

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

Statement on Seasonal Influenza Vaccine for
2023–2024

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH



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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. Please refer to the remainder of the statement for details.

What

- Influenza in humans is a respiratory infection caused primarily by influenza A and B viruses. Seasonal influenza epidemics occur annually in Canada, generally in the late fall and winter months. Prior to the COVID-19 pandemic, influenza had an annual attack rate estimated at 5 to 10% in adults and 20 to 30% in children worldwide¹.
- Symptoms of influenza can range from mild to severe, and typically come on suddenly. They can include 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. Most people will recover within a week 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 heart disease².
- Live attenuated influenza vaccine (LAIV), recombinant influenza vaccine (RIV) and inactivated influenza vaccines (IIV) (which include standard dose [SD], high dose [HD], cell culture-based [cc] or adjuvanted vaccines [Adj]) are all authorized for use in Canada; some protect against 3 strains of influenza virus (i.e., trivalent formulations: IIV3) and some protect against 4 strains of influenza virus (i.e., quadrivalent formulations: IIV4, RIV4, or LAIV4). See [Appendix A](#) for a list of abbreviations used in this document for the different influenza vaccines.
- The influenza vaccines are safe and well-tolerated. The IIVs and RIV cannot cause influenza illness because they do not contain live virus. The live attenuated influenza vaccines contain weakened viruses.

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, [with focus on the groups for whom influenza vaccination is particularly recommended. These groups include:](#)

- 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; and
- People in direct contact with poultry infected with avian influenza during culling operations.

In infants less than 6 months of age, evidence is lacking to demonstrate that influenza vaccine would be effective³. Currently, authorized influenza vaccines are not indicated for use in infants less than 6 months of age. For these reasons, NACI recommends that influenza vaccine should not be offered to infants less than 6 months of age. Since infants less than 6 months of age are at high risk of influenza-related illness, the influenza vaccine should be offered to individuals who are pregnant, breastfeeding, and any household contacts and care providers of young infants.

Recommendation for public health program-level decision-making

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

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

How

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

Choice of influenza vaccine

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

Dose and route of administration

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

- Most IIVs are administered as a 0.5 mL intramuscular (IM) injection
- IIV4-HD (Fluzone[®] High-Dose Quadrivalent) is administered as a 0.7 mL IM injection and authorized for adults 65 years of age and older.
- MF59-adjuvanted IIV3-Adj (Fluad[®]) is administered as a 0.5 mL IM injection and authorized for adults 65 years of age and older. A pediatric formulation is also available

(Fluad Pediatric®), and is administered as a 0.25 mL IM injection for children 6 to 23 months of age.

- RIV4 (Supemtek™) is administered as a 0.5 mL IM injection and authorized for adults 18 years of age and older.
- LAIV (FluMist® Quadrivalent) is administered as 0.2 mL given intranasally (0.1 mL in each nostril) and authorized for individuals 2 to 59 years of age.

See [Appendix B](#) for information on characteristics of all influenza vaccines expected to be available for use in Canada for the 2023–2024 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 one 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.
 - Egg allergy is not a contraindication for influenza vaccination, as there is a low risk of adverse events (AEs) associated with the trace amounts of ovalbumin allowed in some influenza vaccines manufactured using eggs. Egg-allergic individuals may be vaccinated against influenza using any age-appropriate product, including LAIV, without prior influenza vaccine skin test and with the full dose, irrespective of a past severe reaction to egg, and in any setting where vaccines are routinely administered. Cell culture-based (IIV4-cc) and recombinant (RIV4) vaccines are egg-free (ovalbumin-free).
 - As with any vaccine product, all vaccine providers should be prepared to manage possible allergic reactions, including anaphylaxis, and have the necessary equipment to respond to a serious adverse event at all times.
 - 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. Individuals who have an allergy to substances that are not components of the influenza vaccine are not at increased risk of allergy to influenza vaccine.

- People who have developed Guillain-Barré Syndrome (GBS) within 6 weeks of a previous influenza vaccination, unless another cause was found for the GBS
 - For these people, 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, in addition to the above-mentioned contraindications, NACI also recommends that LAIV should not be given to:

- People with severe asthma (defined as currently on oral or high-dose inhaled glucocorticosteroids or active wheezing) or medically attended wheezing in the 7 days prior to the proposed date of vaccination, due to increased risk of wheezing following administration of LAIV
 - LAIV is not contraindicated for people with a history of stable asthma or recurrent wheeze which is not active.
- Children less than 24 months of age, due to increased risk of wheezing following administration of LAIV
- Children 2 to 17 years of age currently receiving aspirin or aspirin-containing therapy, because of the association of Reye’s syndrome with aspirin and wild-type influenza infection
- Pregnant individuals, because it is a live attenuated vaccine and there is a lack of safety data at this time
 - LAIV is not contraindicated in breastfeeding (lactating) individuals; however, there are limited data for the use of LAIV in this population.
- People who are immunocompromised due to underlying disease and/or therapy
 - LAIV is not considered to be contraindicated for children living with stable HIV infection on anti-retroviral therapy (ART; also sometimes referred to as highly active anti-retroviral therapy [HAART]) and with adequate immune function.
 - NACI previously concluded that the quantity of evidence available on the immunogenicity and safety of LAIV in adults with HIV is insufficient to justify a recommendation for the use of LAIV in this group. In addition, NACI considered that most studies found LAIV to have similar or slightly lower efficacy than IIV in adults and consequently recommends IIV for adults with chronic conditions.
 - Refer to the [Recommendation on the Use of Live Attenuated Influenza Vaccine \(LAIV\) in HIV-Infected Individuals](#) for additional information.

LAIV should not be administered until 48 hours after the last dose of an antiviral agent active against influenza (e.g., oseltamivir, zanamivir), and such antiviral agents, unless medically indicated, should not be administered until 2 weeks after receipt of LAIV so that the antiviral agents do not inactivate the replicating vaccine virus.

- If these antiviral agents are administered within this time frame (i.e., from 48 hours pre-vaccination with LAIV to 2 weeks post-vaccination), re-vaccination should take place at least 48 hours after the antivirals are stopped, or a parenteral inactivated or recombinant influenza vaccine could be given at any time.

Precautions

NACI recommends that:

- Influenza vaccination should usually be postponed in people with serious acute illnesses until their symptoms have abated;
 - Influenza vaccination should not be delayed because of minor or moderate acute illness, with or without fever. Immunizers should refer to [Guidance on the use of influenza vaccine in the presence of COVID-19](#) for additional advice on this issue from PHAC.
 - 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](#).
- If significant nasal congestion is present that might impede delivery of LAIV to the nasopharyngeal mucosa, parenteral inactivated or recombinant influenza vaccine can be administered or LAIV can be deferred until resolution of the congestion;
- LAIV recipients should avoid close contact with people with severe immune compromising conditions (e.g., bone marrow transplant recipients requiring isolation) for at least 2 weeks following vaccination, because of the theoretical risk for transmitting a vaccine virus and causing infection; and
- LAIV recipients who are less than 18 years of age should avoid the use of aspirin-containing products for at least 4 weeks after receipt of LAIV because of the association of Reye's syndrome with aspirin-containing products and wild-type influenza infection.

Concurrent administration with other vaccines

NACI recommends that:

- Administration of COVID-19 vaccines may occur concurrently with (i.e., same day), or at any time before or after seasonal influenza immunization for those aged 6 months and older. Readers should consult the [Canadian Immunization Guide COVID-19 chapter](#) for updated NACI guidance on the concurrent administration of influenza and COVID-19 vaccines as the number of authorized COVID-19 vaccines and the age groups eligible to receive them expand.
 - It should be noted that no studies have been conducted on the co-administration of recombinant zoster vaccine (RZV) with adjuvanted or high-dose influenza vaccine. No immune response interference or safety concerns have been demonstrated when RZV is administered concurrently with standard, un-adjuvanted vaccine⁴.

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

Why

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

I. Introduction

The National Advisory Committee on Immunization (NACI) provides PHAC with annual recommendations regarding the use of seasonal influenza vaccines, which reflect identified changes in influenza epidemiology, immunization practices and influenza vaccine products authorized and available for use in Canada. This document, the “National Advisory Committee on Immunization (NACI) Statement on Seasonal Influenza Vaccine for 2023–2024”, updates NACI’s recommendations regarding the use of seasonal influenza vaccines.

I.1 New or Updated Information for 2023–2024

Use of seasonal influenza vaccine in the context of coronavirus disease 2019 (COVID-19)

Guidance on the use of seasonal influenza vaccine in the presence of COVID-19

Seasonal influenza presents an ongoing disease burden in Canada during the fall and winter months. Influenza vaccine is the most effective way to prevent influenza illness and influenza-related complications, and is an important component of managing health care system capacity during the influenza season, particularly in the context of ongoing COVID-19 activity.

PHAC, in consultation with NACI and the Canadian Immunization Committee, has developed guidance on the administration of seasonal influenza vaccine to support provincial and territorial vaccine programs and primary care providers during the COVID-19 pandemic:

- [Guidance on the use of seasonal influenza vaccine in the presence of COVID-19](#)

The guidance on this page is based on currently available scientific evidence and expert opinion and will be updated as necessary throughout the influenza season. This web page should be considered in concert with recommendations regarding the use of seasonal influenza vaccines provided in this NACI Statement.

Guidance on concurrent administration of influenza and COVID-19 vaccines

NACI guidance outlines that administration of COVID-19 vaccines may occur at the same time as, or at any time before or after influenza immunization (including all parenteral or intranasal seasonal influenza vaccines) for those aged 6 months of age and older.

Readers should consult the [COVID-19 vaccine: Canadian Immunization Guide chapter](#) for updated NACI guidance and further information on concurrent administration of COVID-19 vaccines with influenza vaccines and across all eligible age groups.

Updated recommendations on the use of mammalian cell culture-based quadrivalent influenza vaccine (IIV4-cc)

Flucelvax[®] Quad (IIV4-cc) is a standard dose mammalian cell culture-based quadrivalent inactivated seasonal influenza vaccine that was first authorized for use in Canada in adults and children 9 years of age and older on November 22, 2019 with authorization extended to children 2 years of age and older on March 8, 2021. Recommendations and supporting evidence on the use of Flucelvax Quad in adults and children 9 years of age and older can be found in the [NACI Supplemental Statement – Mammalian Cell Culture-Based Influenza Vaccines](#) and were also

incorporated into the Statement on Seasonal Influenza Vaccine for 2021–2022. Recommendations and supporting evidence on the use of Flucelvax Quad in adults and children 2 years of age and older were incorporated into the Statement on Seasonal Influenza Vaccine for 2022–2023.

On March 8, 2022, Health Canada approved an expanded age indication for the use of Flucelvax Quad in children down to 6 months of age and older. Based on a review of Health Canada assessments of clinical trial evidence submitted by the manufacturer in support of the age indication extension, NACI has concluded that Flucelvax Quad is safe and has non-inferior immunogenicity compared to standard quadrivalent inactivated influenza vaccines. Therefore,

NACI recommends that Flucelvax Quad may be considered among the quadrivalent influenza vaccines offered to adults and children 6 months of age and older. (Discretionary NACI recommendation).

Updated recommendations on the use of egg-based quadrivalent influenza vaccine (IIV4-SD)

Influvac® Tetra (IIV4-SD) is a split virus standard quadrivalent inactivated influenza vaccine that was first authorized for use in Canada in adults on March 1, 2019 and subsequently in children 3 years of age and older on February 20, 2020. Recommendations and supporting evidence on the use of Influvac Tetra in adults and children 3 years of age and older were incorporated into the Statement on Seasonal Influenza Vaccine for 2021–2022.

On November 30, 2021, Health Canada approved an expanded age indication for the use of Influvac Tetra in children 6 months of age and older. Based on a review of Health Canada assessments of clinical trial evidence submitted by the manufacturer in support of the age indication extension, NACI has concluded that Influvac Tetra appears to be safe and well-tolerated (relative to the control non-influenza vaccines) based on direct evidence in children 6 to 35 months of age. However, there is currently insufficient evidence that Influvac Tetra is effective and elicits a protective immune response against seasonal influenza in children 6 to 35 months of age. Therefore:

NACI recommends that Influvac Tetra may be considered among the standard dose inactivated quadrivalent influenza vaccines offered to individuals three years of age and older. (Discretionary NACI recommendation)

At this time, **NACI concludes that there is insufficient evidence for recommending vaccination with Influvac Tetra in children younger than 3 years of age. (Discretionary NACI recommendation).**

NACI will continue to monitor the evidence as it emerges, and update recommendations as needed.

Standard-dose trivalent inactivated influenza vaccine (IIV3-SD) authorization and availability

All standard dose, egg-based inactivated influenza vaccines authorized and available in Canada for the 2023–24 season are expected to be quadrivalent. There are no trivalent formulations

(IIV3-SD) authorized (discontinued post-market) or available, but data that involve these vaccines continue to be included for reference.

Updated presentation of the statement

The presentation of this document has been updated from previous seasons' statements to improve readability and access to information. The content in some sections has been reduced in length, while maintaining a focus on key information required for decision making. Links to other published NACI documents containing the more detailed content removed from the current statement have been integrated.

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

I.2 Background

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

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

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

Every year, individuals with influenza and influenza-related complications increase the pressures on the healthcare system in the fall and winter months. Particularly given the added burden on the healthcare system during the COVID-19 pandemic, effective prevention of influenza by vaccination is a critical tool to mitigate on-going health system stress.

II. Methods

Details regarding NACI's evidence-based process for developing a statement are outlined in [Evidence-based Recommendations for Immunization – Methods of the National Advisory Committee on Immunization](#).

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

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

Annual influenza vaccine recommendations are developed by the Influenza Working Group (IWG) for consideration by NACI. Recommendation development includes review of a variety of issues including the burden of influenza illness and the target populations for vaccination; safety, immunogenicity, efficacy, and effectiveness of influenza vaccines; 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 cost-effectiveness, as well as ethics, equity, feasibility, and acceptability (EEFA). NACI uses a published, peer-reviewed framework and evidence-informed tools to ensure that issues related to EEFA are systematically assessed and integrated into its guidance. The NACI Secretariat applied this framework with accompanying evidence-informed tools (Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, Acceptability Matrix) to systematically consider these programmatic factors for the development of clear, comprehensive, appropriate recommendations for timely, transparent decision-making. For details on the development and application of NACI's EEFA Framework and evidence-informed tools, please see [A framework for the systematic consideration of ethics, equity, feasibility, and acceptability in vaccine program recommendations](#).

