIV-cc</li> </ul>	<ul style="list-style-type: none"> <li>• Any age-appropriate quadrivalent or trivalent influenza vaccine should be used for infants and young children who do not have contraindications or precautions, noting the following considerations:               <ul style="list-style-type: none"> <li>○ Currently, there is insufficient evidence for recommending vaccination with Influvac® Tetra (IIV4-SD) in children younger than 3 years of age.</li> </ul> </li> </ul>
<b>2 to 17 years<sup>a</sup></b>	<ul style="list-style-type: none"> <li>• IIV-SD</li> <li>• IIV-cc</li> <li>▪ LAIV</li> </ul>	<ul style="list-style-type: none"> <li>• Any age-appropriate quadrivalent or trivalent influenza vaccine should be used for children and adolescents who do not have contraindications or precautions (see text below applicable to LAIV), including those with chronic health conditions, noting the following considerations and exceptions:               <ul style="list-style-type: none"> <li>○ Influvac® (IIV3-SD) is not authorized for children younger than 3 years of age.</li> <li>○ Currently, there is insufficient evidence for recommending vaccination with Influvac® Tetra (IIV4-SD) in children younger than 3 years of age.</li> <li>○ LAIV may be given to children with:                   <ul style="list-style-type: none"> <li>▪ stable, non-severe asthma;</li> <li>▪ cystic fibrosis who are not being treated with immunosuppressive drugs (e.g., prolonged systemic corticosteroids); and</li> <li>▪ stable HIV infection, i.e., if the child is currently being treated with ART for at least 4 months and has adequate immune function.</li> </ul> </li> <li>○ 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:                   <ul style="list-style-type: none"> <li>▪ severe asthma (defined as currently on oral or high-dose inhaled glucocorticosteroids) or active wheezing;</li> <li>▪ medically attended wheezing in the 7 days prior to vaccination;</li> <li>▪ current receipt of long-term aspirin or aspirin-containing therapy;</li> <li>▪ immune compromising conditions, with the exception of stable HIV infection, i.e., if the child is currently being treated with ART for at least 4 months and has adequate immune function; and</li> <li>▪ pregnancy (in pregnancy, IIV-SD or IIV-cc should be used instead).</li> </ul> </li> </ul> </li> </ul>
<b>18 to 59 years</b>	<ul style="list-style-type: none"> <li>• IIV-SD</li> <li>• IIV-cc</li> <li>• RIV</li> <li>• LAIV</li> </ul>	<ul style="list-style-type: none"> <li>• Any of the available influenza vaccines authorized for this age group should be used for adults 18 to 59 years of age without contraindications or precautions, noting the following considerations and exceptions:               <ul style="list-style-type: none"> <li>○ There is some evidence that IIV may provide better efficacy than LAIV in healthy adults; and</li> <li>○ LAIV is not recommended for:                   <ul style="list-style-type: none"> <li>▪ pregnant women and pregnant individuals (in pregnancy, IIV-SD, IIV-cc, or RIV should be used instead);</li> <li>▪ adults with any of the chronic health conditions identified in <a href="#">List 1</a>, including immune compromising conditions; and</li> <li>▪ health care workers (HCWs).</li> </ul> </li> </ul> </li> </ul>

<b>60 to 64 years</b>	<ul style="list-style-type: none"> <li>• IIV-SD</li> <li>• IIV-cc</li> <li>• RIV</li> </ul>	<ul style="list-style-type: none"> <li>• Any of the available influenza vaccines authorized for this age group should be used for adults 60 to 64 years of age without contraindications or precautions.</li> </ul>
<b>65 years and older<sup>b</sup></b>	<ul style="list-style-type: none"> <li>• IIV-Adj</li> <li>• IIV-SD</li> <li>• IIV-HD</li> <li>• IIV-cc</li> <li>• RIV</li> </ul>	<ul style="list-style-type: none"> <li>• 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 influenza vaccines authorized for this age group should be used.</li> </ul>

**Abbreviations:** ART: 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; IIV-HD: high-dose inactivated influenza vaccine; RIV: recombinant influenza vaccine; LAIV: live attenuated influenza vaccine

<sup>a</sup> Refer to [Table 3](#) for a summary of vaccine characteristics of LAIV compared with IIV in children 2 to 17 years of age.

<sup>b</sup> 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.

## Children

### Children 6 to 23 months of age

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

### Children 2 to 17 years of age

Three types of influenza vaccine are authorized and available for use in children 2 to 17 years of age: IIV-SD, IIV-cc, and LAIV. Although authorized, Fludac<sup>®</sup> Pediatric (IIV-Adj) has not been available in Canada since 2019. Influvac<sup>®</sup> (IIV-SD) is not authorized for children under the age of 3 years.

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.

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

NACI recommends that any age-appropriate quadrivalent or trivalent 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 (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 long-term aspirin or aspirin-containing therapy, and those with immune compromising conditions (excluding those with stable HIV infection on ART 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.

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 ART 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 <sup>a</sup>	LAIV compared with IIV <sup>b</sup>
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 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 (currently on oral or high-dose inhaled glucocorticosteroids) or active wheezing, medically attended wheezing in the 7 days prior to vaccination, and immune compromising conditions (with the exception of children with stable HIV infection on ART and with adequate immune function), as well as those currently receiving long-term 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:** ART: highly active antiretroviral therapy; IIV: inactivated influenza vaccine; IIV-SD: standard-dose inactivated influenza vaccine; IIV-cc: standard-dose inactivated influenza vaccine; LAIV: live attenuated influenza vaccine

<sup>a</sup> NACI has not assessed the comparative cost-effectiveness of authorized influenza vaccine types for children 2 to 17 years of age.

<sup>b</sup> Data comparing LAIV to IIV-cc are not available, however IIV-cc is comparable to egg-based IIV.

## Adults

### Adults 18 to 59 years of age

Three types of influenza vaccine are authorized and available for use in adults 18 to 59 years of age: IIV-SD, IIV-cc, and LAIV. Although authorized, Supemtek® (RIV) is not available for use.

NACI recommends that any of the authorized and available influenza vaccines should be used in adults without contraindications to the vaccine.

## Adults 60 to 64 years of age

Two types of influenza vaccine are authorized and available for use in adults 60 to 64 years of age: IIV-SD, and IIV-cc. Although authorized, Supemtek® (RIV) is not available for use.

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

## Adults 65 years of age and older

Four types of influenza vaccine are authorized and available for use in adults 65 years of age and older: IIV-Adj, IIV-SD, IIV-cc and IIV-HD. Although authorized, Supemtek® (RIV) is not available for use.

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.

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.

## 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. 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. For further information, refer to [Recommendations on the use of live, attenuated influenza vaccine \(FluMist®\) Supplemental Statement on Seasonal Influenza Vaccine for 2011-2012](#).

