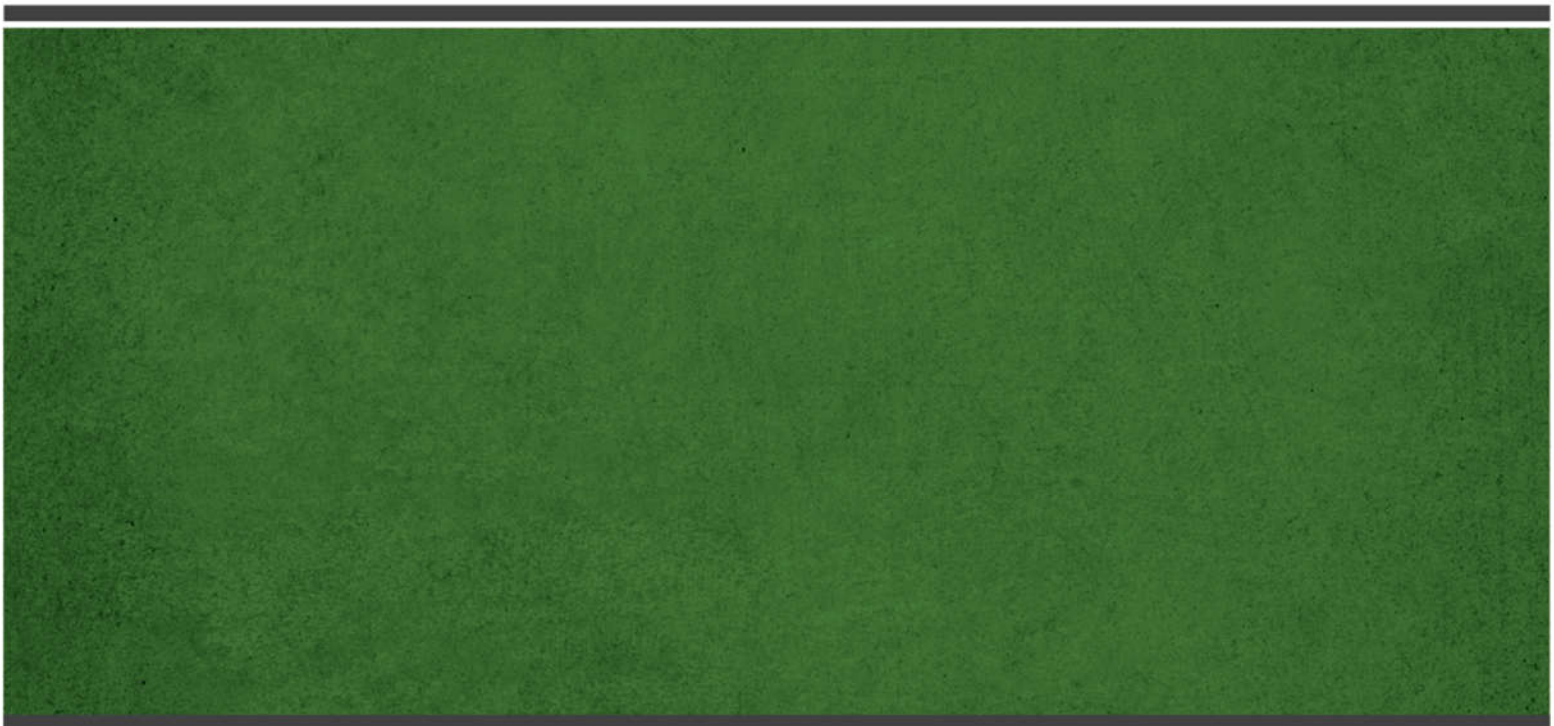
An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2022–2023



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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the 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 considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Over the coming years NACI will be refining methodological approaches to include these factors. Not all NACI Statements will require in-depth analyses of all programmatic factors. As NACI works towards full implementation of the expanded mandate, select Statements will include varying degrees of programmatic analyses for public health programs.

PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) 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 conflicts of interest.

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I. Introduction

This document, the "Advisory Committee Statement: Canadian Immunization Guide Chapter on Influenza and National Advisory Committee on Immunization (NACI) Statement on Seasonal Influenza Vaccine for 2022–2023", updates NACI's recommendations regarding the use of seasonal influenza vaccines.

I.1 New or Updated Information for 2022–2023

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 COVID-19

Seasonal influenza presents an ongoing disease burden in Canada during the fall and winter months, however the epidemiology of influenza has changed during the course of the pandemic. Influenza vaccine is the most effective way to prevent influenza illness and influenza-related complications, and will be an important component of managing health care system capacity during the influenza season in the context of any 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 and added to as necessary throughout the influenza season as new evidence emerges. This web page should be considered in concert with recommendations regarding the use of seasonal influenza vaccines provided in this NACI Statement.

Guidance on concomitant 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 seasonal influenza vaccines or LAIV) for those aged 12 years and older as of September 2021.

Readers should consult the current NACI COVID-19 guidance and the Canadian Immunization Guide (CIG) COVID-19 chapter for updated NACI guidance and further information on concomitant administration of COVID-19 vaccines with influenza vaccines and across all eligible age groups.

Inclusion of recombinant quadrivalent seasonal influenza vaccine

Supemtek™ (RIV4) is a recombinant quadrivalent seasonal influenza vaccine produced by Sanofi Pasteur that was authorized for use in Canada on January 14, 2021, in adults 18 years of age and older. Supemtek is the first and, to date, the only recombinant influenza vaccine licensed in Canada. Based on a review of available pre-licensure and post-market clinical trial and surveillance data, NACI has concluded that Supemtek may be considered for use among the quadrivalent influenza vaccines offered to adults 18 years of age and older *(Discretionary NACI Recommendation).* Refer to the NACI Supplemental Statement: Recombinant Influenza Vaccines, which will be forthcoming, for additional information supporting this recommendation.

Updated recommendations on mammalian cell culture-based quadrivalent influenza vaccine

Flucelvax® Quad (IIV4-cc) is the first and, to date, the only mammalian cell culture-based inactivated seasonal influenza vaccine available for use in Canada. It was first authorized for use in Canada in adults and children 9 years of age and older on November 22, 2019. 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.

On March 8, 2021, Health Canada approved an expanded age indication for the use of Flucelvax Quad in children down to 2 years 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 may be considered among the quadrivalent influenza vaccines offered to adults and children 2 years of age and older. Refer to section IV.1 Inactivated Influenza Vaccine (IIV) later in the statement for additional information supporting this recommendation.

I.2 Abbreviations for Influenza Vaccines

The abbreviations used in this document for the different influenza vaccines are as follows:

Table 1. NACI influenza vaccine abbreviations

Influenza vaccine category	Formulation	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, cell culture-based	IIV4-cc
		High dose[d], unadjuvanted, IM administered, egg-based	IIV4-HD
Recombinant influenza vaccine (RIV)	Quadrivalent (RIV4)	Recombinant[e], unadjuvanted, IM administered	RIV4
Live attenuated influenza vaccine (LAIV)	Trivalent (LAIV3)	Unadjuvanted, Nasal spray, egg-based	LAIV3
	Quadrivalent (LAIV4)	Unadjuvanted, Nasal spray, egg-based	LAIV4

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

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

I.3 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.

Annual recommendations on the use of influenza vaccine in Canada are developed by the NACI Influenza Working Group (IWG) for consideration by NACI. Recommendations are developed based on a review of a variety of issues, which can include: the burden of influenza illness and the target populations for vaccination; efficacy, effectiveness, immunogenicity, and safety of influenza vaccines; vaccine schedules; and other aspects of influenza immunization. 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 economics, ethics, equity, feasibility, and acceptability. 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.

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

Although vaccination before the onset of the influenza season is strongly preferred, influenza vaccine may still be administered up until the end of the season. Delayed administration may result in lost opportunities to prevent infection from exposures that occur prior to vaccination, and individuals seeking 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 demand on the healthcare system in the fall and winter months. During the COVID-19 pandemic, influenza vaccination remains a critical tool to minimize the morbidity and mortality related to potential influenza and COVID-19 co-circulation and to reduce the burden on the Canadian health care system to enhance the capacity to respond to ongoing COVID-19 activity.

