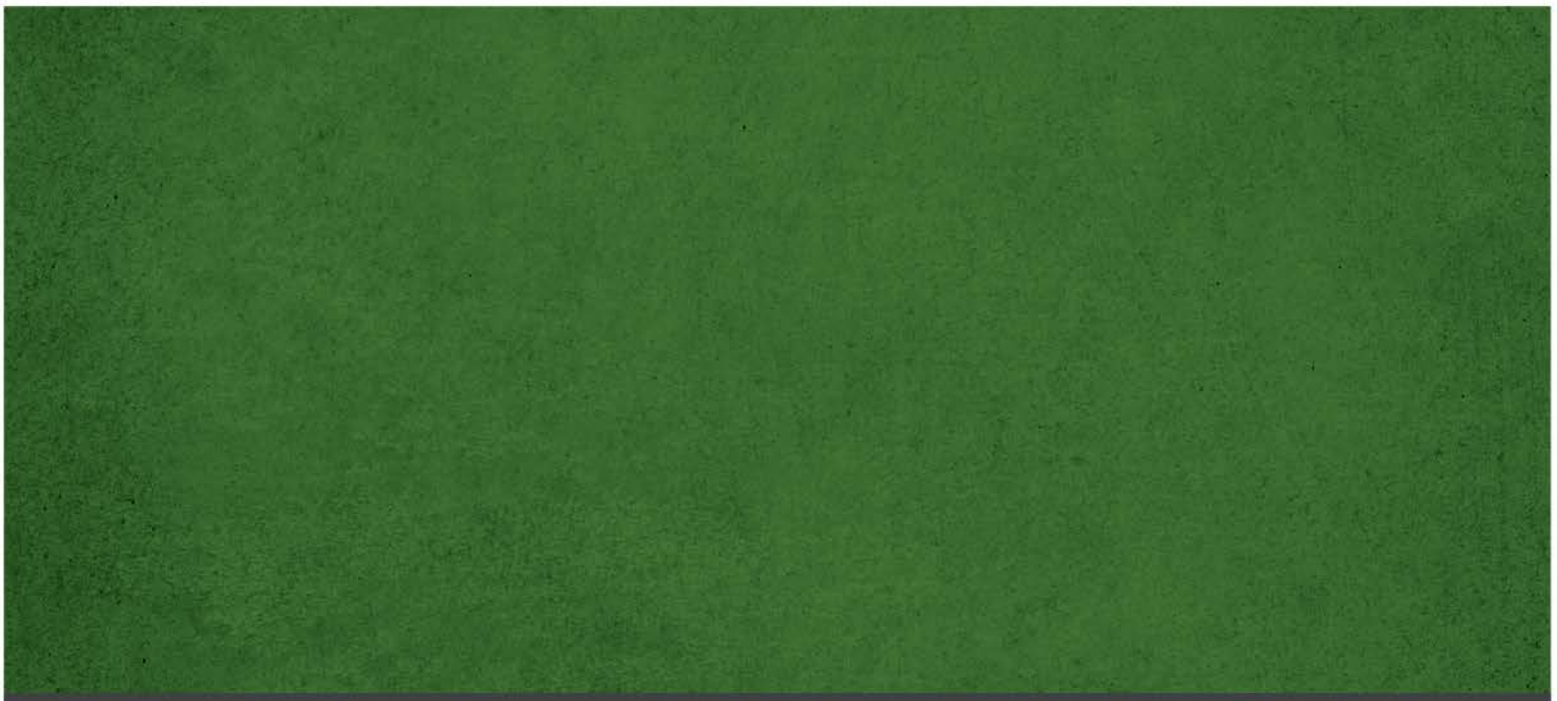
An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2019–2020



PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

—Public Health Agency of Canada

Également disponible en français sous le titre :
Une déclaration d'un comité consultatif (DCC)
Comité consultatif national de l'immunisation (CCNI)
Chapitre sur la grippe du Guide canadien d'immunisation et Déclaration sur la vaccination antigrippale pour la saison 2019-2020

This publication can be made available in alternative formats upon request.