## Pregnant women and pregnant individuals

NACI recommends that any age-appropriate IIV (i.e., IIV-SD, IIV-cc) or RIV, but not LAIV, should be offered to pregnant women and pregnant individuals. There has been no identified safety signal regarding the use of RIV during pregnancy, although published clinical data are limited. Additionally, there has been no identified safety signal regarding the use of LAIV in pregnancy, although there are more data on the safety of other influenza vaccine products in pregnancy and evidence that IIV has higher efficacy than LAIV in healthy adults. However, vaccination with LAIV

should not be considered a reason to terminate pregnancy. Breastfeeding individuals can receive either non-live or live-attenuated influenza vaccines. For further details, refer to the [Updated guidance on influenza vaccination during pregnancy](#).

## Health care workers

NACI recommends that any age-appropriate IIV or RIV, but not LAIV, should be offered to health care workers (HCWs). Comparative studies in healthy adults have found IIV to be similarly or more efficacious or effective compared with LAIV<sup>(84)</sup>. Additionally, 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, due to the theoretical risk of 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.

## Groups for whom influenza vaccination is particularly important

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.

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

#### 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](#), several chronic health conditions are associated with increased risk of influenza-related complications and can be exacerbated by influenza 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 immunocompromising conditions compared to healthy adults.

Influenza infection has been associated with an increased risk of cardiovascular (CV) events, including myocardial infarction (MI), heart failure, and stroke, especially among individuals with pre-existing cardiac disorders <sup>(85)</sup>. A study from 2022 suggested that, globally, 3 to 5% of the total number of ischemic heart disease deaths could be attributed to influenza, corresponding to 200,000 to 400,000 ischemic heart disease deaths annually <sup>(86)</sup>. In addition to the prevention of influenza infection and its complications, influenza vaccination may also have a secondary protective effect against the occurrence of CV events in those with acute and chronic heart disease <sup>(87, 88)</sup>.

Recently, NACI conducted a review of systematic reviews and meta-analyses (SR and MA) published since January 1st, 2000. As of March 2024, 24 SR and MA assessing the effect of influenza vaccination on CV events were retrieved. Overall, the findings provide evidence of a protective effect of influenza vaccination against CV events among high-risk populations, such as those with CV disease <sup>(89-93)</sup>. For example, a 2023 review of 5 randomized-controlled trials (RCT) found that influenza vaccination was associated with 26% and 33% significantly lower risks of MI and CV death, respectively, in patients with CV disease <sup>(89)</sup>. Another MA of 23 observational studies and 3 RCTs investigated the association between influenza immunization and stroke incidence or hospitalization. Although most data were from observational studies with substantial heterogeneity, results showed a significant reduction in CV events among all vaccinated patients, and among vaccinated individuals with atrial fibrillation and hypertension (19%, 32%, and 14% risk reduction, respectively) <sup>(94)</sup>. As influenza vaccine coverage remains sub-optimal in Canada, including in high-risk populations, clear communication about the potential CV benefits associated with influenza vaccination may help increase uptake <sup>(95)</sup>. Refer to [Appendix C](#) for a detailed summary of evidence on the effect of influenza vaccination on CV events.

## Pregnant women and pregnant individuals

Pregnant women and pregnant individuals, along with infants under 6 months of age, are particularly at risk of severe illness from influenza infection <sup>(96)</sup>. Overall, studies support the safety and effectiveness of influenza vaccines during pregnancy <sup>(97)</sup>. Vaccination reduces the morbidity and mortality associated with influenza infection during pregnancy <sup>(98)</sup>. Since influenza-related outcomes experienced during pregnancy can negatively impact the development of the fetus, vaccination during pregnancy also helps protect the fetus <sup>(98)</sup>. 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 (IIV-SD, IIV-cc) or recombinant (RIV) influenza vaccines be offered at any stage of pregnancy. NACI also continues to include pregnant women and 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 [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

Although influenza-associated morbidity and mortality vary each season, there is generally an increased burden of severe disease such as influenza-associated hospitalizations, intensive care unit (ICU) admissions, and deaths in adults 65 years of age and older, especially in seasons when influenza A(H3N2) predominates<sup>(99)</sup>.

For further details on estimated burden of influenza among this population, refer to the [supplemental guidance on influenza vaccination in adults 65 years of age and older](#).

## Individuals in or from First Nations, Inuit, or Métis communities

Based on a body of evidence indicating a higher rate of influenza-associated hospitalization among individuals in or from First Nations, Inuit, and Métis communities, NACI recommends the inclusion of this population among those for whom the influenza vaccine is particularly important, regardless of geographic location<sup>(100)</sup>.

The increased risk of severe influenza among individuals in or from First Nations, Inuit, and Métis communities is a consequence of many factors including medical conditions resulting from intersecting determinants of health. These intersecting determinants of health include social, environmental, and economic factors, rooted in historic and ongoing colonization and systemic racism (i.e., structural inequity). To improve understanding of the disproportionate impact within the current landscape, culturally safe research in collaboration with Indigenous partners should be supported. Autonomous decisions should be made by Indigenous Peoples with the support of culturally safe public health and healthcare partners in accordance with the United Nations Declaration on the Rights of Indigenous Peoples Act (UNDRIP).

## 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 HCWs decreases their own risk of illness, as well as the risk of death and other serious outcomes among the individuals for whom they provide care<sup>(101-106)</sup>. Vaccination of HCWs

and residents of nursing homes is associated with decreased risk of ILI outbreaks <sup>(107)</sup>.

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 are care providers in facilities and community settings, 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 cluster randomized controlled trials (RCTs) conducted in geriatric long-term care settings have demonstrated that vaccination of HCWs is associated with substantial decreases in ILI and all-cause mortality in the residents <sup>(101-104)</sup>. 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 <sup>(108)</sup>.

As previously stated, children 0 to 59 months of age, adults and children with chronic health conditions, pregnant women and 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, it remains below the national goal of 80% coverage for HCWs in Canada <sup>(109-111)</sup>. 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 <sup>(112-117)</sup>.

## 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 <sup>(118)</sup>. 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).

## 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 <sup>(105, 106, 119-121)</sup>.

### People whose occupational or recreational activities increase their risk of exposure to avian influenza A(H5N1) viruses

Since late 2021, multiple outbreaks of avian influenza A(H5N1), specifically clade 2.3.4.4b, have occurred in poultry and wild birds in Canada and the United States (US), with spillover events in dairy cattle and swine in the US and to other mammals in Canada and elsewhere. In the US, documented transmission from cattle to humans and poultry to humans has been reported <sup>(122, 123)</sup>. Some countries and provinces have recommended seasonal influenza vaccination on a yearly basis for those working with poultry, swine, cattle, goats, and wild birds <sup>(124-127)</sup>.

Although there is no evidence that seasonal influenza vaccines protect against avian influenza infection, they may reduce the risk of seasonal human and avian influenza A(H5N1) virus co-infection and possible viral reassortment leading to a human-transmissible virus with pandemic potential <sup>(128-136)</sup>. While the effectiveness of influenza vaccines at preventing medically-attended infection varies year to year, they may attenuate illness by reducing viral replication and accelerating the elimination of infected cells, thereby reducing opportunities for reassortment in the event of co-infection <sup>(137, 138)</sup>.