II. Canadian Immunization Guide Chapter on Influenza: Clinical Information for Vaccine Providers

The Canadian Immunization Guide (CIG) is written primarily for health care providers (frontline clinicians and public health practitioners) but it is also used by policy makers, program planners, and the general public. The CIG has been a trusted, reader-friendly summary of the vaccine statements provided by NACI since 1979.

The information in this section replaces the influenza chapter of the CIG. With a new NACI Statement on Seasonal Influenza Vaccine required each year, readers will have quick access to the information that they require within one document, whether it is the relevant influenza vaccine information written primarily for frontline vaccine providers as is found in this section, or the more detailed technical information that is found in the rest of this statement, commencing in Section III.

II.1 Key Information

The following highlights key information for vaccine providers. Please refer to the remainder of this statement for additional details.

1. 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 occurred globally with an annual attack rate estimated at 5–10% in adults and 20–30% in children [(1)].

- Symptoms of influenza typically 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. Most people will recover within a week to 10 days, but some people are at greater risk of severe complications, such as pneumonia or death. Influenza infection can also worsen certain chronic conditions, such as heart disease [(2)].

- Inactivated influenza vaccines (IIV) (which include standard dose, high dose, cell culture-based or adjuvanted vaccines), recombinant influenza vaccine (RIV), and live attenuated influenza vaccine (LAIV) are all authorized for use in Canada; some protect against 3 strains of influenza (i.e., trivalent formulations, IIV3) and some protect against 4 strains of influenza (i.e., quadrivalent formulations: IIV4, RIV4, or LAIV4).

- The influenza vaccines are safe and well-tolerated. The IIV cannot cause influenza illness because IIV do not contain live virus. Similarly, the RIV does not contain live influenza virus but instead contains non-infectious viral proteins. The live attenuated influenza vaccines contain weakened viruses.

2. 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 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 contraindications to the vaccine, with focus on the groups for whom influenza vaccination is particularly recommended (see List 1). 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 influenza vaccine is less immunogenic than in older children and adults and does not confer sufficient protection to make the vaccine useful in this age group [3]. Currently, authorized influenza vaccines are not indicated for use in infants less than 6 months of age. For these reasons, NACI recommends that influenza vaccine should not be offered to infants less than 6 months of age. However, as 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, and any household contacts and care providers of infants (see List 1).

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 (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 6–59 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 neurodevelopment 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);
  - 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 pregnant individuals;
- 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 0–59 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 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.

3. 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. Therefore, the choice of influenza vaccine has become more complex. Refer to Section II.5 for recommendations on the choice of influenza vaccine by age group.

Dose and route of administration
The dose and route of administration vary by influenza vaccine product (see Section II.6 for details). For recommendations on which vaccines are recommended in different age groups, refer to Table 2.

- With the exception of IIV4-HD, most unadjuvanted IIVs are administered as a 0.5 mL intramuscular (IM) injection for everyone 6 months of age and older, The following IIVs are administered as a 0.5 mL IM injection but are only authorized in older age groups: Afluria® Tetra (5 years and older), Influvac® Tetra (3 years and older), and Flucelvax® Quad (2 years and older);

- IIV4-HD (Fluzone® High-Dose Quadrivalent) is administered as a 0.7 mL IM injection for adults 65 years of age and older;

- MF59-adjuvanted IIV3 (Fluad®) is administered as a 0.5 mL IM injection 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 6–23 months of age;

- RIV4 (Supemtek™) is administered as a 0.5 mL IM injections 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) for individuals 2–59 years of age.

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 properly 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, RIV4 and LAIV), NACI recommends that influenza vaccination should not be given to:

- People who have had an anaphylactic reaction to a specific influenza immunization, or to any of the components of a specific influenza vaccine, with the exception of egg (refer to Section II.7 for more information);
    - 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 expert. 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.
    - 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. The IIV4-cc and RIV4 are completely egg-free (ovalbumin-free).
    - As with any vaccine product, vaccine providers should be prepared for managing possible allergic reactions including anaphylaxis, and have the necessary equipment to respond to a vaccine emergency at all times.
- People who have developed Guillain-Barré Syndrome (GBS) within 6 weeks of a previous influenza vaccination (refer to Section II.7 for more information), unless another cause was found for the GBS.
    - For those 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 immune compromising conditions, with the exception of children 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 (see Section IV.2 for more information);
    - Immune compromising conditions may be due to underlying disease, therapy, or both.
- 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 2–17 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 is limited data for the use of LAIV in this population.

- LAIV should not be administered until 48 hours after antiviral agents active against influenza (e.g., oseltamivir, zanamivir) are stopped, and those 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 anti-viral 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 IIV could be given at any time.

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 and their contents and to Vaccine Safety in Part 2 of the CIG for information regarding the management of adverse events (AEs), including anaphylaxis.

Precautions

NACI recommends that:

- Influenza vaccination should usually be postponed in people with serious acute illnesses until their symptoms have abated;
    - In a regular influenza season, vaccination should not be delayed because of minor or moderate acute illness, with or without fever. During the COVID-19 pandemic, immunizers should refer to Guidance for Influenza Vaccine delivery in the presence of COVID-19 for amended advice on this issue from the Public Health Agency of Canada.

- If significant nasal congestion is present that might impede delivery of LAIV to the nasopharyngeal mucosa, IIV can be administered or LAIV can be deferred until resolution of the congestion;

- 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; 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.

Refer to Section II.7 for additional information on influenza vaccine-related precautions.

Concomitant administration with other vaccines

NACI recommends that:

- Administration of COVID-19 vaccines may occur at the same time as, or at any time before or after influenza immunization (including all seasonal influenza vaccines or LAIV) for those aged 12 years and older as of September 2021. Readers should consult the Canadian Immunization Guide COVID-19 chapter for updated NACI guidance on the concomitant 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 concomitantly with standard dose, unadjuvanted vaccine [(4)].
- Different injection sites and separate needles and syringes should be used for concomitant parenteral injections.

4. Why

- Vaccination is the most effective way to prevent influenza and its complications.
- Vaccinated individuals who are protected from influenza will not pass infection to others.
- Although most people will recover fully from influenza infection in 7–10 days, influenza can lead to severe disease, and/or complications, including hospitalization and death.
- Annual vaccination is required because the specific strains in the vaccine are reviewed each year by WHO and are often changed to provide a better match against the viruses expected to circulate in that given year, and because the body's immune response to influenza vaccination is transient and may not persist beyond a year.

II.2 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, which can result in hospitalization or death. Certain populations, such as young children, older adults, and those with chronic health conditions, may be 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 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 contribute variably to influenza illness each year. Globally, influenza circulation has been at a historical low since the onset of the COVID-19 pandemic, and with the implementation of non-pharmaceutical public health measures against COVID-19 in Canada. There has been a virtual absence of any B/Yamagata detections globally [(5)].

Over time, antigenic variation (antigenic drift) of strains occurs within an influenza A subtype or a B lineage. The ever-present possibility of antigenic drift, which may occur in one or more influenza virus strains, requires seasonal influenza vaccines to be reformulated 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 1–4 days. [(6)]. 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 0–59 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 can last for many months, and more than one influenza strain typically circulates each season.

Spectrum of clinical illness

Symptoms typically 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. Most people will recover within a week or 10 days. More rarely, central nervous system involvement, 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.

Disease incidence

Global
Worldwide, annual epidemics result in approximately one billion cases of influenza, three to five million cases of severe illness, and 290,000 to 650,000 deaths. Prior to the COVID-19 pandemic, the global annual attack rate was estimated to be 5–10% in adults and 20–30% in children [(1)]. For current international influenza activity information, refer to WHO's Global Influenza Program website.