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 and debate at the scientific and clinical practice levels. In the preparation of the 2023–2024 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. For the 2023–2024 influenza season, the NACI IWG reviewed evidence and developed new recommendations regarding the use of two vaccines with changes in authorization (expanded use in individuals six months of age and older): 1) Influvac Tetra, an egg-based, quadrivalent inactivated influenza vaccine (IIV4-SD) and 2) Flucelvax Quad, a mammalian cell culture-based, inactivated seasonal influenza vaccine (IIV4-cc). The NACI IWG reviewed and analyzed the available pre-licensure clinical trial data and Health Canada's Clinical Review Reports for these two vaccines. On October 3rd, 2022, the available evidence and the new recommendations proposed by the IWG were presented for consideration and approval by NACI. Following a thorough review of the evidence, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and identified knowledge gaps are described in this statement.

III. Epidemiology

Disease description

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

Infectious agent

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

Influenza B viruses have evolved into two antigenically distinct lineages since the mid-1980s, represented by B/Yamagata/16/88-like and B/Victoria/2/87-like viruses. Viruses from both the B/Yamagata and B/Victoria lineages have contributed variably to influenza illness each year. Since the onset of the COVID-19 pandemic, a reduction in seasonal influenza virus diversity has been observed globally^{5,6}. In particular, an absence of B/Yamagata detections has been noted⁵.

Over time, antigenic variation (antigenic drift) of strains occurs within an influenza A subtype or a B lineage. The possibility of antigenic drift, which may occur in one or more influenza virus strains, requires the formulation of seasonal influenza vaccines be re-evaluated annually, with one or more vaccine strains changing in most seasons.

Transmission

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

The incubation period of seasonal influenza is usually about 2 days but can range from 1 to 4 days⁷. Adults may be able to spread influenza to others from 1 day before symptom onset to approximately 5 days after symptoms start. Children and people with weakened immune systems may be infectious longer.

Risk factors

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

Seasonal and temporal patterns

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

Spectrum of clinical illness

Classically, symptoms of influenza include the sudden onset of fever, cough, and muscle aches. Other common symptoms include headache, chills, loss of appetite, fatigue, and sore throat. Nausea, vomiting, and diarrhea may also occur, especially in children. However, influenza can cause a range of symptoms, from asymptomatic infection through mild acute respiratory illness (a “cold”) to severe influenza pneumonia. Most people will recover within a week or 10 days. More rarely, central nervous system manifestations, acute myositis, myocarditis, or pericarditis have been described. In addition, complications including pneumonia, respiratory failure, cardiovascular complications, or worsening of underlying chronic medical conditions may occur. Influenza is also associated with a significantly increased risk of myocardial infarction and stroke in the 7 to 14 days after infection, and with Guillain-Barre syndrome with onset 1 to 6 weeks after infection⁸.

Disease incidence

Global

Before the COVID-19 pandemic, worldwide annual epidemics resulted in approximately one billion cases of influenza, three to five million cases of severe illness, and 290,000 to 650,000 deaths. The global annual attack rate is estimated to be 5 to 10% in adults and 20 to 30% in children¹. Global influenza circulation was at a historical low during the 2020-2021 influenza season, when public health measures (e.g., masking, social distancing) effectively suppressed seasonal influenza activity. During the 2021-2022 Northern Hemisphere season, influenza activity returned to varying degrees in different jurisdictions. During the 2022 Southern Hemisphere season, activity appeared to return to a pre-pandemic level, although incomplete data for the season, changes in testing associated with the pandemic, and the substantial inter-season variability of influenza activity make it difficult to make definitive conclusions.

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 Canada⁹. Nationally, influenza has been estimated to cause approximately 12,200 hospitalizations and approximately 3,500 deaths annually^{10,11}. 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 five seasons prior to the COVID-19 pandemic (2014–2015 to 2018-2019 season), an average of 40,000 laboratory-confirmed cases of influenza were reported to FluWatch each year. However, most influenza infections are not laboratory-confirmed,

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

The burden of influenza-associated illness and death varies every year, depending on various factors such as the type of circulating viruses in the season and the populations affected¹². Notably, Canada's 2020-2021 seasonal influenza activity did not reach seasonal threshold and was at a historical low in the context of the public health measures that were implemented to reduce COVID-19 transmission^{13–15}. Only 69 confirmed cases of influenza were identified during the 2020-2021 season¹³, whereas over 50,000 laboratory confirmed cases are reported on average in a typical influenza season¹³. During the 2021-2022 season, influenza circulation in Canada reached the national seasonal threshold that signals the start of seasonal influenza activity for the first time since the spring of 2020. The 2021-2022 influenza epidemic onset was in April 2022, which is an unusually late start to the influenza season. Although the potential impact of upcoming influenza seasons in the context of COVID-19 is unknown, future influenza outbreaks may be characterized by higher infection rates and severity^{14,15}. Influenza infection susceptibility may increase due to low immunity in the population given the extended periods of decreased influenza exposure and infection caused by the implementation of COVID-19-related public health measures^{13,16–18}. Moreover, disease severity may be exacerbated due to the co-circulation and simultaneous infection of COVID-19 and influenza viruses. Additionally, the resurgence of seasonal influenza may not follow usual seasonal patterns^{19,20}. Information about current influenza activity can be found on the [FluWatch website](#). It should be noted that the incidence of influenza is often underreported since the illness may be confused with other viral illnesses and many people with ILI do not seek medical care or have viral diagnostic testing done.

IV. Seasonal Influenza Vaccines

IV.1 Vaccine Products Authorized for Use in Canada

The following sections describe the influenza vaccine products that are authorized for use in Canada for the 2023–2024 season. All influenza vaccines available in Canada have been authorized by Health Canada. However, not all products authorized for use are available in the marketplace. The vaccine manufacturers determine whether they will make any or all of their products available in each market. Provincial and territorial health authorities then determine which of the products available for purchase will be used in their respective publicly funded influenza immunization programs and for which population groups. Not all products will be made available in all jurisdictions and availability of some products may be limited. Officials in individual provinces and territories should be consulted regarding the products available in individual jurisdictions.

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

There are three categories of influenza vaccine authorized for use in Canada: IIV, RIV, and LAIV. Trivalent (3-strain) vaccines contain one A(H1N1) strain, one A(H3N2) strain, and one influenza B strain from one of the two 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 two exceptions. The influenza viruses used to produce Flucelvax Quad are propagated in a mammalian cell line (Madin-Darby Canine Kidney [MDCK] cells), while the Supemtek vaccine technology uses recombinant HA produced in a proprietary insect cell line using a baculovirus vector for protein expression.

A summary of the characteristics of influenza vaccines available in Canada during the 2023–2024 influenza season can be found in Appendix B. For complete prescribing information, readers should consult the product monographs available through Health Canada's [Drug Product Database](#).

Should additional vaccine preparations become available for use in Canada after the release of this statement and prior to the 2023-24 influenza vaccine season, NACI will communicate relevant information regarding the new vaccine preparations if required.

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

Inactivated influenza vaccine (IIV)

IIVs contain standardized amounts of the HA protein from representative seed strains of the two human influenza A subtypes (H3N2 and H1N1) and either one (for trivalent vaccines) or both (for quadrivalent vaccines) of the two influenza B lineages (Yamagata and Victoria). 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 one 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 two B lineages^{21–26}.

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

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

Standard-dose IIVs are available in Canada as quadrivalent formulations (IIV4-SD: Afluria® Tetra, Flulaval® Tetra, Fluzone Quadrivalent, and Influvac Tetra; IIV4-cc: Flucelvax Quad). These vaccines are un-adjuvanted, contain a standard dose of antigen (15 µg HA per strain), and are administered as a 0.5 mL dose by IM injection. Influvac Tetra may be administered by IM or deep subcutaneous injection. Trivalent formulations of standard dose unadjuvanted IIVs are no longer authorized or available for use in Canada.

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

There is one high-dose IIV (IIV-HD) currently authorized for use in Canada; a quadrivalent unadjuvanted, split virus IIV that contains 60 µg HA per strain and is administered as a 0.7 mL dose by IM injection (Fluzone High-Dose Quadrivalent).

Recombinant influenza vaccine (RIV)

There is currently only one RIV authorized for use in Canada: Supemtek (RIV4), a quadrivalent unadjuvanted, baculovirus-expressed seasonal influenza vaccine that contains 45 µg HA per strain and is administered as a 0.5 mL dose by IM injection for adults 18 years of age and older. RIV contains recombinant HAs produced in an insect cell line using genetic sequences from cell-

derived influenza viruses. The production of RIV does not depend on egg supply as it does not require egg-grown candidate vaccine viruses.

Live attenuated influenza vaccine (LAIV)

LAIV contains standardized quantities of fluorescent focus units (FFU) of live attenuated influenza virus reassortants. 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. As a live replicating whole virus formulation administered intranasally by spray, it elicits mucosal immunity, which may more closely mimic natural infection.

A quadrivalent product (LAIV4; FluMist Quadrivalent) is authorized for use in Canada for children 2 to 17 years of age and adults 18 to 59 years of age and is given as a 0.2 mL dose (0.1 mL in each nostril). The trivalent formulation (LAIV3) is no longer available in Canada.

IV.2 Efficacy, Effectiveness, and Immunogenicity

Efficacy and effectiveness

Influenza vaccine has been shown in randomized controlled clinical trials to be efficacious in providing protection against influenza infection and illness. However, the effectiveness of the vaccine—that is, how it performs in settings that are more reflective of usual health care practice—can vary from season to season and by influenza vaccine strain type and subtype. Influenza vaccine effectiveness (VE) depends on how well the vaccine strains match with circulating influenza viruses, the type and subtype of the circulating virus, as well as the health and age of the individual receiving the vaccine. Even when there is a less-than-ideal match or lower VE against one 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.

Immunogenicity

Antibody response after vaccination depends on several factors, including the age of the recipient, prior and subsequent exposure to antigens, and the presence of immune compromising conditions. Protective levels of humoral antibodies, which correlate with protection against influenza infection, are generally achieved by 2 weeks after vaccination; however, there may be some protection afforded before that time.

Additional information

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

Because of potential changes in the circulating influenza virus from year to year and waning immunity in vaccine recipients, annual influenza vaccination is recommended. Although some studies suggest vaccine induced protection may be greater in individuals who have no recent vaccine history, overall, the evidence shows no difference in the effectiveness 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^{27,28}. Additional information regarding the effects of repeated influenza vaccination on vaccine effectiveness, efficacy, and immunogenicity can be found in the NACI Recommendation on Repeated Seasonal Influenza Vaccination. NACI will continue to monitor this issue.

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

IV.3 Vaccine Administration

Dose, route of administration, and schedule

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

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

The first time that children 6 months to less than 9 years of age receive seasonal influenza vaccination, a two-dose schedule is required to achieve protection^{29–31}. Several studies have looked at whether these two initial doses need to be given in the same season^{23,24,32}. Englund et al. reported similar immunogenicity in children 6 to 23 months of age whether 2 doses were given in the same or separate seasons when there was no change, or only minor vaccine strain change, in vaccine formulation between seasons^{23,24}. However, seroprotection rates to the B component were considerably reduced in the group that received only one 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^{22,24}. Issues related to effective prime-boost when there is a major change in influenza B lineage across sequential seasons require further evaluation³³. 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 two-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 2023-2024 influenza season

Age group	Influenza vaccine type (route of administration)						Number of doses required
	IIV4-SD ^a (IM)	IIV4-cc ^b (IM)	IIV3-Adj ^c (IM)	IIV4-HD ^d (IM)	RIV4 ^e (IM)	LAIV4 ^f (intranasal)	
6 to 23 months	0.5 mL ^g	0.5 mL	0.25 mL	-	-	-	1 or 2 ^h
2 to 8 years	0.5 mL	0.5 mL	-	-	-	0.2 mL (0.1 mL per nostril)	1 or 2 ^h
9 to 17 years	0.5 mL	0.5 mL	-	-	-	0.2 mL (0.1 mL per nostril)	1
18 to 59 years	0.5 mL	0.5 mL	-	-	0.5 mL	0.2 mL (0.1 mL per nostril)	1
60 to 64 years	0.5 mL	0.5 mL	-	-	0.5 mL	-	1
65 years and older	0.5 mL	0.5 mL	0.5 mL	0.7 mL	0.5 mL	-	1

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

^a Afluria[®] Tetra (5 years and older), Flulaval[®] Tetra (6 months and older), Fluzone[®] Quadrivalent (6 months and older), Influvac[®] Tetra (3 years and older).

^b Flucelvax[®] Quad (6 months and older)

^c Fluad Pediatric[®] (6 to 23 months) or Fluad[®] (65 years and older)

^d Fluzone[®] High-Dose Quadrivalent (65 years and older)

^e Supemtek[™] (18 years and older)

^f FluMist[®] Quadrivalent (2 to 59 years)

^g Evidence suggests moderate improvement in antibody response in infants, without an increase in reactogenicity, with the use of full vaccine doses (0.5 mL) for unadjuvanted inactivated influenza vaccines^(10, 11). This moderate improvement in antibody response without an increase in reactogenicity is the basis for the full dose recommendation for unadjuvanted inactivated vaccine for all ages. For more information, refer to *Statement on Seasonal Influenza Vaccine for 2011–2012*.

^h Children 6 months to less than 9 years of age receiving seasonal influenza vaccine for the first time in their life should be given 2 doses of influenza vaccine, with a minimum interval of 4 weeks between doses. Children 6 months to less than 9 years of age who have been properly vaccinated with one 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 one dose of influenza vaccine per season is recommended for everyone else. Two doses of seasonal

influenza vaccine in older adults do not appear to improve the immune response to the vaccine compared to one dose³⁴.

Serological testing

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

IV.4 Storage requirements

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

IV.5 Concurrent administration with other vaccines

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

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

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

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

Studies on concurrent administration of LAIV3 with measles, mumps, rubella (MMR); measles, mumps, rubella, varicella (MMRV); or live oral polio vaccines did not find evidence of clinically significant immune interference^{35–37}. One study reported a statistically significant but not clinically meaningful decrease in seroresponse rates to rubella antigen when administered concomitantly with LAIV.

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

Given the lack of data for immune interference, and based on expert opinion, NACI recommends that LAIV can be given together with or at any time before or after the administration of any other live attenuated or inactivated vaccine. However, some vaccine providers may continue to choose

to give LAIV and other live vaccines separated by at least 4 weeks, based on the theoretical possibility of immune interference, although 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 two parenteral live vaccines (e.g., MMR and varicella vaccines) still apply. For more information regarding vaccination administration timing rules, please refer to [Timing of Vaccine Administration](#) in Part 1 of the CIG.