NACI particularly recommends seasonal influenza vaccination for people whose occupational and/or recreational activities increase their risk of exposure to avian influenza A(H5N1) viruses, including contact with certain animal species or their environment. These occupations or activities may include:

- Working with poultry (e.g., chickens, turkeys, ducks) or other livestock (e.g., cattle, goats, swine, mink) on commercial farms including fur farms, small farms, and/or backyard flocks;
- Hunting or trapping wild birds or mammals;
- Handling and/or disposing of sick or dead wild birds, poultry, or mammals (e.g., culling operations), or involvement in the control of avian influenza outbreaks;
- Working with wild birds or mammals for research, conservation, or rehabilitation;
- Working in facilities processing animal products (e.g., meat processing, handling raw milk);
- Workers involved in the transportation of animals, animal products, or agricultural equipment or samples;
- Laboratory workers handling avian influenza viruses;
- Veterinarians and veterinary staff.

Swine workers are included in this recommendation because bidirectional transmission of influenza A viruses between swine and humans is known to occur and may provide opportunity for emergence of a strain with higher pandemic potential through reassortment <sup>(139, 140)</sup>.

In addition to vaccination to help prevent seasonal influenza infection, biosecurity measures, personal protective equipment, and antivirals should be used as recommended for animal contact. Refer to [Human health issues related to avian influenza in Canada](#) for PHAC recommendations on the management of domestic avian influenza outbreaks. NACI will continue to monitor the evolving evidence and update guidance as needed.

## List of abbreviations

<b>Adj</b>	Adjuvanted
<b>AE</b>	Adverse event
<b>AEFI</b>	Adverse event following immunization
<b>ART</b>	Antiretroviral therapy
<b>CAEFISS</b>	Canadian Adverse Events Following Immunization Surveillance System
<b>Cc</b>	Cell cultured
<b>CI</b>	Confidence interval
<b>CIG</b>	Canadian Immunization Guide
<b>CV</b>	Cardiovascular
<b>CVD</b>	Cardiovascular disease
<b>DIN</b>	Drug identification number
<b>EMA</b>	European Medicines Agency
<b>FDA</b>	Food and Drug Administration
<b>FFU</b>	Fluorescent focus units
<b>GBS</b>	Guillain-Barré syndrome
<b>GMT</b>	Geometric mean titre
<b>GMTR</b>	Geometric mean titre ratio
<b>HA</b>	Hemagglutinin
<b>HCW</b>	Health care worker
<b>HD</b>	High dose
<b>HIV</b>	Human immunodeficiency virus
<b>Ig</b>	Immunoglobulin
<b>IIV</b>	Inactivated influenza vaccine
<b>IIV3</b>	Trivalent inactivated influenza vaccine
<b>IIV3-Adj</b>	Adjuvanted trivalent inactivated influenza vaccine (egg-based)
<b>IIV3-HD</b>	High-dose trivalent inactivated influenza vaccine (egg-based)
<b>IIV3-SD</b>	Standard-dose trivalent inactivated influenza vaccine (egg-based)
<b>IIV4</b>	Quadrivalent inactivated influenza vaccine
<b>IIV4-cc</b>	Mammalian cell culture-based quadrivalent inactivated influenza vaccine
<b>IIV4-HD</b>	High-dose quadrivalent inactivated influenza vaccine (egg-based)

<b>IIV4-SD</b>	Standard-dose quadrivalent inactivated influenza vaccine (egg-based)
<b>ILI</b>	Influenza-like illness
<b>IM</b>	Intramuscular
<b>IMPACT</b>	Immunization Monitoring Program Active
<b>LAIV</b>	Live attenuated influenza vaccine (egg based)
<b>LAIV3</b>	Trivalent live attenuated influenza vaccine (egg based)
<b>LAIV4</b>	Quadrivalent live attenuated influenza vaccine (egg based)
<b>LCI</b>	Laboratory-confirmed influenza
<b>MA</b>	Meta-analysis
<b>MDCK</b>	Madin-Darby canine kidney
<b>MI</b>	Myocardial infarction
<b>MMR</b>	Measles, mumps, and rubella
<b>NA</b>	Neuraminidase
<b>NACI</b>	National Advisory Committee on Immunization
<b>ORS</b>	Oculorespiratory syndrome
<b>PHAC</b>	Public Health Agency of Canada
<b>RCT</b>	Randomized controlled trial
<b>RIV</b>	Recombinant influenza vaccine
<b>RIV4</b>	Recombinant quadrivalent influenza vaccine
<b>RNA</b>	Ribonucleic acid
<b>rVE</b>	Relative vaccine efficacy
<b>RZV</b>	Recombinant zoster vaccine
<b>SAE</b>	Serious adverse event
<b>SPSN</b>	Sentinel Practitioner Surveillance Network
<b>SR</b>	Systematic review
<b>US</b>	United States
<b>VE</b>	Vaccine effectiveness
<b>VRBPAC</b>	Vaccines and Related Biological Products Advisory Committee
<b>WHO</b>	World Health Organization

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## Appendix A: Abbreviations for influenza vaccines

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

<sup>a</sup> 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 (IIV3-cc for Flucelvax<sup>®</sup> or IIV4-cc for Flucelvax<sup>®</sup> Quad); “- Adj” (where “Adj” is used to abbreviate “adjuvanted”) refers to an IIV with an adjuvant (IIV3-Adj for Fludac<sup>®</sup> or Fludac Pediatric<sup>™</sup>); and “-HD” refers to an IIV that contains higher antigen content than the 15 µg HA per strain that is contained in the standard IIV dose (IIV3-HD for Fluzone<sup>®</sup> High-Dose or IIV4-HD for Fluzone<sup>®</sup> High-Dose Quadrivalent).

<sup>b</sup> 15 µg HA per strain.

<sup>c</sup> 7.5 µg (in 0.25 mL) or 15 µg (in 0.5 mL) HA per strain.

<sup>d</sup> 60 µg HA per strain.

<sup>e</sup> 45 µg HA per strain.

## Appendix B: Characteristics of influenza vaccines available for use in Canada, 2025–2026<sup>a</sup>

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
<b>Fluzone<sup>®</sup> (Sanofi)</b>	IIV3-SD (split virus)	IM	6 months and older	15 µg HA/0.5 mL dose	None	Single-dose pre-filled syringe without attached needle	Up to expiry date indicated on vial label	Yes (multi-dose vial only)	None	Egg (Avian)
<b>Fluzone<sup>®</sup> High-Dose (Sanofi)</b>	IIV3-HD (split virus)	IM	65 years and older	60 µg HA/0.5 mL dose	None	Single dose pre-filled syringe without attached needle	Not applicable	No	None	Egg (Avian)
<b>Flucelvax<sup>®</sup> (Seqirus)</b>	IIV3-cc (subunit)	IM	6 months and older	15 µg HA/0.5 mL dose	None	5 mL multi-dose vial  Single dose pre-filled syringe without attached needle	28 days	Yes (multi-dose vial only)	None	Cell culture (Mammalian)
<b>FluMist<sup>®</sup> (AstraZeneca)</b>	LAIV3 (live attenuated)	Intranasal	2 to 59 years	10 <sup>6.5-7.5</sup> 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)

<b>Fluad® (Seqirus)</b>	IIV3-Adj (subunit)	IM	65 years and older	15 µg HA /0.5 mL dose	MF59	Single dose pre-filled syringe without a needle	Not applicable	No	Kanamycin and neomycin	Egg (Avian)
<b>Fluviral (GSK)</b>	IIV3-SD	IM	6 months and older	15 µg HA /0.5 mL dose	None	5 mL multi-dose vial	28 days	Yes	None	Egg (Avian)
<b>Influvac® (BGP Pharma ULC, operating as Mylan, d.b.a. Viatris Canada)</b>	IIV3-SD (subunit)	IM	3 years 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 <sup>b</sup>	Egg (Avian)

**Abbreviations:** FFU: fluorescent focus units; HA: hemagglutinin; IIV3-Adj: adjuvanted egg-based trivalent inactivated influenza vaccine; IIV3-cc: standard-dose cell culture-based quadrivalent inactivated influenza vaccine; IIV3-SD: standard-dose egg-based trivalent inactivated influenza vaccine; IM: intramuscular; LAIV3: trivalent live attenuated influenza vaccine; NA: neuraminidase.