National
Together, influenza and pneumonia are ranked among the top 10 leading causes of death in Canada [(7)]. 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. Although the burden of influenza can vary from year to year, it is estimated that there are an average of 12,200 hospitalizations related to influenza and approximately 3,500 deaths attributable to influenza annually [(8, 9)]. Current influenza activity information 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.

II.3 Vaccine Products Authorized for Use in Canada

This section describes the influenza vaccine products that are authorized for use in Canada for the 2022–2023 season. All influenza vaccines available in Canada have been authorized by Health Canada. However, not all products authorized for use are necessarily available in the marketplace. The vaccine manufacturers determine whether they will make any or all of their products available in a given 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.

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 more than 6 months prior to the start of the 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 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 2022–2023 influenza season can be found in Appendix A. For complete prescribing information, readers should consult the product monographs available through Health Canada's Drug Product Database.

Inactivated influenza vaccine (IIV)

IIVs currently authorized for use in Canada are a mix of split virus and subunit vaccines. 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. All IIVs currently available in Canada are produced in eggs, with the exception of 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, through the use of 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 unadjuvanted, contain a standard dose of antigen (15 µg HA per strain), and are administered as a 0.5 mL dose by IM injection. Influvac Tetra may be administered by IM or deep subcutaneous injection.

The adjuvanted IIVs (IIV-Adj) currently authorized for use in Canada are trivalent subunit IIVs that contain 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. IIV-Adj contains 7.5 µg HA per strain administered as a 0.25 mL dose by IM injection for children 6–23 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 is given as an intranasal spray. The influenza viruses contained in LAIV are attenuated so that they do not cause influenza and are cold-adapted and temperature sensitive, so that they replicate in the nasal mucosa rather than the lower respiratory tract. LAIV contains standardized quantities of fluorescent focus units (FFU) of live attenuated reassortants and is given as a 0.2 mL dose (0.1 mL in each nostril).

A quadrivalent product (LAIV4; FluMist® Quadrivalent) is authorized for use in Canada for children 2–17 years of age and adults 18–59 years of age. The trivalent formulation (LAIV3) is no longer available in Canada.

II.4 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.

II.5 Choice of Seasonal Influenza Vaccine

The decision to include specific influenza vaccines as part of publicly funded provincial and territorial programs depends on several factors, including cost-effectiveness evaluation and other

programmatic and operational factors, such as implementation strategies. Not all products will be made available in all jurisdictions and availability of some products may be limited; therefore, officials in individual provinces and territories should be consulted regarding the products available in individual jurisdictions.

With the availability of influenza vaccines that are designed to enhance immunogenicity in specific age groups, the choice of product has become more complex.

Choice of influenza vaccine by age group

Recommendations 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. Table 2 provides age group-specific recommendations for the age-appropriate influenza vaccine types authorized for use in Canada.

Recommendations for public health program-level decision making

- NACI recommends that any of the age-appropriate influenza vaccine types available for use may be considered for people without contraindications to the vaccine. Table 2 provides age group-specific recommendations for the age-appropriate influenza vaccine types authorized in Canada.

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

Recipient by age group	Vaccine types authorized for use	Recommendations on choice of influenza vaccine
6–23 months	• IIV3-SD[a] • IIV3-Adj • IIV4-SD	• 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. • If a quadrivalent vaccine is not available, any of the available trivalent vaccines licensed for this age group should be used.
2–17 years[b]	• IIV3-SD[a] • IIV4-SD • IIV4-cc • LAIV4	• 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. • LAIV4 may be given to children with: - stable, non-severe asthma; - cystic fibrosis who are not being treated with immunosuppressive drugs (e.g., prolonged systemic corticosteroids); and - stable HIV infection, if the child is currently being treated with ART (i.e., HAART) and has adequate immune function • LAIV should not be used in children or adolescents for whom it is contraindicated or for whom there are warning and precautions such as those with: - 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 treated with HAART (for at least 4 months) and has adequate immune function; - pregnancy ▪ In pregnancy, IIV4-SD or IIV4-cc should be used instead. • If IIV4-SD, IIV4-cc, and LAIV4 are not available, IIV3-SD should be used.
18–59 years	• IIV3-SD[a] • IIV4-SD • IIV4-cc • RIV4	• Any of the available influenza vaccines authorized for this age group should be used in adults 18-59 years without contraindications or precautions, noting the following consideration and exceptions:

<table>
<tr><th>Recipient by age group</th><th>Vaccine types authorized for use</th><th colspan="2">Recommendations on choice of influenza vaccine</th></tr>
<tr><td></td><td>• LAIV4</td><td colspan="2">- There is some evidence that IIV may provide better efficacy than LAIV in healthy adults; and

• LAIV is not recommended for:
- pregnant individuals
- adults with any of the chronic health conditions identified in List 1, including immune compromising conditions; and
- health care workers</td></tr>
<tr><td>60–64 years</td><td>• IIV3-SD[a]
• IIV4-SD
• IIV4-cc
• RIV4</td><td colspan="2">• Any of the available influenza vaccines authorized for this age group should be used in adults 60-64 years without contraindications.</td></tr>
<tr><td rowspan="2">65 years and older[c]</td><td rowspan="2">• IIV3-SD[a]
• IIV3-Adj
• IIV4-SD
• IIV4-HD[d]
• IIV4-cc
• RIV4</td><td>Individual-level decision-making</td><td>Public health program-level decision-making</td></tr>
<tr><td>• 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.
- 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.</td><td>• Any of the available influenza vaccines authorized in this age group should be used.
- 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.</td></tr>
</table>

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 available for use in Canada during the 2022-2023 influenza season
[b] Refer to Table 4 for a summary of vaccine characteristics of LAIV compared with IIV in children 2–17 years of age.
[c] Refer to Table 5 for a comparison of the vaccine characteristics of influenza vaccine types available for use in adults 65 years of age and older.
[d] IIV3-HD formulations will not be authorized or available for use in Canada during the 2022-2023 influenza season.

II.6 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 3). Key relevant details and differences between vaccine products are also highlighted in Appendix A.

For influenza vaccines given by the IM route, the anterolateral thigh muscle is the recommended site in infants 6–12 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.

Table 3: Recommended dose and route of administration, by age, for influenza vaccine types authorized for the 2022-2023 influenza season

Age group	Influenza vaccine type (route of administration)						Number of doses required
	IIV3-SD[a] or IIV4-SD[b] (IM)	IIV4-cc[c] (IM)	IIV3-Adj[d] (IM)	IIV4-HD[e] (IM)	RIV4[f] (IM)	LAIV4 [g] (intranasal)	
6–23 months	0.5 mL[h]	-	0.25 mL	-	-	-	1 or 2[i]
2–8 years	0.5 mL	0.5 mL	-	-	-	0.2 mL (0.1 mL per nostril)	1 or 2[i]
9–17 years	0.5 mL	0.5 mL	-	-	-	0.2 mL (0.1 mL per nostril)	1
18–59 years	0.5 mL	0.5 mL	-	-	0.5 mL	0.2 mL (0.1 mL per nostril)	1
60–64 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; IIV3-SD: standard-dose trivalent 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] IIV3-SD formulations (Agriflu® [6 months and older] and Influvac® [3 years and older]) are authorized but will not be available for use in Canada during the 2022-2023 influenza season.
[b] Afluria® Tetra (5 years and older), Flulaval® Tetra (6 months and older), Fluzone® Quadrivalent (6 months and older), Influvac® Tetra (3 years and older).
[c] Flucelvax® Quad (2 years and older)
[d] Fluad Pediatric® (6–23 months) or Fluad® (65 years and older)
[e] Fluzone® High-Dose Quadrivalent (65 years and older)
[f] Supemtek™ (18 years and older)
[g] FluMist® Quadrivalent (2–59 years)
[h] Evidence suggests moderate improvement in antibody response in infants, without an increase in reactogenicity, with the use of full vaccine doses (0.5 mL) for unadjuvanted inactivated influenza vaccines [10, 11]. This moderate improvement in antibody response without an increase in reactogenicity is the basis for the full dose recommendation for unadjuvanted inactivated vaccine for all ages. For more information, refer to Statement on Seasonal Influenza Vaccine for 2011–2012.
[i] Children 6 months to less than 9 years of age receiving seasonal influenza vaccine for the first time in their life should be given 2 doses of influenza vaccine, with a minimum interval of 4 weeks between doses. Children 6 months to less than 9 years of age who have been properly vaccinated with 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 (see Table 3). 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 dose [12].