The target groups for influenza and pneumococcal polysaccharide vaccines overlap considerably. A recent study showed that compared to administration alone, concurrent administration of IIV4 with PCV15 in adults demonstrated non-inferiority of pneumococcal- and influenza-specific antibody responses³⁸. 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.

When more than one 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 one limb should be separated by a distance of at least 2.5 cm (1 inch). A separate needle and syringe should always be used for each injection.

Concurrent administration with other adjuvanted vaccines

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

RZV is an example of a recombinant adjuvanted subunit herpes zoster vaccine (Shingrix[®], GlaxoSmithKline) that is authorized for use in Canada in adults 50 years of age and older, and adults 18 years of age or older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy; therefore, the target age group for herpes zoster vaccine and influenza vaccine overlap. RZV has been shown to be safe and effective when given concurrently with unadjuvanted, standard dose influenza vaccines⁴. However, no studies have been conducted that have assessed the concurrent administration of RZV with adjuvanted or high dose influenza vaccine³⁹. It should be noted that RZV and IIV-adj currently authorized for use in Canada contain the adjuvants AS01_B and MF59 respectively. How these adjuvants may interact when RZV and IIV-adj are administered concurrently is not known.

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

IV.6 Vaccine Safety and Adverse Events

Post-marketing surveillance of influenza vaccines in Canada has shown that seasonal influenza vaccines have a safe and stable profile. In addition to routine surveillance, every year during the seasonal influenza vaccination campaigns, PHAC and the Federal/Provincial/Territorial Vaccine Vigilance Working Group (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 [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^{40,41} to keep the product sterile. Large cohort studies of administrative health databases have found no association between childhood vaccination with thimerosal-containing vaccines and neurodevelopmental outcomes, including autistic-spectrum disorders⁴². 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. IIV3-Adj tends to produce more extensive injection site reactions than un-unadjuvanted IIV3, 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 AEs experienced by recipients of LAIV are nasal congestion and runny nose.

Less common and serious or severe adverse events

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

Other reported adverse events and conditions

Egg-allergic individuals

After careful review of clinical and post-licensure safety data, NACI has concluded that egg-allergic individuals may be vaccinated against influenza using any influenza vaccine, including egg-based vaccines and LAIV, without prior influenza vaccine skin test and with the full dose, irrespective of a past severe reaction to egg and without any particular consideration, including vaccination setting. The amount of trace ovalbumin allowed in influenza vaccines that are authorized for use in Canada is associated with a low risk of AE, and in addition, two of the authorized products do not contain any ovalbumin. 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.

Refer to the [Statement on Seasonal Influenza Vaccine for 2018–2019](#) for safety data supporting this recommendation for IIV and LAIV.

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 vaccination⁴³. The attributable risk of GBS in the period following seasonal and monovalent 2009 pandemic influenza vaccination is about one excess case per million vaccinations^{44,45}. 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 encounters⁴⁵.

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

Although the evidence considering influenza vaccination and GBS is inadequate to accept or reject a causal relation between GBS in adults and seasonal influenza vaccination, avoiding subsequent influenza vaccination of individuals known to have had GBS without other known etiology within 6 weeks of a previous influenza vaccination appears prudent at this time. However, the potential risk of GBS recurrence associated with influenza vaccination must be balanced against the risk of GBS associated with influenza infection itself and the benefits of influenza vaccination^{46–49}.

Oculorespiratory syndrome

Oculorespiratory syndrome (ORS), the presence of bilateral red eyes and one or more associated respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness, or sore throat) that starts within 24 hours of vaccination, with or without facial oedema, was identified during the 2000–2001 influenza season⁵⁰. Since then, there have been far fewer cases per year reported to CAEFISS⁵¹. 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 one vaccine product over another when revaccinating those who have previously experienced ORS.

Allergic reactions to previous vaccine doses

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

health that can be found in various health settings, including the [Special Immunization Clinic \(SIC\) network](#).

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

Drug interactions

Although influenza vaccine can inhibit the clearance of warfarin and theophylline, clinical studies have not shown any adverse effects attributable to these drugs in people receiving influenza vaccine. Statins have effects on the immune system in addition to their therapeutic cholesterol-lowering actions. Two published studies have found that adults who are regular statin users (at least 65 years of age⁵² in one study and 45 years and older in the other⁵³) had a decreased response to influenza vaccination as measured by reduced geometric mean titres (GMT)⁵² or reduced VE against medically attended acute respiratory illness⁵³. 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.

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. Of particular importance are those AEFIs which are serious or unexpected. A serious AEFI is an adverse event that is life threatening or results in death, requires hospitalization or prolongs an existing hospitalization, results in residual disability or causes congenital malformation⁵⁴. An unexpected AEFI is an event that is not listed in the approved product monograph but may be due to the vaccination, or one whose nature, severity, specificity, or outcome is not consistent with the term or description used in the product monograph⁵⁴. 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 adverse events.

V. Recommendations

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

Recommendation for individual-level decision making

NACI recommends that influenza vaccine should be offered annually to anyone 6 months of age and older who does not have a contraindication to the vaccine, with focus on the groups for whom influenza vaccination is particularly recommended (see [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 offered as a priority to the groups for whom influenza vaccination is particularly recommended (see [List 1 in the section below](#)).

List 1: Groups for whom influenza vaccination is particularly recommended

People at high risk of influenza-related complications or hospitalization

- All children 6 to 59 months of age
- Adults and children with the following chronic health conditions^a:
 - Cardiac or pulmonary disorders (includes bronchopulmonary dysplasia, cystic fibrosis, and asthma);
 - Diabetes mellitus and other metabolic diseases;
 - Cancer, immune compromising conditions (due to underlying disease, therapy, or both, such as solid organ transplant or hematopoietic stem cell transplant recipients);
 - Renal disease;
 - Anemia or hemoglobinopathy;
 - Neurologic or neurodevelopmental conditions (includes neuromuscular, neurovascular, neurodegenerative, neurodevelopmental conditions, and seizure disorders [and, for children, includes febrile seizures and isolated developmental delay], but excludes migraines and psychiatric conditions without neurological conditions)^b
 - Morbid obesity (defined as BMI of 40 kg/m² and over); and

- Children 6 months to 18 years of age undergoing treatment for long periods with acetylsalicylic acid, because of the potential increase of Reye’s syndrome associated with influenza
- All individuals who are pregnant;
- People of any age who are residents of nursing homes and other chronic care facilities;
- Adults 65 years of age and older; and
- Indigenous peoples.

People capable of transmitting influenza to those at high risk

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

Others

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

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

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

V.1 Choice of Seasonal Influenza Vaccine

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

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

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

Recipient by age group	Vaccine types authorized ^{a,b} and available for use	Recommendations on choice of influenza vaccine
6 to 23 months	<ul style="list-style-type: none"> • IIV3-Adj • IIV4-SD • IIV4-cc 	<ul style="list-style-type: none"> • A quadrivalent influenza vaccine authorized for this age group should be used in infants and young children without contraindications, given the burden of influenza B disease in this age group and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine. <ul style="list-style-type: none"> - Currently, there is insufficient evidence for recommending vaccination with Influvac Tetra (IIV4-SD) in children younger than 3 years of age. • If a quadrivalent vaccine is not available, a trivalent vaccine licensed for this age group should be used.
2 to 17 years ^c	<ul style="list-style-type: none"> • IIV4-SD • IIV4-cc • LAIV4 	<ul style="list-style-type: none"> • An age-appropriate quadrivalent influenza vaccine (IIV4-SD, LAIV4, or IIV4-cc) should be used in children without contraindications or precautions (see text below applicable to LAIV), including those with chronic health conditions, given the burden of influenza B disease in this age group and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine. <ul style="list-style-type: none"> - Currently, there is insufficient evidence for recommending vaccination with Influvac Tetra (IIV4-SD) in children younger than 3 years of age. • LAIV4 may be given to children with: <ul style="list-style-type: none"> - stable, non-severe asthma; - cystic fibrosis who are not being treated with immunosuppressive drugs (e.g., prolonged systemic corticosteroids); and - stable HIV infection, i.e., if the child is currently being treated with ART (i.e., HAART) for at least 4 months and has adequate immune function. • 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"> - severe asthma (defined as currently on oral or high-dose inhaled glucocorticosteroids or active wheezing); - medically attended wheezing in the 7 days prior to vaccination; - current receipt of aspirin or aspirin-containing therapy; - immune compromising conditions, with the exception of stable HIV infection, i.e., if the child is currently being treated with HAART for at least 4 months and has adequate immune function; - pregnancy <ul style="list-style-type: none"> ▪ in pregnancy, IIV4-SD or IIV4-cc should be used instead.
18 to 59 years	<ul style="list-style-type: none"> • IIV4-SD • IIV4-cc 	<ul style="list-style-type: none"> • Any of the available influenza vaccines authorized for this age group should be used in adults 18-59 years without

Recipient by age group	Vaccine types authorized ^{a,b} and available for use	Recommendations on choice of influenza vaccine			
	<ul style="list-style-type: none"> RIV4 LAIV4 	contraindications or precautions, noting the following consideration and exceptions: <ul style="list-style-type: none"> There is some evidence that IIV may provide better efficacy than LAIV in healthy adults; and LAIV is not recommended for: <ul style="list-style-type: none"> Pregnant individuals <ul style="list-style-type: none"> in pregnancy, IIV4-SD, IIV4-cc or RIV4 should be used instead. adults with any of the chronic health conditions identified in List 1, including immune compromising conditions; and health care workers 			
60 to 64 years	<ul style="list-style-type: none"> IIV4-SD IIV4-cc RIV4 	<ul style="list-style-type: none"> Any of the available influenza vaccines authorized for this age group should be used in adults 60 to 64 years without contraindications. 			
65 years and older ^d	<ul style="list-style-type: none"> IIV3-Adj IIV4-SD IIV4-HD IIV4-cc RIV4 	<th data-bbox="610 756 1045 835">Individual-level decision-making</th> <td data-bbox="1045 756 1458 1472"> <th data-bbox="1045 756 1458 835">Public health program-level decision-making</th> </td>	Individual-level decision-making	<th data-bbox="1045 756 1458 835">Public health program-level decision-making</th>	Public health program-level decision-making
		<ul style="list-style-type: none"> IIV-HD should be used over IIV-SD, given the burden of influenza A(H3N2) disease and the good evidence of IIV3-HD providing better protection compared to IIV3-SD in adults 65 years of age and older. <ul style="list-style-type: none"> Other than a recommendation for using IIV-HD over IIV-SD formulations, NACI has not made comparative individual-level recommendations on the use of the other available vaccines in this age group. In the absence of a specific product, any of the available age-appropriate influenza vaccines should be used. 	<ul style="list-style-type: none"> Any of the available influenza vaccines authorized in this age group should be used. <ul style="list-style-type: none"> There is insufficient evidence on the incremental value of different influenza vaccines (i.e., cost-effectiveness assessments have not been performed by NACI) to make comparative public health program-level recommendations on the use of the available vaccines. 		

Abbreviations: ART: antiretroviral therapy; HAART: highly active antiretroviral therapy; IIV: inactivated influenza vaccine; IIV3-Adj: adjuvanted trivalent inactivated influenza vaccine; IIV3-SD: standard-dose trivalent inactivated influenza vaccine; IIV4-cc: quadrivalent mammalian cell –culture-based inactivated influenza vaccine; IIV4-HD: high-dose quadrivalent inactivated influenza vaccine; IIV4-SD: standard-dose quadrivalent inactivated influenza vaccine; RIV4: quadrivalent recombinant influenza vaccine; LAIV: live attenuated influenza vaccine; LAIV4: quadrivalent live attenuated influenza vaccine.

^a IIV3-SD formulations will not be authorized or available for use in Canada during the 2023-2024 influenza season.

^b IIV3-HD formulations will not be authorized or available for use in Canada during the 2023-2024 influenza season.

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

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

V.2 Children

Burden of disease in children

Children experience a higher burden of disease due to influenza B infection compared to other age groups. Although children less than 24 months of age comprise approximately 2% of the Canadian population⁵⁵, children 0 to 23 months of age averaged 10.8% of reported influenza B cases (range: 8.3 to 13.7%), using case-based laboratory data from 2001–2012 (excluding 2009). With respect to severe outcomes (e.g., hospitalization, intensive care unit admission, and death), influenza B was confirmed in 15.5 to 58.3% (median: 38.4%) of pediatric influenza-associated hospitalizations (children 16 years of age and younger) reported by the Canadian Immunization Monitoring Program Active (IMPACT) surveillance network between 2004–2005 and 2012–2013 (excluding the 2009–2010 pandemic season)⁵⁶. From 2010–2011 to 2018–2019, inclusively, 29% of IMPACT influenza admissions were for influenza B.

The IMPACT study also found that the proportion of deaths attributable to influenza (any strain) was significantly greater for children admitted to hospital with influenza B (1.1%) than for those admitted with influenza A (0.4%). The proportion of hospitalizations due to influenza B relative to all influenza hospitalizations has been generally similar to the proportion of influenza B detections relative to all influenza infections in the general population during the same time period. Additional information can be found in the [Statement on Seasonal Influenza Vaccine for 2014–2015](#).

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

Children 6 to 23 months of age

Three types of influenza vaccine are authorized and available for use in children 6 to 23 months of age: IIV3-Adj, IIV4-SD, and IIV4-cc.

Given the burden of influenza B disease in children and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine, NACI recommends that a quadrivalent influenza vaccine should be used. If a quadrivalent vaccine is not available, an available age-appropriate trivalent vaccine (IIV3-Adj) should be used.

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

Children 2 to 17 years of age

Three types of influenza vaccine are authorized and available for use in children 2 to 17 years of age: IIV4-SD, IIV4-cc, and LAIV4.

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

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

Children 2 to 17 years of age with chronic health conditions

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

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

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

Summary of vaccine characteristics for decision making

IIV4-SD, IIV4-cc, and LAIV4 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 IIV4-cc are not available, IIV-cc is comparable to egg-based IIV.