<sup>a</sup> 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.

<sup>b</sup> 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: Summary of evidence for the effect of influenza vaccination on cardiovascular events, derived from systematic reviews and meta-analyses

Review characteristics				Summary of findings		
Author, Year	Time Period, Study Design (n)	Objective	Population, Intervention, Comparison, Outcome (PICO)	Participant Characteristics	Results Effect Measure (95% CI)	Risk of Bias
Omidi et al., 2023 (89)	Until August 2023 RCT (5)	To assess whether an association exists between influenza vaccination and a decreased likelihood of experiencing cardiovascular (CV) events	<b>P:</b> Patients diagnosed with CVD <b>I:</b> Influenza vaccination <b>C:</b> Placebo <b>O:</b> Major adverse CV events (MACE), including myocardial infarction (MI), stroke, and/or CV death	9,059 patients (4,529 vaccinated, 4,530 controls) Mean age: 61.3 years Mean follow-up: 9 months	Among vaccinated patients, there was a significant reduction in the risk of the following CV events: <b>MACE:</b> RR= 0.70 (0.55–0.91), I <sup>2</sup> = 58% <b>MI:</b> RR= 0.74 (0.56–0.97), I <sup>2</sup> = 0% <b>CV deaths:</b> RR= 0.67 (0.45–0.98), I <sup>2</sup> = 51%	Yes

<p><b>Barbetta et al., 2023</b> <sup>(90)</sup></p>	<p>Until September 2021</p> <p>RCT (5)</p>	<p>To assess the effectiveness of influenza vaccination in patients with acute coronary syndrome (ACS) or stable coronary artery disease (CAD) on several CV outcomes</p>	<p><b>P:</b> Patients with coronary artery disease  <b>I:</b> Influenza vaccination  <b>C:</b> Placebo or no vaccination  <b>O:</b> Primary outcomes included MACE (CV death, non-fatal MI, non-fatal stroke), all-cause mortality, and CV mortality; Secondary outcomes included hospitalization for heart failure (HF), stroke or transient ischemic attack (TIA), revascularization, and acute coronary syndrome (ACS)</p>	<p>4,187 patients (2,098 vaccinated, 2,089 controls)</p> <p><b>Intervention group:</b>  Mean age: 54.9-65 years  61-81.4% males</p> <p><b>Control group:</b>  Mean age: 54.6-67 years  52-82.1% males</p>	<p>Among vaccinated patients, there was a significant reduction in the risk of the following CV events:</p> <p><b>All-cause mortality:</b> RR= 0.56 (0.38-0.84), I<sup>2</sup>= 12%  <b>CV mortality:</b> RR= 0.54 (0.37-0.80), I<sup>2</sup>= 7%  <b>MACE:</b> RR= 0.66 (0.49-0.88), I<sup>2</sup>= 33%  <b>ACS:</b> RR= 0.63 (0.44-0.89), I<sup>2</sup>= 0%</p>	<p>Yes</p>
<p><b>Modin et al., 2023</b> <sup>(92)</sup></p>	<p>Until December 2022</p> <p>RCT (6)</p>	<p>To assess the effect of influenza vaccination on the incidence of CV events as efficacy outcomes in patients with high CV risk</p>	<p><b>P:</b> Patients with high CV risk (ischemic heart disease (IHD) and/or HF)  <b>I:</b> Influenza vaccination  <b>C:</b> Placebo  <b>O:</b> Primary outcomes included composite of CV death, ACS, stent thrombosis or coronary revascularization, stroke, or hospitalization for HF; Secondary outcomes included CV death and all-cause death</p>	<p>9,340 patients (4,670 vaccinated, 4,670 controls)  Mean age: 54.5-67 years  Follow-up: 9.8-36 months</p>	<p>Among vaccinated patients, there was a significant reduction in the incidence of the following CV events: <b>Primary composite endpoints:</b> HR= 0.74 (0.63–0.88), I<sup>2</sup>=52%  <b>CV death:</b> HR= 0.63 (0.42,0.95), I<sup>2</sup> =58%  <b>All-cause death:</b> HR= 0.72 (0.54–0.95), I<sup>2</sup> =52%</p>	<p>Yes</p>

<p><b>Behrouzi et al., 2022</b> (141)</p>	<p>2000-2021 RCT (6)</p>	<p>To assess whether new RCT data from the IAMI trial was consistent with previous MA findings and provided further refinement of the CV risk reduction associated with influenza vaccination</p>	<p><b>P:</b> Patients with cardiac history <b>I:</b> Influenza vaccination <b>C:</b> Placebo/no treatment <b>O:</b> Primary outcomes included composite of MACE (CV death or hospitalization for MI, unstable angina, stroke, HF, or urgent coronary revascularization) within 12 months of follow-up; Secondary outcomes included CV mortality within 12 months of follow-up</p>	<p>9,001 (4,510 vaccinated, 4,491 controls) Mean age: 65.5 years 42.5% females Cardiac history: 52.3% Mean follow-up: 9 months</p>	<p>Among vaccinated patients, there was a significant reduction in the risk of <b>MACE</b>: RR= 0.66 (0.53-0.83), I<sup>2</sup> = 19%  This association was greater among those with recent ACS (RR= 0.55 (0.41-0.75), I<sup>2</sup>=33%) compared to stable outpatients (RR, 1.00 (0.68-1.47), I<sup>2</sup>=0%)</p>	<p>Yes</p>
<p><b>Diaz-Arocutipa et al., 2022</b> (142)</p>	<p>Until September 2021 RCT (5)</p>	<p>To evaluate the effect of the influenza vaccine on cardiovascular outcomes in CAD patients</p>	<p><b>P:</b> Patients with CAD <b>I:</b> Influenza vaccination <b>C:</b> Placebo or standard care <b>O:</b> Primary outcome was MACE; Secondary outcomes included all-cause mortality, CV mortality, and MI</p>	<p>4,175 patients (2,110 vaccinated, 2,065 controls) Mean age: 54.5-67 years 75% males Follow-up: 6-12 months Comorbidities: hypertension (55%), previous myocardial infarction (23%), and diabetes (22%)</p>	<p>Among vaccinated patients, there was a significant reduction in the risk of the following CV events: <b>MACE</b>: RR= 0.63 (0.51–0.77), I<sup>2</sup>=0% <b>All-cause mortality</b>: RR= 0.58 (0.40–0.84), I<sup>2</sup>= 0% <b>CV mortality</b>: RR= 0.53 (0.38–0.74), I<sup>2</sup>= 0%</p>	<p>Yes</p>