Serological testing

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

Storage requirements

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

Concomitant 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 12 years and older as of September 2021. Refer to the CIG and latest NACI COVID-19 vaccine guidance for any additional emerging guidance on concomitant administration with COVID-19 vaccines as new products emerge or there are COVID-19 age eligibility expansions.

In theory, the administration of two live vaccines sequentially within less than 4 weeks could reduce the efficacy of the second vaccine. Studies have been done showing no interference when administering LAIV3 concomitantly with: measles, mumps, rubella (MMR); measles, mumps, rubella, varicella (MMRV); or live oral polio vaccines [13-15]. No studies have been done to assess the possibility of interference between LAIV and other live vaccines during concomitant administration, or on LAIV effectiveness given before or after other live vaccines. Additional information regarding simultaneous administration with other vaccines can be found in Section IV.5 of this statement.

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 an inactivated 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.

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 be used for each injection.

The target groups for influenza and pneumococcal polysaccharide vaccines overlap considerably. Vaccine providers should take the opportunity to vaccinate eligible people against pneumococcal disease when influenza vaccine is given.

Concomitant administration with other adjuvanted vaccines

Data are limited regarding coadministration of adjuvanted vaccines with other adjuvanted or nonadjuvanted 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; therefore, the target age group for herpes zoster vaccine and influenza vaccine overlap. RZV has been shown to be safe and effective when given concomitantly with unadjuvanted, standard dose influenza vaccines [4]. However, no studies have been conducted that have assessed the co-administration of RZV with adjuvanted or high dose influenza vaccine [16]. 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 concomitantly is not known and some providers may prefer to use non-adjuvanted influenza vaccine in this situation.

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

II.7 Vaccine Safety and Adverse Events

Post-marketing surveillance of influenza vaccines in Canada has shown that seasonal influenza vaccines have a safe and stable profile. In addition to routine surveillance, every year during the seasonal influenza vaccination campaigns, PHAC and the Federal/Provincial/Territorial Vaccine Vigilance Working Group (VVWG) of the Canadian Immunization Committee conduct weekly expedited surveillance of adverse events following immunization (AEFI) for current influenza vaccines in order 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 [17, 18] to keep the product sterile. Large cohort studies of administrative health databases have found no association between childhood vaccination with thimerosal-containing vaccines and neurodevelopmental outcomes, including autistic-spectrum disorders [19]. 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 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 LAIV3 are nasal congestion and runny nose, which are also reported for LAIV4. Refer to the relevant subsections of Section IV for additional information.

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. Refer to Section IV.5 below for additional information.

Other reported adverse events and conditions

Guillain-Barré syndrome
Studies suggest that the absolute risk of Guillain-Barré syndrome (GBS) in the period following seasonal and A(H1N1)pdm09 influenza vaccination is about one excess case per million vaccinations [20, 21], and that the risk of GBS associated with influenza illness (about 17 cases per million influenza-coded health care encounters, which are a proxy for influenza illness) is higher than that associated with influenza vaccination [21].

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.

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 season [22]. Since then, there have been far fewer cases per year reported to CAEFISS [23]. ORS is not considered to be 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 age [24] in one study and 45 years and older in the other [25]) had an apparent decreased response to influenza vaccination as measured by reduced geometric mean titres (GMT) [24] or reduced VE against medically attended acute respiratory illness [25]. 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, concomitant 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 and that does not necessarily have a causal relationship with the usage of a vaccine. The AEFI may be any unfavourable or unintended sign, abnormal laboratory finding, symptom, or disease. In general, any AEFI felt to be temporally related to vaccination and for which there is no other clear cause at the time of reporting should be reported. Of particular interest are those AEFIs which are considered serious or unexpected. A serious AEFI is an adverse event that is life threatening or results in death, requires hospitalization or prolongation of an existing hospitalization, results in residual disability or causes congenital malformation [26]. 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 monograph [26]. 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.

II.8 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.

This concludes the summary of relevant influenza vaccine information typically found in the Canadian Immunization Guide. Additional technical information related to seasonal influenza vaccine can be found in the remainder of this statement.

III. Particularly Recommended Vaccine Recipients: Additional Information

The groups for whom influenza vaccination is particularly recommended are presented in List 1 of Section II. Additional information regarding these particularly recommended recipients is provided below.

III.1 People at High Risk of Influenza-Related Complications or Hospitalization

All children 6–59 months of age

On the basis of existing data, NACI recommends the inclusion of all children 6–59 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 6–23 months of age and to the Statement on Seasonal Influenza Vaccine for 2012–2013 for children 24–59 months of age.

Adults and children with chronic health conditions

A number of chronic health conditions, as noted in List 1, are associated with increased risk of influenza-related complications, and influenza can lead to exacerbation of the chronic disease. 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.

Neurologic or neurodevelopment conditions
Neurologic or neurodevelopment conditions (NNCs) that pose increased risk for severe disease or complications from influenza include neuromuscular, neurovascular, neurodegenerative, neurodevelopment conditions, and seizure disorders (and, for children, include febrile seizures and isolated developmental delay), but exclude migraines and psychiatric conditions without neurological conditions. Based on reviews of evidence and expert opinion, NACI includes adults and children with NNCs among the groups for whom influenza vaccination is particularly recommended. Refer to the NACI Statement on Seasonal Influenza Vaccine for 2018–2019 for a summary of the rationale supporting this decision 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.

All pregnant individuals

NACI recommends the inclusion of all pregnant individuals, at any stage of pregnancy, among those who are particularly recommended to receive IIV. This is due to the risk of influenza-associated morbidity amongst those who are pregnant, [27-31], evidence of adverse neonatal outcomes associated with respiratory hospitalization during pregnancy or influenza during pregnancy [32-35], evidence that vaccination of pregnant individuals protects their newborns from

influenza and influenza-related hospitalization [36-39], 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 [40-43]. 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 reviewed [42]. Active studies of influenza vaccination during pregnancy have not shown evidence of harm to the pregnant individual or fetus associated with influenza vaccination [44]. 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 [29, 30, 45, 46]. 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 Europe [47] 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, which will be forthcoming, 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 125–228 per 100,000 healthy people [48], and influenza-attributed mortality rates increase with increased age [49].

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) [50], delayed access to health care, and increased susceptibility to disease because of poor housing and overcrowding [51-53]. Refer to the Statement on Seasonal Influenza Vaccine for 2011–2012 for further details.

III.2 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 (HCW) decreases their own risk of illness [54, 55], as well as the risk of death and other serious outcomes among the individuals for whom they provide care [56-59]. Vaccination of HCWs and residents of nursing homes is associated with decreased risk of ILI outbreaks [60].

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, regular visitors, 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 [57-59] and all-cause mortality [56-59] in the residents. In addition, due to their occupation and close contact with people who may be infected with influenza, HCWs are themselves at increased risk of infection [61].

As previously stated, children 0–59 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 current influenza vaccine coverage for HCWs is higher than in the general public [62, 63], it remains below the national goal of 80% coverage for HCWs in Canada [64]. 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 [65-70].

Outbreak management in health care facilities
As noted in PHAC's Guidance: Infection Prevention and Control Measures for Healthcare Workers in Acute Care and Long-term Care Settings for seasonal influenza, all health care organizations should have a written plan for managing an influenza outbreak in their facilities. Inherent in such plans should be policies and programs to optimize HCW's influenza vaccination [71]. 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 0–59 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 ship).

III.3 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 [54, 55, 72-74].

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

Poultry workers
Although seasonal influenza vaccination will not prevent avian influenza infection, some countries [75] and provinces have recommended influenza vaccination on a yearly basis for poultry workers, based on the rationale that preventing infection with human influenza strains may reduce the

theoretical potential for human-avian reassortment of genes, should such workers become co-infected with human and avian influenza viruses [76].