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

Considerations ^a	LAIV ^b compared with IIV ^c
Efficacy and effectiveness	There was early evidence of superior efficacy of LAIV3 compared with IIV3-SD in children less than 6 years of age from randomized controlled trials, with weaker evidence of superior efficacy in older children. However, later post-marketing and surveillance studies across multiple influenza seasons found comparable protection against influenza for LAIV and IIV, with findings of reduced effectiveness for LAIV against A(H1N1) in some studies.
	Like IIV4-SD, LAIV4 is expected to provide additional protection against the influenza B strain not contained in IIV3-SD.

Immunogenicity	LAIV3 has been shown to be as immunogenic as IIV3-SD, depending on age, with LAIV4 being non-inferior to LAIV3.
Safety	Rhinitis (runny nose) and nasal congestion are more common with LAIV. Clinical studies and post-marketing studies showed a similar safety profile to IIV.
Contraindications	There are vaccine contraindications specific to LAIV. LAIV is contraindicated for children with severe asthma, medically attended wheezing in the 7 days prior to vaccination, and immune compromising conditions (with the exception of children with stable HIV infection on HAART and with adequate immune function), as well as those currently receiving aspirin or aspirin-containing therapy. LAIV is also contraindicated for pregnant adolescents .
Acceptability	Delivery of LAIV as a nasal spray may be preferable for children who are averse to receiving the vaccine by needle injection.

Abbreviations: HAART: highly active antiretroviral therapy; IIV: inactivated influenza vaccine; IIV3-SD: standard-dose trivalent inactivated influenza vaccine; IIV4-SD: standard-dose quadrivalent inactivated influenza vaccine; LAIV: live attenuated influenza vaccine; LAIV3: trivalent live attenuated influenza vaccine; LAIV4: quadrivalent live attenuated influenza vaccine.

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

^b The trivalent formulation of LAIV (LAIV3) received a Notice of Compliance from Health Canada in June 2010 and was first used in publicly funded immunization programs in Canada for the 2012–2013 influenza season. The quadrivalent formulation (LAIV4) was approved for use in Canada for the 2014–2015 season and has been in use since that time. LAIV3 is no longer available in Canada.

^c The trivalent IIV3-SD formulations are not expected to be authorized or available in Canada for the 2023-2024 influenza season. Data comparing LAIV to IIV4-cc are not available, however IIV-cc is comparable to egg-based IIV.

V.3 Adults

Burden of disease in adults

A study focusing on estimates of deaths associated with influenza in the United States has established that the average annual rate of influenza-associated deaths for adults aged 65 years of age and older was 17.0 deaths per 100,000 (range: 2.4 to 36.7)⁵⁷. The study also states that of deaths coded as being influenza- or pneumonia-related, persons 65 years of age and older accounted for 87.9% of the overall estimated annual average number of deaths. When influenza-related deaths among adults 65 years of age and older were estimated using codes for underlying respiratory and circulatory causes of death, these estimates increased to 66.1 deaths per 100,000 (range: 8.0 to 121.1) and 89.4%, respectively. This study described a wide variation in the estimated number of deaths from season to season, which was closely related to the influenza virus types and subtypes in circulation. Estimates presented in the study of yearly influenza-associated deaths with underlying pneumonia and influenza causes (1976 to 2007) reveal a large difference between influenza type A and B with a calculated median of greater than 6,000 deaths associated with influenza type A and half of that number for influenza type B (approximately 3,360) for persons 65 years of age and older. During the 22 seasons in which influenza A(H3N2) was the prominent strain, the average influenza-associated mortality rates were 2.7 times higher than for the nine seasons that it was not (all age groups combined), and on average, there were about 37% more annual influenza-associated deaths, regardless of the primary medical cause of death. A higher risk of hospitalization and death was also reported by Cromer et al. in adults 65 years of

age and older, compared to younger adults in their assessment of the burden of influenza in England by age and clinical risk group⁵⁸.

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

Adults 18 to 59 years of age

Four types of influenza vaccine are authorized and available for use in adults 18 to 59 years of age: IIV4-SD, IIV4-cc, RIV4, and LAIV4.

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

Adults 60 to 64 years of age

Three types of influenza vaccine are authorized and available for use in adults 60 to 64 years of age: IIV4-SD, IIV4-cc, and RIV4.

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

Adults 65 years of age and older

Five types of influenza vaccine are authorized and available for use in adults 65 years of age and older: IIV3-Adj, IIV4-SD, IIV4-cc, IIV4-HD, and RIV4.

Recommendation for individual-level decision making

When available, IIV-HD should be used over IIV-SD, given the burden of influenza A(H3N2) disease and the good evidence of better protection of IIV3-HD compared to IIV3-SD in adults 65 years of age and older. Based on a review of pre-authorization trials, IIV4-HD is non-inferior to IIV3-HD and is therefore expected to provide the same enhanced protection against A(H3N2) compared to SD IIV, including IIV4-SD. Although IIV-HD is expected to provide better protection against influenza A(H3N2) for adults 65 years of age or older, the benefit of providing this vaccine

to all adults 65 and over as opposed to any other influenza vaccine is not clear (refer to the next section). NACI is currently conducting an updated review of influenza vaccines in this population.

Any of the available influenza vaccines would be preferable to remaining unvaccinated or requesting individuals to return for vaccine. Therefore, in the absence of a specific product, NACI recommends that any of the available influenza vaccines authorized for this age group should be used.

Recommendation for public health program-level decision making

IIV3-HD is expected to provide better protection compared to IIV3-SD. Similarly, IIV4-HD is expected to provide better protection compared to IIV4-SD. The previous assessment completed by NACI demonstrated insufficient evidence to make a comparative recommendation on the use of IIV3-HD over IIV3-SD at the programmatic level and a complete assessment that includes economic considerations has not yet been conducted for IIV4-HD. Therefore, NACI currently recommends that any of the available influenza vaccines should be used for public health programs. NACI is in the process of completing an updated assessment on influenza vaccines for adults 65 years of age and older.

Refer to the NACI [Literature Review Update on the Efficacy and Effectiveness of High-Dose \(Fluzone® High-Dose\) and MF59-Adjuvanted \(Fluad\) Trivalent Inactivated Influenza Vaccines in Adults 65 Years of Age and Older](#) for additional information supporting these recommendations.

Summary of vaccine characteristics for decision making

There are four types of inactivated influenza vaccines (IIV3-Adj, IIV4-SD, IIV4-cc, and IIV4-HD) and one type of recombinant influenza vaccine (RIV4) authorized for use in Canada for adults 65 years of age and older. The comparison of vaccine characteristics across vaccine types, in Table 4 below, may be considered when deciding on the preferred vaccine option(s) for use by an individual or a public health program. Due to the limited available data directly comparing the performance of IIV3-Adj, IIV4-HD, IIV4-SD, IIV4-cc, or RIV4, considerations for these vaccines in Table 4 are compared to IIV3-SD for which comparative data on efficacy, effectiveness, and/or immunogenicity with each of IIV3-Adj and IIV4-SD are available. Data directly comparing IIV4-cc and IIV4-HD to IIV3-SD are not available. Comparative data on efficacy, effectiveness, and/or immunogenicity of IIV3-cc and IIV3-SD are available.

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

Considerations ^a	Influenza vaccine type				
	IIV3-Adj	IIV4-HD ^b	IIV4-SD	IIV4-cc ^c	RIV4
Burden of disease	Although influenza-associated morbidity and mortality varies each season, in general there is an increased burden of severe disease in adults 65 years of age and older during influenza seasons when influenza A(H3N2) predominates ⁵⁹ .				

Considerations ^a	Influenza vaccine type				
	IIV3-Adj	IIV4-HD ^b	IIV4-SD	IIV4-cc ^c	RIV4
Efficacy and effectiveness	Overall, insufficient comparative evidence with IIV3-SD to draw conclusion.	Expected ^b better protection compared with IIV3-SD, particularly against influenza A(H3N2). Better protection against the influenza B strain not contained in IIV3-HD.	Better protection against the influenza B strain not contained in IIV3-SD.	Expected ^c better protection against the influenza B strain not contained in IIV3-SD.	Expected ^d better protection against the influenza B strain not contained in IIV3-SD. Potentially ^d better protection compared with IIV4 SD.
Immunogenicity	Non-inferior immune response compared to IIV3-SD. Superiority to IIV3-SD has not been consistently demonstrated.	Expected ^b superior immune response to influenza A strains compared to IIV3-SD. Superior immune response to the additional B strain compared to IIV3-HD.	Non-inferior immune response to the strains contained in IIV3-SD with superior immune response to the additional B strain.	Non-inferior immune response to the strains contained in IIV3-cc. Superior immune response against the influenza B strain not contained in IIV3-SD. Non-inferior response expected ^c compared to IIV3-SD.	Expected ^e non-inferior immune response compared to IIV4-HD, IIV4-cc, IIV3-HD, IIV3-Adj.
Contraindications	Same contraindications as IIV3-SD.				

Considerations ^a	Influenza vaccine type				
	IIV3-Adj	IIV4-HD ^b	IIV4-SD	IIV4-cc ^c	RIV4
Safety	Higher rate of injection site reactions than IIV3-SD. Higher or comparable systemic reactions compared to IIV3-SD; systemic reactions were mild to moderate and transient. SAEs were comparable to IIV3-SD and were uncommon.	Higher rate of some systemic reactions than IIV4-SD and the same is expected ^b compared to IIV3-SD; most systemic reactions were mild and transient. SAEs were rare and similar in frequency to IIV4-SD and the same is expected compared to IIV3-SD ^b .	Pre-licensure clinical trials and post-marketing surveillance showed a similar safety profile to IIV3-SD.	Pre-licensure clinical trials showed a similar safety profile to IIV3-cc. Similar safety profile to IIV3-SD is expected ^c .	Pre-licensure clinical trials showed a similar safety profile to IIV4-SD, IIV3-HD and IIV-Adj. Similar safety profile to IIV3-SD is expected.

Abbreviations: IIV3-Adj: adjuvanted egg-based trivalent inactivated influenza vaccine; IIV3-SD: standard-dose trivalent inactivated influenza vaccine; IIV4-cc: standard-dose cell culture-based quadrivalent inactivated influenza vaccine; IIV4-HD: high-dose quadrivalent inactivated influenza vaccine; IIV4-SD: standard-dose quadrivalent inactivated influenza vaccine; RIV4: quadrivalent recombinant influenza vaccine; SAE: serious adverse event.

^a NACI has not assessed the comparative cost-effectiveness of available influenza vaccine types for adults 65 years of age and older.

^b Data directly comparing IIV4-HD to IIV3-SD are not available; however, IIV4-HD has been shown to be non-inferior to IIV3-HD and has a comparable rate of systemic and local reactions. Therefore, information presented here is expected to apply to IIV4-HD as well.

^c Data directly comparing IIV4-cc to IIV3-SD are not available; however, IIV3-cc (licensure never sought in Canada) has been shown to be non-inferior to IIV3-SD. Therefore, information presented here is expected to apply to IIV4-cc as well.

^d Data directly comparing RIV4 to IIV3-SD are not available; however, RIV4 has been shown to provide better protection than IIV4-SD based on one study conducted during a single influenza season (2014-2015).

^e Data directly comparing RIV4 to IIV3-SD are not available; however, RIV4 has been shown to be non-inferior to IIV4-SD, IIV4-cc, IIV3-HD and IIV3-Adj against all tested influenza strains [A(H1N1), A(H3N2), B/Yamagata lineage, and B/Victoria lineage] and has a comparable rate of AEs based on 3 influenza seasons (2014-2015, 2017-2018, 2018-2019). Therefore, information presented here is expected to apply to IIV3-SD as well.

Adults with chronic health conditions

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

Pregnant individuals

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

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

Health care workers

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

Comparative studies in healthy adults have found IIV to be similarly or more efficacious or effective compared with LAIV⁶⁰. In addition, as a precautionary measure, LAIV recipients should avoid close association with people with severe immune compromising conditions (e.g., bone marrow transplant recipients requiring isolation) for at least 2 weeks following vaccination, because of the theoretical risk for transmitting a vaccine virus and causing infection.

Travellers

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

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

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

V.4 Particularly Recommended Vaccine Recipients

The groups for whom influenza vaccination is particularly recommended are presented in [List 1](#). Additional information regarding these particularly recommended recipients is provided below.

All children 6 to 59 months of age

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

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

Adults and children with chronic health conditions

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

All individuals who are pregnant

NACI recommends the inclusion of all individuals who are pregnant, at any stage of pregnancy, among those who are particularly recommended to receive IIV or RIV. This is due to the risk of influenza-associated morbidity amongst those who are pregnant^{61–65}, evidence of adverse neonatal outcomes associated with respiratory hospitalization during pregnancy or influenza during pregnancy^{66–69}, evidence that vaccination of individuals who are pregnant protects their newborns from influenza and influenza-related hospitalization^{70–73}, and evidence that infants born during influenza season to vaccinated individuals are less likely to be premature, small for gestational age, and of low birth weight than if born to individuals that had not received an influenza vaccine^{74–77}. The risk of influenza-related hospitalization increases with length of gestation (i.e., it is higher in the third trimester than in the second).

The safety of IIV during pregnancy has been reviewed⁷⁶. Active studies of influenza vaccination during pregnancy have not shown evidence of harm to the pregnant individual or fetus associated with influenza vaccination⁷⁸. Although the cumulative sample size of active studies of influenza vaccination in pregnant individuals is relatively small, particularly in the first trimester, passive surveillance has not raised any safety concerns despite widespread use of IIV during pregnancy over several decades^{63,64,79,80}. Surveillance following the use of both adjuvanted and unadjuvanted 2009 pandemic influenza A(H1N1) vaccines in more than 100,000 pregnant women in Canada and more than 488,000 pregnant women in Europe⁸¹ has not revealed any safety concerns.

Very limited peer-reviewed, published data pertaining to safety of vaccination with RIV4 during pregnancy is currently available to inform vaccine-associated risks. Refer to the [Supplemental Statement on Recombinant Influenza Vaccines](#) for more information.

Refer to the [Statement on Seasonal Influenza Vaccine for 2011–2012](#) and the [Statement on Seasonal Influenza Vaccine for 2012–2013](#) for further details 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 one or more chronic health condition and live in institutional environments that may facilitate the spread of influenza.

Adults 65 years of age and older

Hospitalization attributable to influenza in this age group is estimated at 125 to 228 per 100,000 healthy people⁸², and influenza-attributed mortality rates increase with increased age⁸³.