<b>Maniar et al., 2022</b> <sup>(91)</sup>	Until May 2022 RCT (8)	To perform an updated MA of RCTs on influenza vaccination that examine CV outcomes	<b>P:</b> Patients hospitalized for acute MI or HF <b>I:</b> Influenza vaccination within a specified timeframe after hospitalization <b>C:</b> No influenza vaccination, placebo, or delayed vaccination <b>O:</b> MACE, CV mortality, all- cause mortality, MI	14,420 patients Follow-up: 6-12 months	Among vaccinated patients, there was a significant reduction in the risk of <b>MACE</b> : RR=0.75 (0.57–0.97), I <sup>2</sup> =56%	No
<b>Clar et al., 2015</b> <sup>(93)</sup>	Until February 2015 RCT (8)	To assess the potential benefits of influenza vaccination for primary and secondary prevention of CVD	<b>P:</b> Patients aged 18+ years with and without a history of CVD <b>I:</b> Influenza vaccination <b>C:</b> Control treatment <b>O:</b> Primary outcomes included MI, unstable angina, CV death; Secondary outcomes were composite clinical outcomes	12,029 patients (1,682 with known CVD and 10,347 from general population or elderly people) Follow-up: 42 days-1 year	Among vaccinated patients with CVD, there was a significant reduction in the risk of <b>CV mortality</b> : RR= 0.45 (0.26, 0.76), I <sup>2</sup> = 0%	Yes
<b>Udell et al., 2013</b> <sup>(143)</sup>	Until August 2013 RCT (6 in primary MA)	To determine if influenza vaccination is associated with prevention of CV events	<b>P:</b> Patients with high CV risk <b>I:</b> Influenza vaccination <b>C:</b> Placebo or standard care <b>O:</b> MACE, CV mortality, all- cause mortality, and non- fatal CV events (MI, stroke, HF, hospitalization for unstable angina or cardiac ischemia, urgent coronary revascularization)	6,735 patients Mean age: 67 years 51.3% females Cardiac history: 36.2% Mean follow-up: 7.9 months	Among vaccinated patients, there was a significant reduction in the risk of <b>MACE</b> : RR= 0.64 (0.48-0.86), I <sup>2</sup> = 28%  This association was greater among those with recent ACS (RR= 0.45 (0.32-0.63), I <sup>2</sup> =0%) than those without (RR, 0.94 (0.55-1.61), I <sup>2</sup> =0%)	Yes

<p><b>Liu et al., 2024</b> <sup>(144)</sup></p>	<p>Until September 2023</p> <p>RCT (6) Observational (37)</p>	<p>To evaluate the efficacy and safety of influenza vaccines compared to no vaccines or placebo for preventing all-cause/CVD mortality or all-cause/CVD hospitalization in the general population and in those with pre-existing CVD</p>	<p><b>P:</b> Adults aged 18+ years from the general population or with established CVD  <b>I:</b> Influenza vaccination  <b>C:</b> Placebo or no influenza vaccination  <b>O:</b> All-cause or CV mortality, all-cause or CVD hospitalization (CVD was defined as including any diagnoses relating to MI, HF, or stroke)</p>	<p><b>RCT:</b> 12,662 participants Mean age: 62 years  45% females  8,797 (69%) with pre-existing CVD Follow-up: 6-12 months</p> <p><b>Observational:</b> 6,311,703 participants Mean age: 49 years  50% females  1,189,955 (19%) with pre-existing CVD</p>	<p><b>RCT:</b> Among vaccinated participants, there was a significant reduction in the risk of <b>all-cause hospitalization:</b> RR= 0.86 (0.76–0.97), I<sup>2</sup> = 0%</p> <p><b>Observational:</b> There was a stronger protective association between influenza vaccination and outcomes, except for CVD hospitalization (no effect estimated provided)</p>	<p>Yes</p>
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<p><b>Zahhar et al., 2024</b> <sup>(94)</sup></p>	<p>Until December 2022</p> <p>RCT (3) Observational (23)</p>	<p>To investigate the association between influenza immunization and stroke incidence</p>	<p><b>P:</b> Patients aged 18+ years <b>I:</b> Influenza vaccination <b>C:</b> No influenza vaccination <b>O:</b> Incidence/hospitalization due to stroke (any, ischemic, hemorrhagic) and mortality</p>	<p>6,196,668 patients total 42% of studies included patients ≥ 65 years</p>	<p>Overall (all study designs): Among vaccinated patients, there was a significant reduction in the risk of the following CV events: <b>Stroke incidence/hospitalization</b> : OR= 0.81 (0.77–0.86), I<sup>2</sup> =86% <b>Mortality:</b> OR= 0.50 (0.37-0.68), I<sup>2</sup> = 86%</p> <p><b><u>Subgroup analysis by study design:</u></b> Case-control and retrospective cohort studies showed a significant reduction in stroke incidence among vaccinated patients: <b>Case-control:</b> OR= 0.82 (0.77-0.87) <b>Retrospective cohort:</b> OR=0.78 (0.71-0.86)</p> <p><b><u>Subgroup analysis by comorbidity:</u></b> Vaccination significantly reduced the risk of stroke among patients with the following: <b>Atrial fibrillation:</b> OR= 0.68 (0.57–0.81) <b>Diabetes:</b> OR= 0.76 (0.66–0.87) <b>Chronic obstructive pulmonary disease (COPD):</b> OR= 0.70 (0.61–0.81) <b>Hypertension:</b> OR= 0.76 (0.70-0.83)</p>	<p>Yes</p>
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<p><b>Liu et al., 2022</b> <sup>(145)</sup></p>	<p>Until October 2021</p> <p>RCT (1) Observational (6)</p>	<p>To clarify the relationship between the flu vaccine and cardiac arrhythmias, and further explore the associations of specific types of arrhythmias (e.g., atrial fibrillation (AF) and ventricular arrhythmia (VA)) with the flu vaccine</p>	<p><b>P:</b> Adults aged 18+ years <b>I:</b> Influenza vaccination <b>C:</b> No influenza vaccination or received vaccine beyond the period of efficacy <b>O:</b> Arrhythmia, including AF, atrial flutter, ventricular fibrillation, ventricular flutter, and cardiac arrest</p>	<p><b>RCT:</b> 2,532 patients Mean age: 59.85 years 80.51% males Mean/median follow-up: 1 year</p> <p><b>Observational:</b> 3,167,445 patients Age range: 18-73.3 years 55.9-85.29% males Mean/median follow-up: 9 months-3.7 years</p>	<p><b><u>Subgroup analysis by study design:</u></b> Among vaccinated participants, there was a significant reduction in the risk of arrhythmias in <b>observational studies</b> only: OR= 0.82 (0.70–0.97), I<sup>2</sup>= 76%</p> <p><b><u>Subgroup analysis by arrhythmia type:</u></b> Among vaccinated participants, there was a significant reduction in the risk of <b>AF</b> compared to VA: OR= 0.94 (0.90-0.98), I<sup>2</sup>= 0%</p>	<p>Yes</p>
<p><b>Zangiabadi a n et al., 2020</b> <sup>(146)</sup></p>	<p>January 2000- November 2019</p> <p>RCT (6) Observational (11)</p>	<p>To investigate the association between influenza vaccination and risk of CVD</p>	<p><b>P:</b> Patients aged 18+ years <b>I:</b> Influenza vaccination <b>C:</b> No influenza vaccination <b>O:</b> CVD events, including CVD death, non-fatal MI, non-fatal stroke, hospitalization for HF, coronary ischemic events, HF, and vascular death</p>	<p>180,043 cases and 276,898 controls total 47% of studies included patients ≥ 65 years</p> <p><b>RCT:</b> 3,677 cases, 3,681 controls Age range: 18+ years</p> <p><b>Observational:</b> 78,522 cases, 127,833 controls Age range: 31+ years</p>	<p><b><u>Subgroup analysis by study design:</u></b> Among vaccinated patients, there was a significant reduction in the risk of CVD events in RCTs and case-control studies: <b>RCT:</b> RR= 0.55 (0.41-0.73), I<sup>2</sup>= 50% <b>Case-control:</b> OR= 0.70 (0.57-0.86); I<sup>2</sup>= 98%</p>	<p>Yes</p>