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 [77-80]. 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.

IV. Vaccine Preparations Authorized for Use in Canada: Additional Information

The following sections describe 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. Refer to Appendix A for a summary of the characteristics of specific influenza vaccine products available in Canada for the 2022–2023 season.

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 this section may not include the latest studies. However, in accordance with usual practice, NACI continues to closely monitor the emerging evidence on the efficacy and effectiveness, immunogenicity, and safety of influenza vaccines to update and to make recommendations when warranted.

IV.1 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 or Victoria). IIVs currently authorized for use in Canada are a mix of split virus and subunit vaccines, both consisting of disrupted virus particles. Split virus vaccines contain whole inactivated viruses split with detergent, ether, or both, while subunit vaccines are made of purified HA and NA. The amount of NA in the vaccines is not standardized. HA-based serum antibody produced to one influenza A subtype is anticipated to provide little or no protection against strains belonging to the other 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 [81-86].

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 NACI is aware of some recent studies that suggest that vaccine induced protection may be greater in individuals who have no recent vaccine history, optimal protection against influenza, season after season, is best achieved through annual influenza vaccination [87, 88]. NACI will continue to monitor this issue.

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 [10, 11, 89]. On the basis of this moderate improvement in antibody response without an increase in reactogenicity, NACI recommends the use of a 0.5 mL dose for all recipients of IIV-SDs, including young children.

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

Although the initial antibody response in older adults may be lower to some influenza vaccine components 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 groups [(90)].

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 [(91-94)].

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 [(13, 95-97)].

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

Vaccines currently authorized for use:

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

*Vaccine is not currently available in Canada.

Efficacy and effectiveness

The NACI Literature Review on Influenza Vaccination in Healthy 5–18 Year Olds found that vaccine efficacy or vaccine effectiveness (VE) of IIV3-SD against laboratory-confirmed influenza was variable but was most frequently between 65–85% [(98-116)]. In the NACI literature review on Influenza Vaccine Effectiveness, Immunogenicity, and Safety in Healthy Adults 19–64 Years Old, efficacy against laboratory-confirmed influenza for IIV3-SD in healthy adults 18–64 years of age ranged widely from as low as 15% to as high as 75%, with the majority of studies estimating efficacy at 50–60%. Refer to the Statement on Seasonal Influenza Vaccine for 2018–2019 for a more detailed summary of efficacy and effectiveness evidence for IIV3-SD in healthy children 5–18 years of age and healthy adults 19–64 years of age.

In older adults, VE of IIV3-SD is about half of that in healthy adults and varies depending on the outcomes measured and the study population [(117, 118)]. Systematic reviews have demonstrated that influenza vaccine decreases the incidence of pneumonia, hospital admissions, and deaths in older adults [(117)] and reduces exacerbations in people with chronic obstructive pulmonary disease [(119)]. The NACI Literature Review on the Comparative Effectiveness and Immunogenicity of Subunit and Split Virus Inactivated Influenza Vaccines in Adults 65 Years of Age and Older found no statistically significant differences in VE of subunit IIV3-SD compared with split virus IIV3-SD in adults 65 years of age and older against infection with any influenza virus strain, or against infection with influenza A(H1N1), A(H3N2), or B virus specifically.

In observational studies, influenza vaccination has been shown to reduce the number of physician visits, hospitalizations, and deaths in adults 18–64 years of age with high-risk medical conditions [(120)], hospitalizations for cardiac disease and stroke in adults 65 years of age and older [(121)], and hospitalization and deaths in adults 18 years of age and older with diabetes mellitus [(122)] during

influenza epidemics. Observational studies that use non-specific clinical outcomes or that do not take into account differences in functional status or health-related behaviours should be interpreted with caution [123-127].

Immunogenicity
Both humoral and cell-mediated immune responses are thought to play a role in immunity to influenza. While humoral immunity is thought to play a primary role in protection against infection, cell-mediated immunity, notably cytotoxic T lymphocyte responses to internal viral components, is increasingly invoked as important in protecting against severe outcomes of influenza, particularly those associated with subtype HA variations (shift and drift) [128]. The IM administration of IIV3-SD results in the production of circulating immunoglobulin G (IgG) antibodies to the viral HA and NA proteins, as well as a more limited cytotoxic T lymphocyte response.

Safety
Studies evaluating the safety of IIV3-SDs in healthy children have found a good safety profile with no SAE of note [129]. The most common solicited local reactions are pain and redness at the injection site, while the most common solicited systemic reactions are irritability, malaise, and headache. Mild injection site reactions, primarily soreness at the vaccination site, have been found to occur in 7% or less of healthy children who are less than 3 years of age [130-132]. Post-vaccination fever may be observed in 12% or less of vaccinated children 1–5 years of age [103, 132].

For adults, IIV3-SDs have been demonstrated to have a good safety profile with acceptable reactogenicity [129]. Common local reactions at injection site include redness, swelling, pain, and induration. These reactions last 2–3 days and rarely interfere with normal activities. Common systemic reactions include headache, malaise, myalgia, fatigue, arthralgia, and fever.

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

Vaccines currently authorized for use:

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

Efficacy and effectiveness
In the NACI Literature Review on Quadrivalent Influenza Vaccines, only one study was identified that measured IIV4-SD efficacy. In that study, efficacy was estimated at 59% in children 3–8 years of age, in comparison to children who received hepatitis A vaccine [133]. No literature was found in this review on efficacy or effectiveness directly comparing trivalent and quadrivalent formulations.

Immunogenicity
In the same review of the literature noted above, NACI reviewed the immunogenicity data for IIV4-SD produced by manufacturers who supplied influenza vaccine in Canada at the time of the literature review: AstraZeneca, GlaxoSmithKline, and Sanofi Pasteur. 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. These findings were consistent across age groups. Refer to the Literature Review on Quadrivalent Influenza Vaccines for additional details.

In the phase III trials, recipients of the trivalent formulations showed, to a lesser degree, some immune response to the B strain not contained in the trivalent formulation. In one study of adults, both the trivalent and quadrivalent vaccines met all the European Medicines Agency Committee for Medicinal Products for Human Use and the United States Food and Drug Administration criteria for evaluation of influenza vaccine immunogenicity, including for the B strain not in the trivalent vaccine.

In all other studies, the trivalent vaccine failed at least one of the criteria for seroprotection or seroconversion for the missing B strain. It has been hypothesized that there is some level of cross-reactivity between B strains. The degree of cross protection against infection with one lineage provided by immunization against the other lineage is uncertain [134].

Safety
Pre-licensure clinical trials (refer to Literature Review on Quadrivalent Influenza Vaccines) and post-marketing surveillance showed that IIV4-SD had a similar safety profile to IIV3-SD [135].

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

Vaccine currently authorized for use:

- Flucelvax® Quad (Seqirus)

Methods

NACI reviewed the Health Canada assessment of a Phase 3/4 randomized clinical trial of Flucelvax Quad efficacy, immunogenicity and safety in children 2 years to less than18 years of age submitted by the manufacturer in support of an age extension for the use of the vaccine to adults and children 2 years of age and older. The clinical trial was conducted in 8 countries in Europe and South East Asia over three influenza seasons (Southern Hemisphere 2017 influenza season and the 2017–2018 and 2018–2019 Northern Hemisphere influenza seasons). Overall, the quality of the evidence was considered good.

In support of the original recommendation for use of the Flucelvax Quad in adults and children 9 years of age and older, NACI conducted a systematic review of the literature to examine vaccine efficacy, effectiveness, immunogenicity, and safety data for this age group.