Indigenous peoples

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

It has been proposed that the increased risk of severe influenza outcomes in the Indigenous populations is a consequence of many factors, including high prevalence of chronic health conditions (e.g., diabetes, chronic lung disease, end-stage kidney disease, cardiovascular disease, obesity)⁸⁴, delayed access to health care, and increased susceptibility to disease because of poor housing and overcrowding^{85–87}. A review of the available evidence and update to the recommendations for Indigenous peoples as a group at high-risk of influenza-related complications is planned, with inclusion and consideration of key stakeholder engagement.

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

People who are potentially capable of transmitting influenza to those at high risk should receive annual vaccination, regardless of whether the high-risk individual has been vaccinated. Vaccination of Health Care Workers (HCWs) decreases their own risk of illness^{88,89}, as well as the risk of death and other serious outcomes among the individuals for whom they provide care^{90–93}. Vaccination of HCWs and residents of nursing homes is associated with decreased risk of ILI outbreaks⁹⁴.

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

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

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

Vaccination of health care workers and other care providers

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

Transmission of influenza to patients at high risk of influenza-associated complications results in significant morbidity and mortality. Four cluster randomized controlled trials (RCTs) conducted in geriatric long-term care settings have demonstrated that vaccination of HCWs is associated with substantial decreases in influenza-like illness^{91–93} and all-cause mortality^{90–93} in the residents. In addition, due to their occupation and close contact with people who may be infected with influenza, HCWs are themselves at increased risk of infection⁹⁵.

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

Although the current influenza vaccine coverage rate for HCWs is higher than for the general public^{96,97}, it remains below the national goal of 80% coverage for HCWs in Canada⁹⁸. 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^{99–104}.

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 vaccination¹⁰⁵. As part of outbreak management, the above-mentioned PHAC guidance suggests consideration of chemoprophylaxis for all unvaccinated HCWs, unless contraindications exist. Refer to the Association of Medical Microbiology and Infectious Disease Canada (AMMI Canada) website for guidelines regarding the use of antiviral medications for prophylaxis.

Contacts of individuals at high risk of influenza complications

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

V.6 Others

People who provide essential community services

Vaccination for these individuals should be encouraged to minimize the disruption of services and routine activities during annual influenza epidemics. People who provide essential community services, including healthy working adults, should consider annual influenza vaccination, as this intervention has been shown to decrease work absenteeism due to respiratory and related illnesses^{88,89,106–108}.

People in direct contact with poultry infected with avian influenza during culling operations

Poultry handlers

Although seasonal influenza vaccination will not prevent avian influenza infection, some countries¹⁰⁹ and provinces have recommended influenza vaccination on a yearly basis for those working with poultry, based on the rationale that preventing infection with human influenza strains may reduce the theoretical potential for human-avian reassortment of genes, should such workers become co-infected with human and avian influenza viruses¹¹⁰.

NACI recommends seasonal influenza vaccination for people who may be in direct contact with poultry infected with avian influenza during culling operations, as these individuals may be at increased risk of avian influenza infection because of exposure during the culling operation^{111–114}. Refer to the [Statement on Seasonal Influenza Vaccine for 2013–2014](#) for further information supporting this recommendation.

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

Swine workers

NACI has concluded that there is insufficient evidence at this time to recommend routine influenza vaccination specifically for swine workers; however, NACI recommends that influenza vaccination

should be offered to anyone 6 months of age and older who does not have contraindications to the vaccine.

Refer to the [Statement on Seasonal Influenza Vaccine for 2013–2014](#) for further information supporting this recommendation.

List of Abbreviations

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

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

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References

1. World Health Organization. Influenza (seasonal): fact sheet N°211 [Internet]. Vol. 2016. 2014. Available from: <http://www.who.int/mediacentre/factsheets/fs211/en/>
2. Mamas MA, Fraser D, Neyses L. Cardiovascular manifestations associated with influenza virus infection. *IntJCardiol.* 2008;130(3):304–9.
3. Moriarty L, Omer S. Infants and the seasonal influenza vaccine. A global perspective on safety, effectiveness, and alternate forms of protection. *Hum Vaccin Immunother.* 2014;10(9):2721–8.
4. Schwarz TF, Aggarwal N, Moeckesch B, Schenkenberger I, Claeys C, Douha M, et al. Immunogenicity and Safety of an Adjuvanted Herpes Zoster Subunit Vaccine Coadministered With Seasonal Influenza Vaccine in Adults Aged 50 Years or Older. *JInfectDis.* 2017;216(11):1352–61.
5. Koutsakos M, Wheatley A, Laurie K, et. al. Influenza Lineage Extinction during the COVID-19 Pandemic? *Nature Reviews Microbiology.*
6. Dhanasekaran V, Sullivan S, Edwards KM, Xie R, Khvorov A, Valkenburg SA, et al. Human seasonal influenza under COVID-19 and the potential consequences of influenza lineage elimination. *Nat Commun.* 2022 Dec;13(1):1721.
7. Lessler J, Reich N, Brookmeyer R, et. al. Incubation periods of acute respiratory viral infections: a systematic review. *Lancet Infect Dis.* 2009;9:291–300.
8. Behrouzi B, Bhatt D, Cannon C, et. al. Association of Influenza Vaccination with Cardiovascular Risk: A Meta-analysis. *JAMA Netw Open.* 2022;5(4):e228873.
9. Statistics Canada. The 10 leading causes of death, 2011 [Internet]. Vol. 2015. 2014. Available from: <http://www.statcan.gc.ca/pub/82-625-x/2014001/article/11896-eng.htm>
10. Schanzer DL, McGeer A, Morris K, Et. Al. Statistical estimates of respiratory admissions attributable to seasonal and pandemic influenza for Canada. *Influenza and Other Respiratory Viruses.* 2013;7(5):799–808.
11. Schanzer DL, Sevenhuysen C, Winchester B, Et. Al. Estimating Influenza Deaths in Canada, 1992–2009. *PLoS ONE.* 2013;8(11):e80481.
12. World Health Organization. Fact Sheet: Estimating Disease Burden of Influenza [Internet]. Available from: <https://www.who.int/europe/activities/estimating-disease-burden-of-influenza>
13. Nwosu A, Lee L, Schmidt K, et. al. National Influenza Annual Report, Canada, 2020–2021, in the global context. *Can Commun Dis Rep.* 2021;47(10):405–13.
14. Groves HE, Papenburg J, Mehta K, Bettinger JA, Sadarangani M, Halperin SA, et al. The effect of the COVID-19 pandemic on influenza-related hospitalization, intensive care admission and mortality in children in Canada: A population-based study. *The Lancet Regional Health - Americas.* 2022 Mar;7:100132.

15. He D, Lui R, Wang L, et. al. Global Spatio-temporal Patterns of Influenza in the Post-pandemic Era. *Sci Rep.* 2015;5(1):11013.
16. The Academy of Medical Sciences. COVID-19: Preparing for the future. London, UK. AMS [Internet]. 2021 [cited 2021 Jul 30]; Available from: <https://acmedsci.ac.uk/file-download/4747802>
17. Baker RE, Park SW, Yang W, Vecchi GA, Metcalf CJE, Grenfell BT. The impact of COVID-19 nonpharmaceutical interventions on the future dynamics of endemic infections. *Proc Natl Acad Sci USA.* 2020 Dec 1;117(48):30547–53.
18. Centers for Disease Control and Prevention. Selecting Viruses for the Seasonal Influenza Vaccine. Atlanta (GA). [cited 2021 Aug 30]; Available from: <https://www.cdc.gov/flu/prevent/vaccine-selection.htm>
19. Government of Canada. Respiratory Virus Detections in Canada [Internet]. Available from: canada.ca/en/public-health/services/surveillance/respiratory-virus-detections-canada.html
20. Tang JW, Bialasiewicz S, Dwyer DE, Dilcher M, Tellier R, Taylor J, et al. Where have all the viruses gone? Disappearance of seasonal respiratory viruses during the COVID-19 pandemic. *J Med Virol.* 2021 Jul;93(7):4099–101.
21. Heckler R, Baillot A, Engelmann H, Neumeier E, Windorfer A. Cross-protection against homologous drift variants of influenza A and B after vaccination with split vaccine. *Intervirology.* 2007;50(1):58–62.
22. Walter EB, Neuzil KM, Zhu Y, Fairchok MP, Gagliano ME, Monto AS, et al. Influenza vaccine immunogenicity in 6- to 23-month-old children: are identical antigens necessary for priming? *Pediatrics.* 2006;118(3):e570–8.
23. Englund JA, Walter EB, Fairchok MP, Monto AS, Neuzil KM. A comparison of 2 influenza vaccine schedules in 6- to 23-month-old children. *Pediatrics.* 2005;115(4):1039–47.
24. Englund JA, Walter EB, Gbadebo A, Monto AS, Zhu Y, Neuzil KM. Immunization with trivalent inactivated influenza vaccine in partially immunized toddlers. *Pediatrics.* 2006;118(3):e579-85.
25. Levandowski RA, Gross PA, Weksler M, Staton E, Williams MS, Bonelli J. Cross-reactive antibodies induced by a monovalent influenza B virus vaccine. *J Clin Microbiol.* 1991;29(7):1530–2.
26. Levandowski RA, Regnery HL, Staton E, Burgess BG, Williams MS, Groothuis JR. Antibody responses to influenza B viruses in immunologically unprimed children. *Pediatrics.* 1991;88(5):1031–6.
27. McLean HQ, Thompson MG, Sundaram ME, Et. Al. Influenza Vaccine Effectiveness in the United States During 2012-2013: Variable Protection by Age and Virus Type. *Journal of Infectious Diseases.* 2015;211(10):1529–40.

28. McLean HQ, Thompson MG, Sundaram ME, Meece JK, McClure DL, Friedrich TC, et al. Impact of repeated vaccination on vaccine effectiveness against influenza A(H3N2) and B during 8 seasons. *ClinInfectDis*. 2014;59(10):1375–85.
29. Ritzwoller DP, Bridges CB, Shetterly S, Yamasaki K, Kolczak M, France EK. Effectiveness of the 2003–2004 influenza vaccine among children 6 months to 8 years of age, with 1 vs 2 doses. *Pediatrics*. 2005;116(1):153–9.
30. Neuzil KM, Jackson LA, Nelson J, Klimov A, Cox N, Bridges CB, et al. Immunogenicity and reactogenicity of 1 versus 2 doses of trivalent inactivated influenza vaccine in vaccine-naïve 5–8-year-old children. *JInfectDis*. 2006;194(8):1032–9.
31. Shuler CM, Iwamoto M, Bridges CB, Marin M, Neeman R, Gargiullo P, et al. Vaccine effectiveness against medically attended, laboratory-confirmed influenza among children aged 6 to 59 months, 2003–2004. *Pediatrics*. 2007;119(3):e587–95.
32. Allison MA, Daley MF, Crane LA, Barrow J, Beaty BL, Allred N, et al. Influenza vaccine effectiveness in healthy 6- to 21-month-old children during the 2003–2004 season. *JPediatr*. 2006;149(6):755–62.
33. Skowronski DM, Hottes TS, De Serres G, Ward BJ, Janjua NZ, Sabaiduc S, et al. Influenza B/Victoria antigen induces strong recall of B/Yamagata but lower B/Victoria response in children primed with two doses of B/Yamagata. *PediatrInfectDisJ*. 2011;30(10):833–9.
34. McElhaney JE, Hooton JW, Hooton N, Bleackley RC. Comparison of single versus booster dose of influenza vaccination on humoral and cellular immune responses in older adults. *Vaccine*. 2005;23(25):3294–300.
35. Breiman RF, Brooks WA, Goswami D, Lagos R, Borja-Tabora C, Lanata CF, et al. A multinational, randomized, placebo-controlled trial to assess the immunogenicity, safety, and tolerability of live attenuated influenza vaccine coadministered with oral poliovirus vaccine in healthy young children. *Vaccine*. 2009;27(40):5472–9.
36. Lum LC, Borja-Tabora C, Breiman RF, Vesikari T, Sablan BP, Chay OM, et al. Influenza vaccine concurrently administered with a combination measles, mumps, and rubella vaccine to young children. *Vaccine*. 2010;28(6):1566–74.
37. Nolan T, Bernstein DI, Block SL, Hilty M, Keyserling HL, Marchant C, et al. Safety and immunogenicity of concurrent administration of live attenuated influenza vaccine with measles-mumps-rubella and varicella vaccines to infants 12 to 15 months of age. *Pediatrics*. 2008;121(3):508–16.
38. Severance R, Schwartz H, Dagan R, et al. Safety, tolerability, and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, administered concomitantly with influenza vaccine in healthy adults aged ≥50 years: a randomized phase 3 trial (PNEU-FLU). *Hum Vaccin Immunother*. 2022;18(1):1–14.
39. National Advisory Committee on Immunization. Updated Recommendations on the Use of Herpes Zoster Vaccines. Ottawa: Public Health Agency of Canada [Internet]. 2018. 2018.

- Available from: <https://www.canada.ca/en/services/health/publications/healthy-living/updated-recommendations-use-herpes-zoster-vaccines.html>
40. National Advisory Committee on Immunization. Statement on thimerosal. *CanCommunDisRep*. 2003;29(1):1–12.
 41. National Advisory Committee on Immunization. Thimerosal: updated statement. An Advisory Committee Statement (ACS). *CanCommunDisRep*. 2007;33(6):1–13.
 42. Gerber JS, Offit PA. Vaccines and autism: a tale of shifting hypotheses. *ClinInfectDis*. 2009;48(4):456–61.
 43. Institute of Medicine of the National Academies. Immunization safety review: influenza vaccines and neurological complications. Institute of Medicine of the National Academies. Washington, DC: National Academy of Sciences; 2008.
 44. Centers for Disease Control and Prevention. Preliminary results: surveillance for Guillain-Barré syndrome after receipt of influenza A (H1N1) 2009 monovalent vaccine - United States, 2009-2010. *MMWR MorbMortalWklyRep*. 2010;59(21):657–61.
 45. Kwong JC, Vasa PP, Campitelli MA, Hawken S, Wilson K, Rosella LC, et al. Risk of Guillain-Barré syndrome after seasonal influenza vaccination and influenza health-care encounters: a self-controlled study. *Lancet Infect Dis*. 2013;13(9):769–76.
 46. Sivadon-Tardy V, Orlikowski D, Porcher R, Sharshar T, Durand MC, Enouf V, et al. Guillain-Barre syndrome and influenza virus infection. *ClinInfectDis*. 2009;48(1):48–56.
 47. Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenza like illness using the United Kingdom General Practice Research Database. *AmJEpidemiol*. 2009;169(3):382–8.
 48. Tam CC, O'Brien SJ, Petersen I, Islam A, Hayward A, Rodrigues LC. Guillain-Barre syndrome and preceding infection with campylobacter, influenza and Epstein-Barr virus in the general practice research database. *PLoS One*. 2007;2(4):e344.
 49. Andrews N, Stowe J, Al-Shahi Salman R, Miller E. Guillain-Barre syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: self-controlled case series. *Vaccine*. 2011;29(45):7878–82.
 50. National Advisory Committee on Immunization. Supplementary statement on influenza vaccination: continued use of Fluviral® influenza vaccine in the 2000-2001 season. *Can Commun Dis Rep*. 2001;27(ACS-1):1-3(Journal Article).
 51. Ahmadipour N, WK Fréchette M, Coulby C, Anyoti H, Johnson K. Vaccine safety surveillance in Canada: Reports to CAEFISS, 2013–2016. *Can Commun Dis Rep*. 2018;44((9)):206–14.
 52. Black S, Nicolay U, Del Giudice G, Rappuoli R. Influence of statins on influenza vaccine response in elderly individuals. *JInfectDis*. 2016;213(8):1224–8.