<p><b>Gupta et al., 2024</b> (147)</p>	<p>N/A (study dates are from 2000-2021)</p> <p>RCT (6) Observational (9)</p>	<p>To evaluate the impact of influenza vaccination on the incidence of CV events</p>	<p><b>P:</b> Patients with and without CVD <b>I:</b> Influenza vaccination <b>C:</b> No influenza vaccination <b>O:</b> All-cause mortality, CV death, stroke, MI, hospitalization for HF</p>	<p>745,001 patients Mean age: 70.11 years (vaccinated) and 64.55 (unvaccinated) years 49.3% females (vaccinated) 40.86% females (unvaccinated) Mean follow-up: 6 months-2 years</p>	<p>Among vaccinated patients with CVD, there was a significant reduction in the risk of the following CV events: <b>All-cause mortality:</b> OR= 0.74, (0.64-0.86), I<sup>2</sup> = 95% <b>CV death:</b> OR= 0.73 (0.59-0.92), I<sup>2</sup> = 57% <b>Stroke:</b> OR= 0.71 (0.57-0.89), I<sup>2</sup> = 83%</p>	<p>No</p>
<p><b>Jaiswal et al., 2022</b> (148)</p>	<p>Until April 2022</p> <p>RCT (5) Observational (13)</p>	<p>To estimate the effect of influenza vaccination on cardiovascular and cerebrovascular outcomes among patients with established CVD</p>	<p><b>P:</b> Patients with established CVD or at high CV risk <b>I:</b> Influenza vaccination <b>C:</b> No influenza vaccination or placebo <b>O:</b> Primary outcomes included all-cause mortality and MACE; Secondary outcomes included HF, MI, CV mortality, and stroke</p>	<p>22,532,165 patients total 217,072 with high CV risk or established CVD (111,073 vaccinated, 105,999 unvaccinated) Mean age: 68 years Mean follow-up: 1.5 years</p>	<p>Among vaccinated patients with high CV risk or established CVD, there was a significant reduction in the risk of the following CV events: <b>All-cause mortality:</b> HR= 0.71 (0.63-0.80), I<sup>2</sup>= 85% <b>MACE:</b> HR= 0.83 (0.72-0.96), I<sup>2</sup>= 68% <b>CV mortality:</b> HR= [0.78 (0.68-0.90), I<sup>2</sup>= 47% <b>MI:</b> HR= 0.82 (0.74-0.92), I<sup>2</sup>=0%</p>	<p>Yes</p>
<p><b>Yedlapati et al., 2021</b> (149)</p>	<p>Until January 2020</p> <p>RCT (4) Observational (12)</p>	<p>To assess the effects of the influenza vaccine on mortality and CV outcomes in patients with CVD</p>	<p><b>P:</b> Patients with CVD (atherosclerotic CVD or HF) <b>I:</b> Influenza vaccination <b>C:</b> Placebo <b>O:</b> All-cause mortality, CV mortality, MACE, HF, and MI</p>	<p>237,058 patients total (RCT: 1,667 patients; Observational: 235,391 patients) Mean age: 69.2±7.01 years 36.6% females Median follow-up: 19.5 months</p>	<p>Among vaccinated patients with high CV risk or established CVD, there was a significant reduction in the risk of the following CV events: <b>All-cause mortality:</b> RR= 0.75 (0.60–0.93), I<sup>2</sup>= 97% <b>CV mortality:</b> RR= 0.82 (0.80-0.84), I<sup>2</sup>= 31% <b>MACE:</b> RR= 0.87 (0.80-0.94), I<sup>2</sup>= 51%</p>	<p>Yes</p>