Efficacy and effectiveness
Four observational studies, two peer-reviewed and two not peer-reviewed (conference abstracts and posters) were identified through the systematic review, which assessed the VE of IIV4-cc compared to egg-based IIV against laboratory-confirmed influenza infection during the 2017–2018 influenza season in the United States [136-139]. Of these four studies, two were of good quality [137, 138], while the quality of the other two studies [136, 139] could not be assessed because they were published as conference abstracts or posters. IIV4-cc may be more effective than egg-based IIV3 and IIV4 influenza vaccines against non-laboratory confirmed influenza-related outcomes, including influenza-related health care interactions and ILI. Although some data suggests that IIV4-cc may be more effective against laboratory-confirmed influenza A(H3N2)

virus infection than egg-based IIV, there was no consistent and statistically significant difference in effectiveness identified for adults or children vaccinated with IIV4-cc compared to egg-based IIV. Evidence for the efficacy of IIV4-cc is based on the efficacy studies for the trivalent formulation, IIV3-cc.

Refer to the NACI Supplemental Statement on Mammalian Cell Culture-Based Influenza Vaccines for further details.

The Phase 3/4 RCT of Flucelvax Quad for children 2 years to 18 years met the pre-defined success criterion for efficacy against PCR- or culture-confirmed influenza due to any strain starting 14 days after the last dose in these children. The overall estimate of vaccine efficacy did not differ significantly when analyzed by subgroup (e.g., age, sex, race, influenza vaccination history, influenza season). When analyzed by influenza subtype/lineage in children 2 years to less than 18 years of age, the vaccine was found to be more efficacious against influenza A/H1N1 than against either A/H3N2 or influenza B during the three influenza seasons. Estimates of efficacy by influenza subtype/lineage in children 2 years to less than 4 years of age and children 2 years to less than 9 years of age were comparable to the estimates in children 2 years to less than 18 years of age, although with wider confidence intervals around the point estimates (which included zero for estimates of efficacy against influenza A/H3N2).

Immunogenicity

The immunogenicity for IIV4-cc is supported by evidence from the clinical development program for the IIV3-cc (authorization never sought in Canada), which has been licensed in the US and Europe and is produced using the same Madin-Darby Canine Kidney (MDCK) manufacturing platform [140-143]. IIV3-cc has demonstrated non-inferiority to standard egg-based IIV3 comparators, for hemagglutinin inhibition antibody responses to A(H3N2), A(H1N1) and B strains in adults 18 years of age and older, and for A(H1N1) and B strains specifically, but not A(H3N2), in children, based on post-vaccination GMT ratios and seroconversion rates [144-147]. There is fair evidence that IIV4-cc has non-inferior immunogenicity to other inactivated influenza vaccines, based on direct and indirect evidence in adults and children 9 years of age and older.

Two studies [148, 149] that assessed the immunogenicity of IIV4-cc compared to different IIV3-cc formulations (produced by Seqirus using the same MDCK cell culture-based manufacturing process) were identified in this review; one study was conducted with adult participants18 years of age and older, while the other study focused on pediatric participants. In both studies, Flucelvax Quad demonstrated non-inferiority, based on geometric mean titre rise and seroconversion rates, and met the threshold for seroprotection for all influenza strains contained in the IIV3-cc vaccines, including superior immunogenicity for the B strain not contained in IIV3-cc.

In support of the use of the vaccine in adults and children 2 years of age and older, immunogenicity was assessed in a subset of the phase 3/4 RCT study participants 2 years to less than 9 years of age during the Northern Hemisphere influenza seasons (2017–2018 and 2018–2019), based on blood samples collected on the day of vaccination and 21 days after receipt of the last dose of vaccine. Participants experienced a substantial increase in antibody titres in response to vaccination, based on GMT ratios, seroconversion rates and seroprotection rates. The responses were generally highest against influenza A/H1N1 than for the other influenza subtypes/lineages. However, the immunogenicity results for influenza A/H3N2 were affected by differing hemagglutination abilities of the circulating strains and differences in the hemagglutination inhibition assays used in the two influenza seasons.

Safety
There is fair evidence that IIV4-cc is a safe and well-tolerated alternative to conventional egg-based influenza vaccines for children and adults. Two peer-reviewed randomized controlled trials assessed the safety of IIV4-cc; with one focused on healthy adults [148] and the other on healthy children [149]. Most systemic reactions were mild and resolved within 3 days. SAEs were rare and similar in frequency between cell culture-based and conventional egg-based influenza vaccines. Studies that assessed the safety of Flucelvax were considered to supplement the evidence base for safety. Overall, local and systemic solicited reactions as well as unsolicited AEs and SAE are comparable to those typically observed with other injectable egg-derived IIV3s. The evidence on safety was consistent across studies and showed that there was no significant difference in adults and children compared to comparator vaccines. Flucelvax, also has an established record of safety in other jurisdictions, and no new safety signals have been identified through routine pharmacovigilance in the US or Europe where the vaccine is licensed [144, 145, 150]. The vaccine is safe to use during pregnancy, as no safety signals have been detected in this population. IIV4-cc is made using MDCK cells, which are developed from a canine source. An allergy to dogs is not considered a contraindication to the vaccine, based on a review of two in vitro allergenicity studies [151, 152].

The analysis of vaccine safety in a clinical trial in children 2 years to less than 18 years of age were consistent with the findings of the previous NACI systematic literature review summarized above. The majority of solicited (local and systemic) and unsolicited adverse events were mild to moderate in severity and resolved spontaneously within 1 to 3 days post-vaccination, with no significant differences in rates between the Flucelvax Quad and comparator vaccine recipients. There were low (less than or equal to 1.3%) and comparable proportions of serious adverse events identified in Flucelvax Quad and comparator vaccine recipients, with no serious adverse events determined to be related to receipt of the assigned vaccine.

Adjuvanted inactivated influenza vaccine (IIV-Adj)

Vaccines currently authorized for use:

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

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

Efficacy and effectiveness
There is fair evidence that the MF59-adjuvanted Fluad (IIV3-Adj) may be effective at reducing the risk of hospitalization for influenza and influenza complications in older adults compared to unvaccinated individuals. However, there is insufficient evidence that IIV3-Adj is more effective at reducing the risk of hospitalization for influenza and influenza complications in older adults compared to those who received unadjuvanted 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.

Immunogenicity

The mechanism of action of MF59 is not fully determined and has primarily been studied using in vitro and mouse models. From these studies, it appears that MF59 may act differently from aluminum-based adjuvants. These studies show that MF59 acts in the muscle fibres to create a

local immune-stimulatory environment at the injection site [153]. 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 [154, 155]. MF59 further facilitates the internalization of antigen by these dendritic cells [154, 156] . The overall higher number of cells available locally increases the likelihood of interaction between an antigen presenting cell and the antigen, leading to more efficient transport of antigen to the lymph nodes, with resulting improved T cell priming [154].

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 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.

Safety

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

2. Fluad Pediatric (children 6–23 months of age)

Efficacy and effectiveness

A pre-licensure efficacy trial in children 6–71 months of age found a higher relative efficacy for IIV-Adj than the unadjuvanted IIV3-SD [157]. 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 Fluad® Influenza Vaccine Use in Children 6–72 Months of Age 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 [157-162]. 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 A [162]. 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 6–35 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 6–23 month age group. Refer to the NACI Literature Review on Pediatric Fluad® Influenza Vaccine Use in Children 6–72 Months of Age 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 10–15% more solicited local and systemic reactions. However, most reactions were mild and resolved quickly. A dose-ranging study of MF59-adjuvanted 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 formulations [160].

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-adjuvanted A(H1N1) pandemic vaccine that has been associated with an increased risk of narcolepsy. A study comparing two AS03-adjuvanted 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 vaccines [163]. 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 Fluad® Influenza Vaccine Use in Children 6-72 Months of Age for additional information on the safety of IIV3-Adj in children.

High-dose inactivated influenza vaccine (IIV-HD)

Vaccines currently authorized for use:

- Fluzone® High-Dose Quadrivalent (Sanofi Pasteur)

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 65–74 years of age [164, 165]. The efficacy results for IIV3-HD are inferred to IIV4-HD based on the non-inferior immunogenicity, described in the next section.

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-HD in adults 65 years of age and older.