53. Omer SB, Phadke VK, Bednarczyk RA, Chamberlain AT, Brosseau JL, Orenstein WA. Impact of statins on influenza vaccine effectiveness against medically attended acute respiratory illness. *J Infect Dis*. 2016;213(8):1216–23.
54. Public Health Agency of Canada. Reporting adverse events following immunization (AEFI) in Canada: User guide to completion and submission of the AEFI reports. Ottawa, PHAC [Internet]. Vol. 2019. 2004. Available from: <https://www.canada.ca/en/public-health/services/immunization/reporting-adverse-events-following-immunization/user-guide-completion-submission-ae-fi-reports.html>
55. Statistics Canada. Table 051-0001 - Estimates of population, by age group and sex for July 1, Canada, provinces and territories, annual (persons unless otherwise noted), CANSIM (database) [Internet]. Vol. 2015. 2014. Available from: <http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo10a-eng.htm>
56. Tran D, Vaudry W, Moore D, et. al. Hospitalization for Influenza A versus B. *Pediatrics*. 2016;138(3):e20154643.
57. Centers for Disease Control and Prevention. Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. *MMWR Morb Mortal Wkly Rep*. 2010;59(33):1057–62.
58. Cromer D, van Hoek AJ, Jit M, Edmunds WJ, Fleming D, Miller E. The burden of influenza in England by age and clinical risk group: a statistical analysis to inform vaccine policy. *J Infect*. 2014;68(4):363–71.
59. Groves H, Piché-Renaud P, Peci A, et. al. The impact of the COVID-19 pandemic on influenza, respiratory syncytial virus, and other seasonal respiratory virus circulation in Canada: A population-based study. *Lancet Reg Health Am*. 2021;1:100015.
60. Grohskopf L, Sokolow L, Fry A, et. al. Update: ACIP Recommendations for the Use of Quadrivalent Live Attenuated Influenza Vaccine (LAIV4) - United States, 2018-19 Influenza Season. *MMWR Morb Mortal Wkly Rep*. 2018;67(22):643–5.
61. Louie JK, Acosta M, Jamieson DJ, Honein MA, California Pandemic (H1N1) WG. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. Aranki F, Byron-Cooper O, Cheung M, Cody S, Farley S, Ginsberg M, et al., editors. *N Engl J Med*. 2010;362(1):27–35.
62. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA*. 2010;303(15):1517–25.
63. Mak TK, Mangtani P, Leese J, Watson JM, Pfeifer D. Influenza vaccination in pregnancy: current evidence and selected national policies. *Lancet Infect Dis*. 2008;8(1):44–52.
64. McNeil S, Halperin B, MacDonald N. Influenza in pregnancy: the case for prevention. *Adv Exp Med Biol*. 2009;634(Journal Article):161–83.
65. Rasmussen SA, Jamieson DJ, Bresee JS. Pandemic influenza and pregnant women. *Emerg Infect Dis*. 2008;14(1):95–100.

66. Centers for Disease Control and Prevention. Maternal and infant outcomes among severely ill pregnant and postpartum women with 2009 pandemic influenza A (H1N1)-- United States, April 2009-August 2010. *MMWR MorbMortalWklyRep*. 2011;60(35):1193–6.
67. Pierce M, Kurinczuk J, Spark P, Brocklehurst P, Knight M. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. *BMJ*. 2011;342(Journal Article):d3214–d3214.
68. Goldenberg R, Culhane J, Iams J, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606):75–84.
69. McNeil SA, Dodds LA, Fell DB, Allen VM, Halperin BA, Steinhoff MC, et al. Effect of respiratory hospitalization during pregnancy on infant outcomes. *AmJObstetGynecol*. 2011;204(6):S54-7.
70. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. *NEnglJMed*. 2008;359(15):1555–64.
71. Poehling K, Szilagyi P, Staat M, Snively B, Payne D, Bridges C, et al. Impact of maternal immunization on influenza hospitalizations in infants. *ObstetGynecol*. 2011;204(6):S141–8.
72. Eick AA, Uyeki TM, Klimov A, Hall H, Reid R, Santosham M, et al. Maternal influenza vaccination and effect on influenza virus infection in young infants. *ArchPediatrAdolescMed*. 2011;165(2):104–11.
73. France EK, McClure D, Hambidge S, Xu S, Yamasaki K, Shay D, et al. Impact of maternal influenza vaccination during pregnancy on the incidence of acute respiratory illness visits among infants. *ArchPediatrAdolescMed*. 2006;160(12):1277–83.
74. Steinhoff M, Omer S, Roy E, El Arifeen S, Raqib R, Dodd C, et al. Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial. *CMAJ*. 2012;184(6):645–53.
75. Fell DB, Sprague AE, Liu N, Yasseen AS 3, Wen SW, Smith G, et al. H1N1 influenza vaccination during pregnancy and fetal and neonatal outcomes. *AmJPublic Health*. 2012;102(6):e33-40.
76. Omer S, Goodman D, Steinhoff M, Rochat R, Klugman K, Stoll B, et al. Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study. *PLoS Med*. 2011;8(5):e1000441.
77. Dodds L, MacDonald N, Scott J, Spencer A, Allen VM, McNeil SA. The association between influenza vaccine in pregnancy and adverse neonatal outcomes. *J Obstetr Gynecol Can*. 2012;34(8):714–20.
78. MacDonald NE, Riley LE, Steinhoff MC. Influenza immunization in pregnancy. *ObstetGynecol*. 2009;114(2):365–8.

79. Tamma PD, Ault KA, del Rio C, Steinhoff MC, Halsey N, Omer S. Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol.* 2009;201(6):547–52.
80. Moro PL, Broder K, Zheteyeva Y, Walton K, Rohan P, Sutherland A, et al. Adverse events in pregnant women following administration of trivalent inactivated influenza vaccine and live attenuated influenza vaccine in the Vaccine Adverse Event Reporting System, 1990-2009. *Am J Obstet Gynecol.* 2011;204(2):146e1–7.
81. European Medicines Agency. Fifteenth pandemic pharmacovigilance update. <http://www.ema.europa.eu/pdfs/influenza/21323810en.pdf>. London: European Medicines Agency; 2010.
82. Simonsen L, Fukuda K, Schonberger LB, Cox NJ. The impact of influenza epidemics on hospitalizations. *J Infect Dis.* 2000;181(3):831–7.
83. Schanzer DL, Tam TW, Langley JM, Winchester BT. Influenza-attributable deaths, Canada 1990-1999. *Epidemiol Infect.* 2007;135(7):1109–16.
84. Centers for Disease Control and P. Deaths related to 2009 pandemic influenza A (H1N1) among American Indian/Alaska Natives - 12 states, 2009. *MMWR Morb Mortal Wkly Rep.* 2009;58(48):1341–4.
85. National Center for Education Statistics. Individuals, families and children in poverty. In: Status and trends in the education of American Indians and Alaska Natives. http://nces.ed.gov/pubs2008/nativetrends/ind_1_6.asp. Washington, DC: US Department of Education; 2008.
86. Indigenous and Northern Affairs Canada. Highlights from the report of the Royal Commission on Aboriginal Peoples - people to people, nation to nation [Internet]. Vol. 2016. 2010. Available from: <https://www.rcaanc-cirnac.gc.ca/eng/1100100014597/1572547985018>
87. Clark M, Riben P, Nowgesic E. The association of housing density, isolation and tuberculosis in Canadian First Nations communities. *Int J Epidemiol.* 2002;31(5):940–5.
88. Saxen H, Virtanen M. Randomized, placebo-controlled double blind study on the efficacy of influenza immunization on absenteeism of health care workers. *Pediatr Infect Dis J.* 1999;18(9):779–83.
89. Wilde JA, McMillan JA, Serwint J, Butta J, O’Riordan MA, Steinhoff MC. Effectiveness of influenza vaccine in health care professionals: a randomized trial. *JAMA.* 1999;281(10):908–13.
90. Carman WF, Elder AG, Wallace LA, McAulay K, Walker A, Murray GD, et al. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. *Lancet.* 2000;355(9198):93–7.
91. Hayward AC, Harling R, Wetten S, Johnson AM, Munro S, Smedley J, et al. Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. *BMJ.* 2006;333(7581):1241.

92. Potter J, Stott DJ, Roberts MA, Elder AG, O'Donnell B, Knight PV, et al. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. *JInfectDis*. 1997;175(1):1–6.
93. Lemaitre M, Meret T, Rothan-Tondeur M, Belmin J, Lejonc JL, Luquel L, et al. Effect of influenza vaccination of nursing home staff on mortality of residents: a cluster-randomized trial. *JAmGeriatrSoc*. 2009;57(9):1580–6.
94. Shugarman LR, Hales C, Setodji CM, Bardenheier B, Lynn J. The influence of staff and resident immunization rates on influenza-like illness outbreaks in nursing homes. *JAmMedDirAssoc*. 2006;7(9):562–7.
95. Kuster SP, Shah PS, Coleman BL, Lam PP, Tong A, Wormsbecker A, et al. Incidence of influenza in healthy adults and healthcare workers: a systematic review and meta-analysis. *PLoS One*. 2011;6(10):e26239.
96. Buchan SA, Kwong JC. Influenza immunization among Canadian health care personnel: a cross-sectional study. *CMAJ Open*. 2016;4(3):E479–88.
97. Hussain H, McGeer A, McNeil S, Katz K, Loeb M, Simor A, et al. Factors associated with influenza vaccination among healthcare workers in acute care hospitals in Canada. *Influenza Other RespirViruses*. 2018;12(3):319–25.
98. Public Health Agency of Canada. Vaccination Coverage Goals and Vaccine Preventable Disease Reduction Targets by 2025. [Internet]. Vol. 2019. 2019. Available from: <https://www.canada.ca/en/public-health/services/immunization-vaccine-priorities/national-immunization-strategy/vaccination-coverage-goals-vaccine-preventable-diseases-reduction-targets-2025.html#det22>.
99. Bish A, Yardley L, Nicoll A, Michie S. Factors associated with uptake of vaccination against pandemic influenza: a systematic review. *Vaccine*. 2011;29(38):6472–84.
100. Dini G, Toletone A, Sticchi L, Orsi A, Bragazzi NL, Durando P. Influenza vaccination in healthcare workers: A comprehensive critical appraisal of the literature. *HumVaccin Immunother*. 2018;14(3):772–89.
101. Hakim H, Gaur AH, McCullers JA. Motivating factors for high rates of influenza vaccination among healthcare workers. *Vaccine*. 2011;29(35):5963–9.
102. Lytras T, Kopsachilis F, Mouratidou E, Papamichail D, Bonovas S. Interventions to increase seasonal influenza vaccine coverage in healthcare workers: A systematic review and meta-regression analysis. *HumVaccin Immunother*. 2016;12(3):671–81.
103. Schmid P, Rauber D, Betsch C, Lidolt G, Denker ML. Barriers of Influenza Vaccination Intention and Behavior - A Systematic Review of Influenza Vaccine Hesitancy, 2005 - 2016. *PLoS One*. 2017;12(1):e0170550.
104. Vasilevska M, Ku J, Fisman D. Factors associated with healthcare worker acceptance of vaccination: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol*. 2014;35(6):699–708.

105. Accreditation Canada. Infection prevention and control standards. 9th ed. Ottawa: Accreditation Canada; 2013.
106. Grotto I, Mandel Y, Green MS, Varsano N, Gdalevich M, Ashkenazi I, et al. Influenza vaccine efficacy in young, healthy adults. *ClinInfectDis*. 1998;26(4):913–7.
107. Leighton L, Williams M, Aubery D, Parker SH. Sickness absence following a campaign of vaccination against influenza in the workplace. *OccupMed(Lond)*. 1996;46(2):146–50.
108. Nichol KL, Lind A, Margolis KL, Murdoch M, McFadden R, Hauge M, et al. The effectiveness of vaccination against influenza in healthy, working adults. *NEnglJMed*. 1995;333(14):889–93.
109. Department of Health (UK). Flu vaccination for poultry workers. London: Department of Health; 2007.
110. Gray GC, Trampel DW, Roth JA. Pandemic influenza planning: shouldn't swine and poultry workers be included? *Vaccine*. 2007;25(22):4376–81.
111. Bridges CB, Lim W, Hu-Primmer J, Sims L, Fukuda K, Mak KH, et al. Risk of influenza A (H5N1) infection among poultry workers, Hong Kong, 1997-1998. *JInfectDis*. 2002;185(8):1005–10.
112. Puzelli S, Di Trani L, Fabiani C, Campitelli L, De Marco MA, Capua I, et al. Serological analysis of serum samples from humans exposed to avian H7 influenza viruses in Italy between 1999 and 2003. *JInfectDis*. 2005;192(8):1318–22.
113. Tweed SA, Skowronski DM, David ST, Larder A, Petric M, Lees W, et al. Human illness from avian influenza H7N3, British Columbia. *EmergInfectDis*. 2004;10(12):2196–9.
114. Skowronski DM, Li Y, Tweed SA, Tam TW, Petric M, David ST, et al. Protective measures and human antibody response during an avian influenza H7N3 outbreak in poultry in British Columbia, Canada. *CMAJ*. 2007;176(1):47–53.
115. Langley JM, Vanderkooi OG, Garfield HA, Hebert J, Chandrasekaran V, Jain VK, et al. Immunogenicity and safety of 2 dose levels of a thimersol-free trivalent seasonal influenza vaccine in children aged 6-35 months. *J Ped Infect Dis*. 2012;1(1):55–8.
116. Skowronski DM, Hottes TS, Chong M, De Serres G, Scheifele DW, Ward BJ, et al. Randomized controlled trial of dose response to influenza vaccine in children aged 6 to 23 months. *Pediatrics*. 2011;128(2):e276-89.
117. Pavia-Ruz N, Weber MAR, Lau YL, Nelson EAS, Kerdpanich A, Huang LM, et al. A randomized controlled study to evaluate the immunogenicity of a trivalent inactivated seasonal influenza vaccine at two dosages in children 6 to 35 month of age. *Human Vaccines & Immunotherapeutics*. 2013;9(9):1978–88.
118. Skowronski DM, Tweed SA, De Serres G. Rapid decline of influenza vaccine-induced antibody in the elderly: is it real, or is it relevant? *JInfectDis*. 2008;197(4):490–502.