<p><b>Cheng et al., 2020</b> (150)</p>	<p>Until November 2018</p> <p>RCT (6) Observational (69)</p>	<p>To address the breadth and validity of the reported protective effects of influenza vaccination against CV and respiratory adverse outcomes and all-cause mortality in adults</p>	<p><b>P:</b> Adults <b>I:</b> Influenza vaccination <b>C:</b> Placebo <b>O:</b> CVD (including stroke, MACE, MI, HF, IHD, TIA, ACS, cardiac arrest, CV mortality, AF) and all-cause mortality</p>	<p>4,419,747 patients total Follow-up: 4 months-9 years</p>	<p>Among vaccinated patients with high CV risk or established CVD, there was a significant reduction in the risk of the following CV events: <b>CVD overall:</b> RR= 0.74 (0.70-0.78) <b>Stroke:</b> RR= 0.80 (0.72-0.88) <b>MI:</b> RR= 0.81 (0.76-0.86) <b>ACS:</b> RR= 0.44 (0.32-0.60) <b>HF:</b> RR= 0.60 (0.44-0.83) <b>IHD:</b> RR= 0.83 (0.77-0.90) <b>MACE:</b> RR= 0.71 (0.62-0.82) <b>CV mortality:</b> RR= 0.78 (0.65-0.94) <b>All-cause mortality:</b> RR= 0.57 (0.51-0.63)</p> <p><b><u>Subgroup analysis:</u></b> Vaccinated patients with <b>pre-existing diseases</b> had a lower risk of CVD (RR= 0.62 (0.54-0.72)) compared to those without (RR= 0.83 (0.80-0.86))</p>	<p>Yes</p>
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<p><b>Tsivgoulis, 2018</b> <sup>(151)</sup></p>	<p>Until March 2017</p> <p>RCT (5) Observational (6; 4 included only influenza vaccine and 2 included influenza and pneumococcal vaccine coadministration)</p>	<p>To evaluate the association of influenza and pneumococcal vaccination with the risk of ischemic stroke and other CV outcomes</p>	<p><b>P:</b> Adult patients at risk of cerebrovascular ischemia <b>I:</b> Influenza vaccination <b>C:</b> No influenza vaccination <b>O:</b> Primary outcome was cerebrovascular ischemia (specifically acute ischemic stroke); Secondary outcomes were myocardial ischemic events and CV death</p>	<p>431,937 patients total Mean age range: 59.9 + 10.3 years and older 19.9-59.7% vaccinated 38.9-72.5% males Follow-up: 6 months-2 years</p>	<p>Among vaccinated patients, there was a significant reduction in the risk of <b>ischemic stroke</b>: RR= 0.87 (0.79–0.96), I<sup>2</sup> = 53%</p>	<p>Yes</p>
<p><b>Loomba et al., 2012</b> <sup>(152)</sup></p>	<p>N/A (study dates are from 1998-2011)</p> <p>RCT (3) Observational (2)</p>	<p>To assess the association between influenza vaccination and CV morbidity and mortality</p>	<p><b>P:</b> Patients with or at risk of CVD <b>I:</b> Influenza vaccination <b>C:</b> No influenza vaccination <b>O:</b> MI, all-cause mortality, and MACE</p>	<p>292,383 patients total (169,203 vaccinated and 123,481 unvaccinated) Mean age: 58-77 years 42.6-73.9% males</p>	<p>Among vaccinated patients, there was a significant reduction in the risk of the following outcomes: <b>MI:</b> OR= 0.73 (0.57-0.93) <b>All-cause mortality:</b> OR= 0.60 (0.57-0.64) <b>MACE:</b> OR= 0.47 (0.29-0.74)</p>	<p>Not specified, although authors state that quality assessment was performed</p>
<p><b>Tavabe et al., 2023</b> <sup>(153)</sup></p>	<p>1980-July 2021</p> <p>Observational (14)</p>	<p>To investigate the relationship between receiving the flu vaccine with stroke and its hospitalization</p>	<p><b>P:</b> Elderly people <b>I:</b> Influenza vaccination <b>C:</b> No influenza vaccination <b>O:</b> Stroke occurrence or hospitalization due to stroke</p>	<p>3,198,646 patients total Mean follow-up: 30 months 71% of studies included adults ≥ 65 years old</p>	<p>Among vaccinated patients, there was a significant reduction in the risk of the <b>occurrence and hospitalization from stroke</b>: OR= 0.84 (0.78-0.90), I<sup>2</sup>= 66%</p> <p>Elderly &lt;70 years: OR= 0.85 (0.73-0.99) Elderly ≥ 70 years: OR= 0.82 (0.75-0.89)</p>	<p>Yes</p>

<p><b>Gupta et al., 2022</b> (154)</p>	<p>Until October 2021  Observational (7)</p>	<p>To address whether vaccination against influenza reduces adverse vascular events and mortality in heart failure patients</p>	<p><b>P:</b> Adult patients with HF <b>I:</b> Influenza vaccination <b>C:</b> No influenza vaccination <b>O:</b> All-cause mortality and hospitalization, CV mortality and hospitalization, non- fatal stroke, and non-fatal MI within 12 months of receiving the influenza vaccine</p>	<p>247,842 patients total Mean age: 68-77 years</p>	<p>Among vaccinated patients, there was a significant reduction in the risk of the following outcomes: <b>All-cause mortality:</b> RR= 0.75 (0.71–0.79), I<sup>2</sup>= 72% <b>CV mortality:</b> RR= 0.77 (0.73–0.81), I<sup>2</sup>= 31%  Among vaccinated patients, there was a significantly higher risk of <b>all-cause hospitalization:</b> RR= 1.24 (1.13–1.35), I<sup>2</sup>= 90%</p>	<p>Yes</p>
<p><b>Rodrigues et al., 2020</b> (155)</p>	<p>Until December 2018  Cohort (6)</p>	<p>To evaluate the effect of influenza vaccination in the morbimortality of patients with HF</p>	<p><b>P:</b> Adults diagnosed with HF and/or a reported abnormal/reduced ejection fraction (&lt;50%) <b>I:</b> Influenza vaccination <b>C:</b> No influenza vaccination <b>O:</b> Primary outcome was all-cause mortality; Secondary outcomes included HF mortality, CV mortality, all-cause hospitalizations, CV hospitalization rates, HF-related hospitalization rates, hospitalization length, and VA</p>	<p>179,158 patients total Mean age: 62-75 years Follow-up: 3 months-8 years</p>	<p>Among vaccinated patients, there was a significant reduction in the risk of <b>all- cause mortality:</b> HR= 0.83 (0.76, 0.91), I<sup>2</sup>=75%</p>	<p>Yes</p>

<p><b>Caldeira, 2019</b> <sup>(156)</sup></p>	<p>Until September 2019</p> <p>Self-controlled case series (2)</p>	<p>To review the risk of myocardial infarction (MI) associated with Influenza infection and the safety of vaccination</p>	<p><b>P:</b> Adult (18+ years) patients with a first recorded acute MI in the study period and recorded influenza vaccination  <b>I:</b> Influenza vaccination  <b>C:</b> No influenza vaccination  <b>O:</b> Acute MI within 1 month of influenza vaccination</p>	<p>32,676 patients total  Median age: 72.3-77 years</p>	<p>Among vaccinated patients, there was a significant reduction in the risk of <b>acute MI</b>:  RR= 0.84 (0.78–0.91), I<sup>2</sup>= 0%</p>	<p>Yes</p>
<p><b>Lee et al., 2017</b> <sup>(157)</sup></p>	<p>Until November 2016</p> <p>Observational (11)</p>	<p>To investigate the protective effect of influenza vaccination against stroke</p>	<p><b>P:</b> Adults (18+ years) at risk of stroke  <b>I:</b> Influenza vaccination  <b>C:</b> No influenza vaccination  <b>O:</b> Stroke (any, first, recurrent)</p>	<p>593,513 participants total 45% of studies included participants ≥ 60 years</p>	<p>Among vaccinated patients, there was a significant reduction in the risk of <b>stroke</b>: OR= 0.82 (0.75–0.91), I<sup>2</sup>=63.5%</p>	<p>Yes</p>

<b>Barnes et al., 2015</b> <small>(158)</small>	Until June 2014 Case-control (7)	To estimate the association between influenza infection and acute MI	<b>P:</b> Adult patients with acute MI <b>I:</b> Influenza vaccination <b>C:</b> Patients without acute MI, including those who did and did not receive influenza vaccination <b>O:</b> Fatal or non-fatal acute MI, including first or subsequent episode(s); AMI was defined as a constellation of clinical features, including ischemic symptoms, biochemical and/or electrical evidence of myocardial ischemia, evidence of critical artery stenosis on coronary angiography or autopsy evidence of myocardial infarction	17,695 cases with acute MI (9,428 vaccinated) and 65,343 controls without acute MI (33,819 vaccinated) Age: ≥40 years	The odds of influenza vaccination was significantly lower in those with acute MI compared to controls: OR= 0.71 (0.56 to 0.91), I <sup>2</sup> = 63%	Yes (authors used and developed their own modified GRADE tool)
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**Abbreviations:** ACS: acute coronary syndrome; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CV: cardiovascular; CVD: cardiovascular disease; HF: heart failure; HR: hazard ratio; MACE: major adverse CV events; MI: myocardial infarction; TIA: transient ischemic attack; ACS: acute coronary syndrome; IHD: ischemic heart disease; AF: atrial fibrillation; VA: ventricular arrhythmia; N/A: not applicable; OR: odds ratio; RCT: randomized-controlled trial; RR: relative risk; SCCS: self-controlled case series; SR&MA: systematic reviews and meta-analyses.