Immunogenicity
Five studies compared the rates of seroconversion for study participants receiving IIV3-HD and IIV3-SD among those 65 years of age and older [166-171]. Rates of seroconversion were found to be about 19% higher (ranging from 8–39% higher) for those receiving the higher dose vaccine across all three vaccine strains. Similarly, rates of seroconversion were higher for those receiving the high- compared to standard-dose vaccines for participants 75 years of age and older and for a cohort of participants with underlying cardiopulmonary disease.

Eight studies reported higher rates of seroprotection for older adults receiving IIV3-HD compared to those vaccinated with IIV3-SD [166-173]. Seroprotection was significantly higher for all 3 strains in the vaccine in three of five studies assessing significance. There were different results in the remaining studies. In the study by Couch et al., seroprotection was higher only against A(H1N1), possibly attributed to the fact that 78% of participants were vaccinated against the same influenza strains within 6 months prior to the study [167]. In Nace et al., seroprotection was higher against A(H3N2) and B but not A(H1N1); the lack of higher seroprotection against A(H1N1) may be attributed to strain circulation during the study that made it difficult to assess seroprotection against this subtype [152].

GMT ratios (GMTR) of participants' responses to high- versus standard-dose influenza vaccines were reported in several studies and were calculated for those that provided group-specific, post-vaccination titres for each of the vaccines [166-170, 172, 173]. Seroresponse to the B strains in the vaccines was about 1.5 times greater (1.3–1.7) in the IIV3-HD recipients than the IIV3-SD recipients. The GMTR of the A strains was about 1.8 times higher for those receiving IIV3-HD compared to IIV3-SD, ranging from 1.6–2.3.

There is good evidence that the immunogenicity for Fluzone High Dose Quadrivalent (IIV4-HD) is non-inferior to IIV3-HD [174, 175]. In a pivotal RCT, IIV4-HD met all non-inferiority criteria set by the US Food and Drug Administration, based on GMTR and seroconversion rates when compared to IIV3-HD [175]. Immunogenicity for IIV4-HD was superior for the influenza B strain not contained within the trivalent high dose vaccine [175].

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 AEs [175].

Refer to NACI's A Review of the Literature of High Dose Seasonal Influenza Vaccine for Adults 65 Years and Older for details on IIV3-HD.

IV.2 Recombinant quadrivalent influenza vaccine (RIV4)

Vaccines currently authorized for use:

- Supemtek™ (Sanofi Pasteur)

Methods

For the review of evidence relating to RIV, NACI used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework to organize the information and develop recommendations for RIV. Further information on this framework can be found in the GRADE handbook.

Efficacy and effectiveness

One RCT was identified that assessed the relative vaccine efficacy (rVE) of RIV4 compared to egg-based IIV4 against laboratory confirmed influenza infection in adults 50 years of age and older during the 2014-2015 influenza season in the United States [176]. The certainty of evidence for this outcome was rated as low and suggested that RIV4 may be more effective than egg-based IIV4 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.

Refer to the NACI Supplemental Statement on Recombinant Influenza Vaccines, which will be forthcoming, for further details.

Immunogenicity

Eight RCTs [176-183] were identified that assessed the immunogenicity of RIV4. Of these studies, two were conducted during the 2014-2015 influenza season [176, 179], three were conducted over the 2017-2018 influenza season [177, 181, 182], and three were conducted over the 2018-2019 influenza season [178, 180, 183]. The RCTs were of good quality overall. Non-inferiority was assessed using the criteria specified by the US FDA [139].

The eight RCTs compared rates of seroconversion for RIV4 recipients with IIV3-HD, IIV3-Adj, IIV4-SD, and IIV4-cc recipients aged 18 years of age or older. In four [177, 178, 181, 183] of the eight studies, rates of seroconversion were similar in those receiving RIV4 compared to those receiving IIV3-HD, IIV3-Adj, IIV4-SD, and IIV4-cc against influenza A/H1N1, A/H3N2, B/Yamagata lineage and B/Victoria lineage. There were different results in the remaining studies. The two studies by Dunkle et al. [176, 179] demonstrated that, compared to IIV4-SD, RIV4 did not meet the non-inferiority threshold in HI antibody responses against B/Victoria lineage in adults 18 to 64 years of age. Additionally, rates of seroconversion following RIV4 did not meet the non-inferiority threshold compared to IIV4-SD against influenza A/H1N1 in adults 64 and older [176]. Non-inferiority could not be assessed for the remaining two RCTs [180, 182] as these studies did not state confidence intervals for seroconversion estimates. Pooled seroconversion data from three [176, 178, 181] of the eight RCTs identified in adult participants 50 years of age and older using a random-effects model revealed that RIV4 induced similar antibody responses compared to IIV4-SD, IIV3-HD, and IIV3-Adj.

Four RCTs reported comparable or greater rates of seroprotection for study participants receiving RIV4 compared to those receiving IIV3-HD, IIV3-Adj, IIV4-SD, and IIV4-cc among adults 18 years of age and older [176-178, 183]. The four studies had varying findings. In two of the four studies, RIV4 met the non-inferiority criteria specified by the US FDA for all tested influenza strains including A/H1N1, A/H3N2, B/Yamagata lineage, and B/Victoria lineage [178, 183]. Across the four RCTs, RIV4 met non-inferiority criteria against five of seven tested strains of A/H3N2. In the study by

Belongia et al. [177], RIV4 demonstrated lower rates of seroprotection for older adults 65 to 74 years of age against two of four tested strains of A/H3N2. However, one limitation was the small sample size of the study. In the study by Dunkle et al. (2017a) [176], RIV4 met the non-inferiority threshold for seroprotection against influenza A/H1N1, A/H3N2, and B/Yamagata lineage, but not against influenza B/Victoria lineage in adults aged 50 and older.

GMTR of participants' responses to RIV4 versus IIV4-SD were reported in three RCTs [176,179,183,184]. In one study, RIV4 met the non-inferiority criteria specified by the US FDA for all tested A/H1N1, A/H3N2, B/Yamagata lineage, and B/Victoria lineage influenza strains [183]. In two of the three studies, seroresponses to A/H1N1, A/H3N2, and B/Yamagata lineage in RIV4 recipients were comparable to seroresponses in IIV4-SD recipients based on the GMTR [176, 179, 184]. However, the GMTR against B/Victoria lineage for IIV4-SD recipients compared to RIV4 recipients did not meet the non-inferiority criteria set by the US FDA [139].

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 [176, 178, 179, 181, 185, 186] were identified that assessed the safety of RIV4 in adults, including five RCTs and one review of post-marketing surveillance data from the United States. Of these studies, two were conducted during the 2014-2015 influenza season [176, 179], two were conducted during the 2017-2018 influenza season [181, 186], one was conducted during the 2018-2019 influenza season [178], and one study reported data from the Vaccine Adverse Event Reporting System (VAERS) from July 1, 2017 through June 30, 2020 [185]. Most systemic reactions reported by the clinical trials were mild to moderate in severity and were transient in nature. Adverse events were similar in frequency between recombinant and conventional egg-based influenza vaccines. Although serious AEs were reported across clinical trials, none were considered by the authors to be related to the trial vaccines. RIV4 also has an established record of safety in other jurisdictions, and no safety signals have been identified through routine pharmacovigilance in the US, where the vaccine is licensed [185]. Most AE reported to VAERS following RIV4 administration were non-serious. When data from two RCTs [176, 178] conducted among adult participants 50 years of age and older were combined and weighted using a random-effects model, there was no difference in the odds of experiencing a SAE following administration of RIV4 and traditional egg-based IIV3-HD and IIV4-SD vaccine comparators. No published clinical data pertaining to safety of vaccination with RIV4 during pregnancy is currently available to inform vaccine-associated risks.

Overall, there is evidence of moderate certainty that RIV4 is a safe and well-tolerated alternative to conventional egg-based influenza vaccines for adults.

IV.3 Live Attenuated Influenza Vaccine (LAIV)

LAIV contains standardized quantities of 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, it elicits mucosal immunity, which may more closely mimic natural infection.