119. Anema A, Mills E, Montaner J, Brownstein JS, Cooper C. Efficacy of influenza vaccination in HIV-positive patients: a systematic review and meta-analysis. *HIVMed*. 2008;9(1):57–61.
120. Cooper C, Hutton B, Fergusson D, Mills E, Klein MB, Boivin G, et al. A review of influenza vaccine immunogenicity and efficacy in HIV-infected adults. *Can J Infect Dis Med Microbiol*. 2008;19(6):419–23.
121. Scharpe J, Evenepoel P, Maes B, Bammens B, Claes K, Osterhaus AD, et al. Influenza vaccination is efficacious and safe in renal transplant recipients. *AmJTransplant*. 2008;8(2):332–7.
122. Manuel O, Humar A, Chen MH, Chernenko S, Singer LG, Cobos I, et al. Immunogenicity and safety of an intradermal boosting strategy for vaccination against influenza in lung transplant recipients. *AmJTransplant*. 2007;7(11):2567–72.
123. Buxton JA, Skowronski DM, Ng H, Marion SA, Li Y, King A, et al. Influenza revaccination of elderly travelers: antibody response to single influenza vaccination and revaccination at 12 weeks. *JInfectDis*. 2001;184(2):188–91.
124. Ljungman P, Nahi H, Linde A. Vaccination of patients with haematological malignancies with one or two doses of influenza vaccine: a randomised study. *BrJHaematol*. 2005;130(1):96–8.
125. Gross PA, Weksler ME, Quinnan GV J, Douglas RG J, Gaerlan PF, Denning CR. Immunization of elderly people with two doses of influenza vaccine. *JClinMicrobiol*. 1987;25(9):1763–5.
126. Mosca F, Tritto E, Muzzi A, Monaci E, Bagnoli F, Iavarone C, et al. Molecular and cellular signatures of human vaccine adjuvants. *ProcNatlAcadSciUSA*. 2008;105(30):10501–6.
127. Calabro S, Tortoli M, Baudner B, Pacitto A, Cortese M, O’Hagan D, et al. Vaccine adjuvants alum and MF59 induce rapid recruitment of neutrophils and monocytes that participate in antigen transport to draining lymph nodes. *Vaccine*. 2011;29(9):1812–23.
128. Seubert A, Monaci E, Pizza M, O’Hagan D, Wack A. The adjuvants aluminum hydroxide and MF59 induce monocyte and granulocyte chemoattractants and enhance monocyte differentiation toward dendritic cells. *JImmunol*. 2008;180(8):5402–12.
129. O’Hagan DT, Rappuoli R, De Gregorio E, Tsai T, Del Giudice G. MF59 adjuvant: the best insurance against influenza strain diversity. *Expert RevVaccines*. 2011;10(4):447–62.
130. Vesikari T, Knuf M, Wutzler P, Karvonen A, Kieninger-Baum D, Schmitt HJ, et al. Oil-in-water emulsion adjuvant with influenza vaccine in young children. *NEnglJMed*. 2011;365(Journal Article):1406–16.
131. Vesikari T, Groth N, Karvonen A, Borkowski A, Pellegrini M. MF59 (R)-adjuvanted influenza vaccine (FLUAD (R)) in children: Safety and immunogenicity following a second year seasonal vaccination. *Vaccine*. 2009;27(Journal Article):6291–5.

132. Vesikari T, Pellegrini M, Karvonen A, Groth N, Borkowski A, Hagan DT, et al. Enhanced immunogenicity of seasonal influenza vaccines in young children using MF59 adjuvant. *PediatrInfectDisJ.* 2009;28(Journal Article):563–71.
133. Della Cioppa G, Vesikari T, Sokal E, Lindert K, Nicolay U. Trivalent and quadrivalent MF59 (R)-adjuvanted influenza vaccine in young children: A dose- and schedule-finding study. *Vaccine.* 2011;29(Generic):8696–704.
134. Zedda L, Forleo-Neto E, Vertruyen A, Raes M, Marchant A, Jansen W, et al. Dissecting the immune response to MF59-adjuvanted and nonadjuvanted seasonal influenza vaccines in children less than three years of age. *PediatrInfectDisJ.* 2015;34(1):73–8.
135. Nolan T, Bravo L, Ceballos A, Mitha E, Gray G, Quiambao B, et al. Enhanced and persistent antibody response against homologous and heterologous strains elicited by a MF59-adjuvanted influenza vaccine in infants and young children. *Vaccine.* 2014;32(46):6146–56.
136. Vaarala O, Vuorela A, Partinen M, Baumann M, Freitag TL, Meri S, et al. Antigenic differences between AS03 adjuvanted influenza A (H1N1) pandemic vaccines: implications for pandemrix-associated narcolepsy risk. *PLoS One.* 2014;9(12):e114361.
137. Jain VK, Rivera L, Zaman K, Espos Jr. RA, Sirivichayakul C, Quiambao BP, et al. Vaccine for prevention of mild and moderate-to-severe influenza in children. *NEnglJMed.* 2013;369(26):2481–91.
138. Haber P, Moro PL, Lewis P, Woo EJ, Jankosky C, Cano M. Post-licensure surveillance of quadrivalent inactivated influenza (IIV4) vaccine in the United States, Vaccine Adverse Event Reporting System (VAERS), July 1, 2013– May 31, 2015. *Vaccine.* 2016;34(22):2507–12.
139. Eposito A, Nauta J, Lapini G, et. al. Efficacy and safety of a quadrivalent influenza vaccine in children aged 6–35 months: A global, multiseasonal, controlled, randomized Phase III study. *Vaccine.* 2022;40(18):2626–34.
140. Diaz Granados CA, Dunning AJ, Robertson CA, Talbot HK, Landolfi V, Greenberg DP. Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty. *JAmGeriatrSoc.* 2014;62(Journal Article):S37–8.
141. Izurieta HS, Thadani N, Shay DK, Lu Y, Maurer A, Foppa IM, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. *Lancet InfectDis.* 2015;15(3):293–300.
142. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *JInfectDis.* 2009;200(2):172–80.
143. Couch RB, Winokur P, Brady R, Belshe R, Chen WH, Cate TR, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. *Vaccine.* 2007;25(44):7656–63.

144. Keitel WA, Atmar RL, Cate TR, Petersen NJ, Greenberg SB, Ruben F, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. *ArchInternMed*. 2006;166(10):1121–7.
145. Sanofi Pasteur. Study of Fluzone® influenza virus vaccine 2011-2012 formulation (intramuscular route) among adults [Internet]. Vol. 2014. 2013. Available from: <https://www.clinicaltrials.gov/ct2/show/study/NCT01430819>
146. Tsang P, Gorse GJ, Strout CB, Sperling M, Greenberg DP, Ozol-Godfrey A, et al. Immunogenicity and safety of Fluzone intradermal and high-dose influenza vaccines in older adults >65 years of age: A randomized, controlled, phase II trial. *Vaccine*. 2014;32(21):2507–17.
147. Nace DA, Lin CJ, Ross TM, Saracco S, Churilla RM, Zimmerman RK. Randomized, controlled trial of high-dose influenza vaccine among frail residents of long-term care facilities. *JInfectDis*. 2015;211(12):1915–24.
148. DiazGranados CA, Dunning AJ, Jordanov E, Landolfi V, Denis M, Talbot HK. High-dose trivalent influenza vaccine compared to standard dose vaccine in elderly adults: safety, immunogenicity and relative efficacy during the 2009-2010 season. *Vaccine*. 2013;31(6):861–6.
149. DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *NEnglJMed*. 2014;371(7):635–45.
150. Sanofi Pasteur. Product Monograph: FLUZONE® High-Dose Quadrivalent [Internet]. 2019 [cited 2020 Sep 15]. Available from: <https://Health-Products.Canada.Ca/Dpd-Bdpp/Info.Do?Lang=En&Code=99020>
151. Chang LJ, Meng Y, Janoszyk H, et. al. Safety and Immunogenicity of High-Dose Quadrivalent Influenza Vaccine in Adults ≥65 Years of Age: A Phase 3 Randomized Clinical Trial. *Vaccine*. 2019;37(39):5825–34.
152. Dunkle LM, Izikson R, Patriarca P, Goldenthal KL, Muse D, Callahan J, et al. Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older. *N Engl J Med*. 2017 Jun 22;376(25):2427–36.
153. Belongia EA, Levine MZ, Olaiya O, Gross FL, King JP, Flannery B, et al. Clinical trial to assess immunogenicity of high-dose, adjuvanted, and recombinant influenza vaccines against cell-grown A(H3N2) viruses in adults 65 to 74 years, 2017–2018. *Vaccine*. 2020 Mar;38(15):3121–8.
154. Shinde V, Cai R, Plested J, Cho I, Fiske J, Pham X, et al. Induction of Cross-Reactive Hemagglutination Inhibiting Antibody and Polyfunctional CD4+ T-Cell Responses by a Recombinant Matrix-M–Adjuvanted Hemagglutinin Nanoparticle Influenza Vaccine. *Clinical Infectious Diseases*. 2021;73(11):e4278–87.
155. Dunkle LM, Izikson R, Patriarca PA, Goldenthal KL, Muse D, Cox MMJ. Randomized Comparison of Immunogenicity and Safety of Quadrivalent Recombinant Versus

- Inactivated Influenza Vaccine in Healthy Adults 18–49 Years of Age. *The Journal of Infectious Diseases*. 2017 Dec 5;216(10):1219–26.
156. Wang W, Alvarado-Facundo E, Vassell R, Collins L, Colombo RE, Ganesan A, et al. Comparison of A(H3N2) Neutralizing Antibody Responses Elicited by 2018–2019 Season Quadrivalent Influenza Vaccines Derived from Eggs, Cells, and Recombinant Hemagglutinin. *Clinical Infectious Diseases*. 2021 Dec 6;73(11):e4312–20.
 157. Cowling BJ, Perera RAPM, Valkenburg SA, Leung NHL, Iuliano AD, Tam YH, et al. Comparative Immunogenicity of Several Enhanced Influenza Vaccine Options for Older Adults: A Randomized, Controlled Trial. *Clinical Infectious Diseases*. 2020 Oct 23;71(7):1704–14.
 158. Gouma S, Zost SJ, Parkhouse K, Branche A, Topham DJ, Cobey S, et al. Comparison of Human H3N2 Antibody Responses Elicited by Egg-Based, Cell-Based, and Recombinant Protein-Based Influenza Vaccines During the 2017–2018 Season. *Clinical Infectious Diseases*. 2020 Sep 12;71(6):1447–53.
 159. Dawood FS, Naleway AL, Flannery B, Levine MZ, Murthy K, Sambhara S, et al. Comparison of the Immunogenicity of Cell Culture-Based and Recombinant Quadrivalent Influenza Vaccines to Conventional Egg-Based Quadrivalent Influenza Vaccines Among Healthcare Personnel Aged 18–64 Years: A Randomized Open-Label Trial. *Clinical Infectious Diseases*. 2021 Dec 6;73(11):1973–81.
 160. European Medicines Agency (EMA). Assessment report: Supemtek [Internet]. Vol. 2021. 2020. Available from: https://www.ema.europa.eu/en/documents/assessment-report/supemtek-epar-public-assessment-report_en.pdf
 161. US Food and Drug Administration. Guidance for industry: Clinical data needed to support the licensure of seasonal inactivated influenza vaccines [Internet]. Vol. 2021. 2007. Available from: <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091990.pdf>
 162. Woo EJ, Moro PL. Postmarketing safety surveillance of quadrivalent recombinant influenza vaccine: Reports to the vaccine adverse event reporting system. *Vaccine*. 2021 Mar;39(13):1812–7.
 163. Cowling BJ, Thompson MG, Ng TWY, Fang VJ, Perera RAPM, Leung NHL, et al. Comparative Reactogenicity of Enhanced Influenza Vaccines in Older Adults. *The Journal of Infectious Diseases*. 2020 Sep 14;222(8):1383–91.
 164. National Advisory Committee on Immunization. Recommendations on the use of live, attenuated influenza vaccine (FluMist®): supplemental statement on seasonal influenza vaccine 2011-2012. *CanCommunDisRep*. 2011;37(7):1–77.
 165. Block SL, Falloon J, Hirschfield JA, Krilov LR, Dubovsky F, Yi T, et al. Immunogenicity and safety of a quadrivalent live attenuated influenza vaccine in children. *PediatrInfectDisJ*. 2012;31(7):745–51.

166. Block SL, Yi T, Sheldon E, Dubovsky F, Falloon J. A randomized, double-blind noninferiority study of quadrivalent live attenuated influenza vaccine in adults. *Vaccine*. 2011;29(50):9391–7.
167. MedImmune. A randomized, partially blind active controlled study to evaluate the immunogenicity of MEDI8662 in adults 18-49 years of age [Internet]. Vol. 2015. 2011. Available from: <https://clinicaltrials.gov/ct2/show/results/NCT00952705?term=MEDI8662&rank=1>
168. Public Health Agency of Canada. Recommendation on the Use of Live Attenuated Influenza Vaccine (LAIV) in HIV-Infected Individuals [Internet]. 2020. Available from: <https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/live-attenuated-influenza-vaccine-hiv-infected-individuals.html>

Appendix A: Abbreviations for influenza vaccines

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

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

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

^b 15 µg HA per strain.

^c 7.5 µg (in 0.25 mL) or 15 µg (in 0.5 mL) HA per strain.

^d 60 µg HA per strain.