# Appendix D: 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 <sup>(159-161)</sup>. 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 <sup>(162)</sup>.

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 <sup>(163-166)</sup>.

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 <sup>(42, 167-169)</sup>.

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

Vaccines currently authorized for use:

- Fluviral (GSK)
- Fluzone<sup>®</sup> (Sanofi)
- Influvac<sup>®</sup> (BGP Pharma ULC, operating as Mylan, doing business as (d.b.a.) Viatris Canada)

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<sup>®</sup> (Seqirus)

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. Additionally, refer to the [Supplementary guidance on influenza vaccination in adults 65 years of age and older](#) and Table 4 in the [Statement on seasonal influenza vaccine for 2024-2025](#) for more detailed information on the efficacy and effectiveness of IIV3-SD in adults 65 years of age and older.

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

Vaccines currently authorized for use:

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

## 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 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 <sup>(170)</sup>.

### 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 <sup>(171)</sup>.

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

Vaccines currently authorized for use:

- Flucelvax<sup>®</sup> (Seqirus) (IIV3-cc)
- Flucelvax<sup>®</sup> Quad (Seqirus) (IIV4-cc)

## Methods

Following the IIV4-cc vaccination recommendations published in the [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 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 than 18 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.

## Adjuvanted inactivated trivalent influenza vaccine (IIV3-Adj)

Vaccines currently authorized for use:

- Flud® (Seqirus)
- Flud Pediatric™ (Seqirus)

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

#### Efficacy and effectiveness

Available evidence shows a protective effect of IIV3-Adj compared to IIV3-SD for influenza-associated hospitalization in older adults, with pooled relative vaccine effectiveness estimates of 12% (95% CI: 3 to 20%) and 25% (95% CI: 3 to 42%) against hospitalization and vaccine efficacy estimates of 25% (95% CI: -236 to 83%) against death. Refer to the [Supplemental guidance on influenza vaccination in adults 65 years of age and older](#) and Table 4 in the [Statement on seasonal influenza vaccine for 2024–2025](#) for more detailed 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<sup>(173)</sup>. 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<sup>(174, 175)</sup>. MF59 further facilitates the internalization of antigen by these dendritic cells<sup>(173, 175)</sup>. 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<sup>(174)</sup>.

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

Evidence from RCTs shows that IIV3-Adj led to fewer solicited systemic reactions grade 3 or higher compared to IIV-SD (pooled risk ratio [RR] of 0.77, 95% CI: 0.34 to 1.76). Additionally, a meta-analysis of RCTs showed that IIV3-Adj led to more solicited injection site reactions grade 3 or higher compared to IIV-SD (pooled RR of 3.39, 95% CI: 1.32 to 8.72). However, there were no differences in SAEs between IIV3-Adj and IIV3-SD, though these estimates lacked precision (pooled RR of 1.07, 95% CI: 0.92 to 1.26). Lastly, an observational study comparing IIV3-Adj to IIV-SD found no cases of GBS among 170,988 recipients. Refer to the [Supplemental guidance on influenza vaccination in adults 65 years of age and older](#) and Table 4 in the [Statement on seasonal influenza vaccine for 2024–2025](#) for more detailed information on the safety of IIV3-Adj in adults 65 years of age and older.

## 2. Flud 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 <sup>(176)</sup>. 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 Flud 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 <sup>(176-181)</sup>. 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 <sup>(181)</sup>. 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 Flud 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 <sup>(179)</sup>.

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 <sup>(182)</sup>. 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.

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

Vaccines currently authorized for use:

- Fluzone<sup>®</sup> High-Dose (Sanofi) (IIV3-HD)
- Fluzone<sup>®</sup> High-Dose Quadrivalent (Sanofi) (IIV4-HD)

Refer to the [Supplemental guidance on influenza vaccination in adults 65 years of age and older](#) and Table 4 in the [Statement on seasonal influenza vaccine for 2024–2025](#) for more detailed information on the efficacy/effectiveness and safety of IIV3-HD in adults 65 years of age and older.

## Methods

Fluzone<sup>®</sup> High-Dose Quadrivalent (IIV4-HD) builds on the clinical development of its trivalent predecessor Fluzone<sup>®</sup> 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<sup>®</sup> High-Dose (IIV3-HD) provides better protection compared with IIV3-SD in adults 65 years of age and older. Two 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 <sup>(183, 184)</sup>. 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 <sup>(185-192)</sup>. 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<sup>®</sup> High Dose Quadrivalent (IIV4-HD) is non-inferior to IIV3-HD <sup>193, 194</sup>. 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 <sup>(194)</sup>. Immunogenicity for IIV4-HD was superior for the influenza B strain not contained within the trivalent high dose vaccine <sup>(194)</sup>.

## 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 <sup>(194)</sup>.

## Recombinant quadrivalent influenza vaccine (RIV4)

Vaccines currently authorized for use:

- Supemtek<sup>®</sup> (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 RCT that evaluated the efficacy of RIV4 demonstrated that Supemtek<sup>®</sup> was statistically significantly more efficacious than egg-based IIV4-SD in preventing laboratory confirmed influenza illness in adults 50 years of age and older <sup>(195)</sup>. Non-inferiority assessments suggested that RIV4 may be more effective than IIV4-SD influenza vaccines against laboratory-confirmed influenza (LCI) A virus infection, but not LCI 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 RCTs assessed the immunogenicity of RIV4. The immunogenicity outcomes reported included seroconversion rates, seroprotection rates, and GMTR<sup>(195-203)</sup>. Across the 8 studies, Supemtek<sup>®</sup> 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, seroprotection, and GMTR<sup>(195, 198, 204)</sup>.

Pooled seroconversion data from 3 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<sup>(195, 197, 200)</sup>.

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 studies 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)<sup>(195, 197, 198, 200, 205, 206)</sup>. 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 AEs reported to VAERS following RIV4 administration were non-serious. When data from 2 RCTs 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<sup>(195, 197)</sup>. 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<sup>®</sup> (AstraZeneca) (LAIV-3)
- FluMist<sup>®</sup> Quadrivalent (AstraZeneca) (LAIV-4)

## 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)<sup>(84)</sup>. 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 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<sup>(207)</sup>.

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<sup>(208)</sup>. 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<sup>(209-211)</sup>.

## 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<sup>(207)</sup>. 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 ART and with adequate immune function. In addition, NACI concluded that LAIV appears to have a similar safety profile as IIV in children on ART and with stable HIV infection with regard to frequency and severity of AEs <sup>(212)</sup>. 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 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 ART and with adequate immune function.

LAIV should be considered only in children with HIV who meet all of the following criteria:

- Receiving ART for 4 months or longer
- CD4 count equal to or greater than 500/ $\mu$ L if 2 to 5 years of age, or  $\geq$ 200/ $\mu$ L 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.