Vaccine currently authorized for use:

- FluMist® Quadrivalent (AstraZeneca)

Efficacy and effectiveness
After careful review of the available Canadian and international LAIV VE data over many influenza seasons, NACI concluded that the current evidence is consistent with LAIV providing comparable protection against influenza to that afforded by IIV and does not support a recommendation for the preferential use of LAIV in children 2–17 years of age.

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) [187]. 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 well [188]. 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 [189-191].

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 6–23 months of age for LAIV3 compared to IIV3-SD [188]. 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 individuals with HIV infection
Following a review of the literature regarding the use of LAIV in HIV-infected individuals, NACI concluded that LAIV is immunogenic in children with stable HIV infection on HAART and with adequate immune function. In addition, NACI concluded that LAIV appears to have a similar safety profile as IIV in children on HAART and with stable HIV infection with regard to frequency and severity of AEs [192]. As expected, injection site reactions were seen only with IIV and nasal symptoms were more common with LAIV. However, the evidence base is too small to effectively detect uncommon, rare, and very rare AEs related to the use of LAIV in in this population. Nasal spray may be preferable to IM injection for some individuals who are averse to receiving the vaccine by injection. Therefore, NACI recommends that LAIV may be considered as an option for children 2–17 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 the following criteria:

- Receiving ART for 4 months or longer;
- CD4 count equal to or greater than 500/μL if 2–5 years of age, or ≥200/μL if 6–17 years of age (measured within 100 days before administration of LAIV); and
- 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.

IV.4 Schedule

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 [193-195]. Several studies have looked at whether these two initial doses need to be given in the same season [83, 84, 196]. Englund et al. reported similar immunogenicity in children 6–23 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 [83, 84]. 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 [82, 84]. Issues related to effective prime-boost when there is a major change in influenza B lineage across sequential seasons require further evaluation [197]. Because children 6–23 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.

IV.5 Concomitant 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, including COVID-19 vaccines for those aged 12 years and older as of September 2021.

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 NACI Statement on the Use of COVID-19 Vaccines and the CIG COVID-19 chapter for current recommendations concerning the use of COVID-19 vaccines and further information on concomitant administration of COVID-19 vaccines with other vaccines.

In general, NACI recommends that two live parenteral vaccines be administered either on the same day or at least 4 weeks apart [198]. This recommendation is based largely on a single study from 1965 that demonstrated immune interference between smallpox vaccine and measles vaccine administered 9–15 days apart. Subsequent studies have revealed conflicting results on immune interference between live vaccines [199-202]. No studies were found on potential immune interference between LAIV and other live attenuated vaccines (oral or parenteral) administered within 4 weeks. A few studies on concomitant administration of LAIV3 with MMR, varicella, and oral polio vaccines did not find evidence of clinically significant immune interference [12, 14, 15]. 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 an inactivated influenza vaccine would avoid this theoretical concern.

IV.6 Additional Vaccine Safety Considerations

Influenza vaccine is safe and well tolerated. Contraindications, precautions, and common AEs are described in Section II. Additional information regarding egg-allergic individuals and GBS is provided below.

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 a vaccine emergency 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 vaccination [203]. The attributable risk of GBS in the period following seasonal and monovalent 2009 pandemic influenza vaccination is about one excess case per million vaccinations [20, 21]. In a self-controlled study that explored the risk of GBS after seasonal influenza vaccination and after influenza health care encounters (a proxy for influenza illness), the attributable risks were 1.03 GBS admissions per million vaccinations compared with 17.2 GBS admissions per million influenza-coded health care encounters [21]. This finding 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 2–4, 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. The risk of GBS associated with influenza vaccination must be balanced against the risk of GBS associated with influenza infection itself and all the other benefits of influenza vaccination [204-207].

V. Choice of Seasonal Influenza Vaccine: Additional Information

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. Section II.5 summarizes NACI's recommendations on the choice of currently authorized influenza vaccines. This section provides more details for these recommendations.

V.1 Children

Burden of disease in children

Canadian surveillance data from 2001–2002 to 2012–2013 has shown that influenza B strains accounted for 17% of laboratory-confirmed tests for influenza in children, which is a higher proportion of disease burden due to influenza B infection compared to other age groups.

Although children less than 24 months of age comprise approximately 2% of the Canadian population [(208)], children 0–23 months of age averaged 10.8% of reported influenza B cases (range: 8.3–13.7%), 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 15.5–58.3% (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) [(209)].

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 6–23 months of age

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

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, any of the available age-appropriate trivalent vaccines should be used.

There is insufficient evidence to make comparative recommendations on the use of IIV3-Adj over IIV3-SD.

Children 2–17 years of age

Four types of influenza vaccine have been authorized for use in children 2–17 years of age (IIV3-SD, IIV4-SD, IIV4-cc, and LAIV4.

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 an age appropriate quadrivalent vaccine should be used. If a quadrivalent vaccine is not available, an age-appropriate trivalent vaccine should be used.

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

Children 2–17 years of age with chronic health conditions
NACI recommends that any age-appropriate influenza vaccine (IIV or LAIV) may be considered for children 2–17 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 pregnant adolescents. 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
IIV3-SD, IIV4-SD, IIV4-cc, and LAIV4 are authorized for use in Canada for children 2–17 years of age. The comparison of the vaccine characteristics of IIV and LAIV, in Table 4 below, may be considered in making a decision 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 4: Vaccine characteristics of live attenuated influenza vaccine (LAIV) compared with inactivated influenza vaccine (IIV) in children 2–17 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 2–17 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] Both trivalent and quadrivalent IIV-SD (IIV3-SD and IIV4-SD) are authorized for use in Canada for the 2022-2023 influenza season. Data comparing LAIV to IIV4-cc are not available, however IIV-cc is comparable to egg-based IIV.

V.2 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: 2.4–36.7) [(210)]. 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: 8.0–121.1) 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 particular influenza virus types and subtypes in circulation. Estimates presented in the study of yearly influenza-associated deaths with underlying pneumonia and influenza causes (1976–2007) 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 group [211].

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, disproportionally affected adults 65 years of age and older, while seasons with greater A(H1N1) detections resulted in a higher proportion of positive cases in younger age groups.

Adults 18–59 years of age

Five types of influenza vaccine are authorized for use in adults 18–59 years of age: IIV3-SD, IIV4-SD, IIV4-cc, RIV4, and LAIV4.

NACI recommends that any of the available influenza vaccines should be used in adults without contraindications. IIV or RIV should be used for adults with chronic health conditions identified in List 1, HCWs or pregnant women (noting that no published clinical data pertaining to safety of vaccination with RIV4 during pregnancy is currently available to inform vaccine-associated risks for this population).

Adults 60–64 years of age

Four types of influenza vaccine are authorized for use in adults 60–64 years of age: IIV3-SD, 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

Six types of influenza vaccine are authorized for use in adults 65 years of age and older: IIV3-SD, 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 standard dose 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+ 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 six types of inactivated influenza vaccines (IIV3-SD, 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 5 below, may be considered in making a decision 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, IIV-HD, IIV4-SD, IIV4-cc, or RIV4, considerations for these vaccines in Table 5 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 5: 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 [(210)].				
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 adverse events 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 no published clinical data pertaining to safety of vaccination with RIV4 during pregnancy is currently available to inform vaccine-associated risks).

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

Health care workers

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

Comparative studies in healthy adults have found IIV to be similarly or more efficacious or effective compared with LAIV [187]. 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.

List of Abbreviations

Abbreviation	Term
AE	Adverse event
AEFI	Adverse event following immunization
ART	Antiretroviral therapy
CAEFISS	Canadian Adverse Events Following Immunization Surveillance System
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
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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Appendix A: Characteristics of influenza vaccines available for use in Canada, 2022–2023[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 Pasteur)	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 Pasteur)	IIV4-HD (split virus)	IM	65 years and older	60 µg HA /0.7 mL dose	None	Single dose pre-filled syringe without attached needle	Not applicable	No	None	Egg (Avian)

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