^e 45 µg HA per strain

Appendix B: Characteristics of influenza vaccines available for use in Canada, 2023–2024^a

Product name (manufacturer)	Vaccine Characteristic									
	Vaccine type	Route of administration	Authorized ages for use	Antigen content for each vaccine strain	Adjuvant	Formats available	Post-puncture shelf life for multi-dose vials	Thimerosal	Antibiotics (traces)	Production medium
Quadrivalent										
Flulaval® Tetra (GSK)	IIV4-SD (split virus)	IM	6 months and older	15 µg HA /0.5 mL dose	None	5 mL multi-dose vial	28 days	Yes (multi-dose vial only)	None	Egg (Avian)
Fluzone® Quadrivalent (Sanofi)	IIV4-SD (split virus)	IM	6 months and older	15 µg HA /0.5 mL dose	None	5 mL multi-dose vial Single-dose pre-filled syringe without attached needle	Up to expiry date indicated on vial label	Yes (multi-dose vial only)	None	Egg (Avian)
Afluria® Tetra (Seqirus)	IIV4-SD (split virus)	IM	5 years and older	15 µg HA /0.5 mL dose	None	5 mL multi-dose vial Single dose pre-filled syringe without attached needle	Up to expiry date indicated on vial label	Yes (multi-dose vial only)	Neomycin and polymyxin B	Egg (Avian)
Influvac® Tetra (BGP Pharma ULC, operating as Mylan, d.b.a. Viatris Canada)	IIV4-SD (subunit)	IM or deep subcutaneous injection	6 months and older	15 µg HA /0.5 mL dose	None	Single dose pre-filled syringe with or without attached needle	Not applicable	No	Gentamicin or neomycin and polymyxin B ^b	Egg (Avian)
Flucelvax® Quad (Seqirus)	IIV4-cc (subunit)	IM	6 months and older	15 µg HA /0.5 mL dose	None	5 mL multi-dose vial Single dose pre-filled syringe without attached needle	28 days	Yes (multi-dose vial only)	None	Cell culture (Mammalian)
Fluzone® High-Dose Quadrivalent (Sanofi)	IIV4-HD (split virus)	IM	65 years and older	60 µg HA /0.7 mL dose	None	Single dose pre-filled syringe without attached needle	Not applicable	No	None	Egg (Avian)
Supemtek™ (Sanofi)	RIV4 (recombinant protein)	IM	18 years and older	45 µg HA /0.5 mL dose	None	Single dose pre-filled syringe without attached needle	Not applicable	No	None	Recombinant (Insect vector-expressed)

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
FluMist® Quadrivalent (AstraZeneca)	LAIV4 (live attenuated)	Intranasal	2 to 59 years	10 ^{6.5-7.5} FFU of live attenuated reassortants /0.2 mL dose (given as 0.1 mL in each nostril)	None	Single use pre-filled glass sprayer	Not applicable	No	Gentamicin	Egg (Avian)
Trivalent										
Fluad Pediatric® and Fluad® (Seqirus)	IIV3-Adj (subunit)	IM	Pediatric: 6 to 23 months Adult: 65 years and older	Pediatric: 7.5 µg HA /0.25 mL dose Adult: 15 µg HA /0.5 mL dose	MF59	Single dose pre-filled syringe without a needle	Not applicable	No	Kanamycin and neomycin	Egg (Avian)

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

^a Full details of the composition of each vaccine authorized for use in Canada, including other non-medicinal ingredients, and a brief description of its manufacturing process can be found in the product monograph.

^b Neomycin and polymyxin B are only used if gentamicin cannot be used. No trace amounts of neomycin or polymyxin B are present if gentamicin was used.

Appendix C: Additional information on vaccine efficacy, effectiveness, immunogenicity, and safety

Inactivated Influenza Vaccine (IIV)

Immunological considerations related to children

Young children have a high burden of illness and their vaccine-induced immune response is not as robust as older children. However, some studies suggest moderate improvement in antibody response in young children, without an increase in reactogenicity, with the use of a full vaccine dose (0.5 mL) for IIV-SDs^{115–117}. 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

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, a literature review identified no evidence for a subsequent antibody decline that was any more rapid in older adults than in younger age groups¹¹⁸.

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^{119–122}.

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^{35,123–125}.

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

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

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

All IIV-SD products expected to be available in Canada for the 2023-2024 season are quadrivalent. Refer to the [Statement on Seasonal Influenza Vaccine for 2022-2023](#) for more detailed information on the use of IIV3-SD and a summary of efficacy, effectiveness, immunogenicity, and safety evidence across eligible age groups.

Adjuvanted inactivated influenza vaccine (IIV3-Adj)

Vaccines currently authorized for use:

- Flud[®] (Seqirus)
- Flud Pediatric[®] (Seqirus)

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

Efficacy and effectiveness

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

Immunogenicity

The mechanism of action of MF59 is not fully determined and has primarily been studied using in vitro and mouse models. From these studies, it appears that MF59 may act differently from aluminum-based adjuvants. These studies show that MF59 acts in the muscle fibres to create a local immune-stimulatory environment at the injection site¹²⁶. 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^{127,128}. MF59 further facilitates the internalization of antigen by these dendritic cells^{127,129}. 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 priming¹²⁷.

There is evidence from RCTs that IIV3-Adj elicits non-inferior immune responses compared to the unadjuvanted 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 [NACI Statement on Seasonal Influenza Vaccine for 2018–2019](#) for more information on the immunogenicity of IIV3-Adj in adults 65 years of age and older. for more information on the immunogenicity of IIV3-Adj in adults 65 years of age and older.

Safety

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

additional information on the safety of IIV3-Adj in adults 65 years of age and older. for additional information on the safety of IIV3-Adj in adults 65 years of age and older.

2. 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 unadjuvanted IIV3-SD¹³⁰. However, the findings of this study should be interpreted with caution. The comparator unadjuvanted IIV3 used in this trial was shown, in an unrelated study, to induce a lower immune response compared to another unadjuvanted 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 unadjuvanted IIV3-SD for children less than 36 months of age, which is lower than the dose of 0.5 mL of unadjuvanted 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^{130–135}. In particular, a single dose of IIV3-Adj is more immunogenic than a single dose of IIV3-SD and has been shown in one study to produce greater GMTs than 2 doses of IIV3-SD against influenza A¹³⁵. 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 unadjuvanted 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 unadjuvanted 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 adjuvanted and unadjuvanted vaccines compared to the corresponding 7.5 µg formulations¹³³.

There are currently no data on the effects of long-term or repeated administration of adjuvanted influenza vaccines in children. The most significant experience with an adjuvanted 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 two 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 two A(H1N1) pandemic vaccines¹³⁶. However, the pandemic vaccine was a single strain adjuvanted vaccine administered only during one season, and it is unknown what effects a multi-strain adjuvanted vaccine or an adjuvanted vaccine administered for more than one season may have in young children.

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

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

Vaccines currently authorized for use:

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

1. Literature review on quadrivalent influenza vaccines (IIV4)

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

Efficacy and effectiveness

One 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 vaccine¹³⁷.

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-SD¹³⁸.

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

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

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

A second age indication extension to children 6 to 35 months was authorized on March 8, 2022. NACI reviewed the Health Canada assessment of the efficacy, immunogenicity, and safety of Influvac Tetra compared to non-influenza vaccines (NIVs) in children 6 to 35 months of age (n= 2,007). The RCT was conducted across Europe and Asia over three influenza seasons (Southern Hemisphere 2019 and the 2017–2018 and 2018–2019 Northern Hemisphere influenza seasons). Refer to the [product monograph](#) for further details and supporting evidence on the use of Influvac Tetra in the various age groups mentioned above.

Efficacy and effectiveness

The absolute vaccine efficacy of Influvac Tetra compared with NIV against any seasonal strain in children 6 to 35 months was 54% (VE: 0.54; 95% CI: 0.37 to 0.66%). The estimated vaccine efficacy was higher for antigenically matching strains (VE: 0.68; 95% CI: 0.45 to 0.81%). Vaccine efficacy was estimated to be 21% in children 6 to 11 months of age (VE: 0.21; 95 % CI: -0.70 to 0.64%); however, the study was not powered for subgroup analyses by age group¹³⁹.

Immunogenicity

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

A review of clinical data submitted to Health Canada by the manufacturer was conducted to examine the use of Influvac Tetra in children 6 months to less than 3 years (i.e., 35 months) of age. Specifically, the immunogenicity of Influvac Tetra was assessed in a phase 3 RCT conducted in children 6 to 35 months of age. Participants experienced a substantial increase in

hemagglutinin inhibition antibody titres in response to vaccination against influenza type A [A(H1N1) and A(H3N2)], based on GMTs, geometric mean fold increase (GMFI), seroconversion rates and seroprotection rates. However, immunogenicity results for influenza type B (B/Yamagata lineage and B/Victoria lineage) were noted to be low for the four immunogenicity outcomes included in the study. Refer to the product monograph for additional details.

Safety

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

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

Vaccine currently authorized for use:

- Flucelvax[®] Quad (Seqirus)

Methods

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

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

An age indication extension for the use of Flucelvax Quad in adults and children 2 years and older was authorized on March 8, 2021. Recommendations were developed based on a review of the Health Canada assessment of a multi-country phase 3/4 RCT on the efficacy, immunogenicity and safety of Flucelvax Quad in children 2 years to less than 18 years of age conducted over three 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 one SAE in each study arm. No SAE were determined to be related to receipt of the study vaccines. Overall, there is fair evidence that IIV4-cc is a safe and well-tolerated alternative to conventional egg-based influenza vaccines for children and adults.

High-dose inactivated influenza vaccine (IIV-HD)

Vaccines currently authorized for use:

- Fluzone® High-Dose Quadrivalent (Sanofi)

The trivalent formulations of high-dose inactivated influenza vaccines have recently been discontinued and are no longer authorized or available for use in Canada. All IIV-HD products expected to be available in Canada for the 2023-2024 season are quadrivalent.

Methods

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

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

Efficacy and effectiveness

There is good evidence that Fluzone High-Dose (IIV3-HD) provides better protection compared with IIV3-SD in adults 65 years of age and older. Two 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^{140,141}.

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^{142–149}. Across all three 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 (cite). There is good evidence that the immunogenicity for Fluzone High Dose Quadrivalent (IIV4-HD) is non-inferior to IIV3-HD^{150,151}. 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-HD¹⁵¹. Immunogenicity for IIV4-HD was superior for the influenza B strain not contained within the trivalent high dose vaccine¹⁵¹.

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 two 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 AEs¹⁵¹.

Recombinant quadrivalent influenza vaccine (RIV4)

Vaccines currently authorized for use:

- Supemtek™ (Sanofi)

Methods

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

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

Efficacy and effectiveness

One RCT that evaluated the efficacy of RIV4 demonstrated that Supemtek was statistically significantly more efficacious than egg-based IIV4-SD in preventing laboratory confirmed influenza illness in adults 50 years of age and older¹⁵². Non-inferiority assessments suggested

that RIV4 may be more effective than IIV4-SD influenza vaccines against laboratory-confirmed influenza A virus infection, but not laboratory-confirmed influenza B virus infection in older adults. Overall, there is fair evidence (of low certainty) that the efficacy of RIV4 is non-inferior to traditional egg-based comparators, based on data in adults aged 50 years and older.

Immunogenicity

Eight RCTs^{152–159} assessed the immunogenicity of RIV4. The immunogenicity outcomes reported included seroconversion rates^{152–159}, seroprotection rates^{152–154,159}, and GMTR^{152,155,159,160}. Across the eight studies, Supemtek demonstrated non-inferiority compared to previously authorized IIVs (IIV3-HD, IIV3-Adj, IIV4-SD, and IIV4-cc) against A(H1N1), most strains of A(H3N2), and B/Yamagata lineage. In some studies, RIV4 did not meet non-inferiority criteria against B/Victoria lineage compared to previously authorized IIVs based on seroconversion^{152,155}, seroprotection¹⁵², and GMTR¹⁶¹.

Pooled seroconversion data from three^{152,154,157} of the eight RCTs conducted in adult participants 50 years of age and older identified that RIV4 induced similar antibody responses compared to IIV4-SD, IIV3-HD, and IIV3-Adj.

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

Safety

Six studies^{152,154,155,157,162,163} assessed the safety of RIV4 in adults, including five RCTs and one post-marketing surveillance study using data from the United States Vaccine Adverse Event Reporting System (VAERS)¹⁶². The five RCTs found RIV4 to be safe and well-tolerated compared to conventional egg-based IIVs (noting that no published clinical data pertaining to safety of vaccination with RIV4 during pregnancy were available at the time of the review). Most AE reported to VAERS following RIV4 administration were non-serious. When data from two RCTs^{152,154} conducted among adult participants 50 years of age and older were pooled, no difference in the odds of experiencing a SAE following administration of RIV4 and traditional egg-based IIV3-HD and IIV4-SD vaccine comparators was detected. Overall, there is evidence of moderate certainty that RIV4 is a safe and well-tolerated alternative to conventional egg-based influenza vaccines for adults.

Live Attenuated Influenza Vaccine (LAIV)

Vaccine currently authorized for use:

- FluMist® Quadrivalent (AstraZeneca)

All LAIV products expected to be available in Canada for the 2023-2024 season are quadrivalent.

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 two 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)⁶⁰. 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.

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 well¹⁶⁴. 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^{165–167}.

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-SD¹⁶⁴. This finding is expected to be the same for recipients of LAIV4; however, pre-licensure clinical studies for LAIV4 were conducted only in adults and children 2 years of age and older. LAIV4 is not authorized in children less than 2 years of age.

Studies on LAIV3 have shown that vaccine virus can be recovered by nasal swab in children and adults following vaccination (i.e., “shedding”). The frequency of shedding decreases with increasing age and time since vaccination. Shedding is generally below the levels needed to

transmit infection, although in rare instances, shed vaccine viruses can be transmitted from vaccine recipients to unvaccinated people. Refer to the NACI [Recommendations on the Use of Live, Attenuated Influenza Vaccine \(FluMist®\): Supplemental Statement on Seasonal Influenza Vaccine for 2011–2012](#) for more information on LAIV and viral shedding.

Considerations related to children living with HIV infection

Following a review of the literature regarding the use of LAIV in individuals living with HIV, NACI concluded that LAIV is immunogenic in children with stable HIV infection on HAART and with adequate immune function. In addition, NACI concluded that LAIV appears to have a similar safety profile as IIV in children on HAART and with stable HIV infection with regard to frequency and severity of AEs¹⁶⁸. 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 HAART 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/ μ L if 2 to 5 years of age, or \geq 200/ μ 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.