Publication date: May 2019

Cat.: HP37-25E-PDF
ISBN: 2371-5375
Pub.: 180883

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, the Public Health Agency of Canada 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 conflict of interest.

TABLE OF CONTENTS

I. INTRODUCTION

This document, the National Advisory Committee on Immunization (NACI): Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2019–2020, updates NACI's recommendations regarding the use of seasonal influenza vaccines.

I.1 New or Updated Information for 2019–2020

New influenza vaccine product

Afluria® Tetra (Seqirus) is a split virus quadrivalent inactivated influenza vaccine that was authorized for use in Canada in adults and children 5 years of age and older on February 22, 2018. Based on a review of available pre-licensure clinical trial data, NACI has concluded that Afluria Tetra has a comparable safety and immunogenicity profile to already authorized quadrivalent inactivated influenza vaccines. Therefore, NACI recommends that Afluria Tetra may be considered among the quadrivalent inactivated influenza vaccines offered to adults and children 5 years of age and older (Discretionary NACI Recommendation). Refer to the NACI Supplemental Statement on Afluria® Tetra for additional information supporting this recommendation.

Comparative effectiveness and immunogenicity of subunit and split virus inactivated influenza vaccines in adults 65 years of age and older

Unadjuvanted subunit and split virus inactivated influenza vaccines are two commonly used types of seasonal influenza vaccines in Canada. A difference in vaccine effectiveness between these formulations would be especially important for adults 65 years of age or older, since there is evidence that older adults experience more severe illness due to influenza and that influenza vaccines are less effective in this age group, compared to younger adults. Based on a systematic review of the literature, NACI has concluded that there is insufficient evidence at this time on the comparative effectiveness and immunogenicity of unadjuvanted subunit and split virus inactivated influenza vaccines in adults 65 years of age and older to support specific recommendations on the differential use of these vaccines (Grade I Evidence). Refer to 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 for additional information supporting this conclusion.

Updated presentation of the statement

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

Updated abbreviations for influenza vaccines

With the availability of many different influenza vaccines in Canada, the abbreviations used in this document have been updated to describe the defining features of the various types of influenza vaccines better. The new NACI abbreviations are as follows:

Influenza vaccine category	Formulation	Type	New NACI abbreviation*	Former NACI abbreviation
Inactivated influenza vaccine			IIV	IIV
	Trivalent		IIV3	TIV
		Standard dose†, unadjuvanted, IM administered	IIV3-SD	Standard dose TIV
		Adjuvanted‡, IM administered	IIV3-Adj	ATIV or adjuvanted TIV
		High dose§, unadjuvanted, IM administered	IIV3-HD	High dose TIV
	Quadrivalent		IIV4	QIV
		Standard dose†, unadjuvanted, IM administered	IIV4-SD	Standard dose QIV
Live attenuated influenza vaccine			LAIV	LAIV
	Trivalent	Nasal spray	LAIV3	Trivalent LAIV
	Quadrivalent	Nasal spray	LAIV4	Quadrivalent LAIV

Abbreviations: IIV: inactivated influenza vaccine; IIV3: trivalent inactivated influenza vaccine; IIV3-Adj: adjuvanted trivalent inactivated influenza vaccine; IIV3-HD: high-dose trivalent inactivated influenza vaccine; IIV3-SD: standard-dose trivalent inactivated influenza vaccine; IIV4: quadrivalent inactivated influenza vaccine; IIV4-SD: standard-dose quadrivalent inactivated influenza vaccine; IM: intramuscular; LAIV: live attenuated influenza vaccine; LAIV3: trivalent live attenuated influenza vaccine; LAIV4: quadrivalent live attenuated influenza vaccine.

* 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" 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; "-Adj" refers to an IIV with an adjuvant (e.g., IIV3-Adj for Fluad® or Fluad Pediatric®); and "-HD" refers to an IIV that contains higher antigen content than 15 µg HA per strain (e.g., IIV3-HD for Fluzone® High-Dose).
† 15 µg HA per strain.
‡ 7.5 µg (in 0.25 mL) or 15 µg (in 0.5 mL) HA per strain.
§ 60 µg HA per strain.

I.2 Background

The World Health Organization's (WHO) recommendations on the composition of influenza virus vaccines are typically available in February of each year for the upcoming season in the Northern Hemisphere. The WHO recommends that, where available, seasonal quadrivalent influenza vaccines contain the recommended three viruses for the trivalent vaccine, as well as the influenza B virus 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. 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 November 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, vaccine may still be administered up until the end of the season. Although its utility may be compromised if exposure to influenza has already occurred, vaccine providers should use every opportunity to give influenza vaccine to individuals at risk who have not been immunized during the current season, even after influenza activity has been documented in the community.

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 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 constitutes the influenza chapter of the CIG and is adapted for inclusion in the NACI Statement on Seasonal Influenza Vaccine. 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 is a respiratory infection caused primarily by influenza A and B viruses. In Canada, influenza generally occurs each year in the late fall and winter months. Influenza occurs globally with an annual attack rate estimated at 5–10% in adults and 20–30% in children[(1)].

- Symptoms of influenza typically include: 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, but some are at greater risk of more severe complications, such as pneumonia. People with chronic diseases may have worsening of their underlying disease.

- Both inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV) are authorized for use in Canada; some protect against 3 strains of influenza (i.e., trivalent formulation, IIV3) and some protect against 4 strains of influenza (i.e., quadrivalent formulation, IIV4 or LAIV4).

- Influenza vaccine is safe and well-tolerated. Influenza vaccine cannot cause influenza illness because inactivated influenza vaccines do not contain live virus and live attenuated influenza vaccines contain weakened viruses.

2. Who

NACI makes the following recommendations for individual-level and public health program-level decision making.

Recommendation for individual-level decision making

(i.e., individuals wishing to protect themselves from influenza or vaccine providers wishing to advise individual patients about preventing influenza)

- 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 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.

Influenza vaccine is less immunogenic in infants less than 6 months of age than in older children and adults and does not confer sufficient protection to make it useful before 6 months of age [(2)]. Currently available influenza vaccines are not authorized for use for 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, noting that influenza vaccine should be offered to their household contacts and care providers (see List 1).

Recommendation for public health program-level decision-making

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

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).

List 1: Groups for whom influenza vaccination is particularly recommended

People at high risk of influenza-related complications or hospitalization

- All pregnant women*;
- Adults and children with the following chronic health conditions:
  - 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);
  - 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 (body mass index [BMI] of 40 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.
- People of any age who are residents of nursing homes and other chronic care facilities;
- Adults 65 years of age and older;
- All children 6–59 months of age; 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 6–59 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.

* The risk of influenza-related hospitalization increases with length of gestation (i.e., it is higher in the third trimester than in the second).

3. How

Benefits and risks of influenza vaccination, as well as the risks of not being immunized, should be discussed prior to vaccination.

Choice of influenza vaccine

A variety of influenza vaccines are available 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 below for recommendations on choice of influenza vaccine by age group.

Dose and route of administration

The dose and route of administration varies by product (see Section II.6 below for details):

- MF59-adjuvanted trivalent inactivated influenza vaccine (IIV3-Adj; Fluad Pediatric®) for children 6–23 months of age is 0.25 mL by intramuscular (IM) injection;
- All other IIVs for all age groups is 0.5 mL by IM injection; and
- LAIV (FluMist® Quadrivalent) for people 2–59 years of age is 0.2 mL given intranasally (0.1 mL in each nostril).

Schedule

NACI recommends that:

- Children 9 years of age and older and adults should receive 1 dose of influenza vaccine each year; and
- 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.

Contraindications

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

- People who have had an anaphylactic reaction to a previous dose of influenza vaccine;
- People who have had an anaphylactic reaction to any of the vaccine components, with the exception of egg (refer to Section II.7 below for more information);
    - If an individual is found to have an allergy to a component in one influenza vaccine, consideration may be given to offering another influenza vaccine if there is a formulation not containing 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 associated with the trace amounts of ovalbumin allowed in 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.
    - As with any vaccine product, vaccine providers should be prepared for 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 below for more information).
    - 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.

For LAIV, in addition to the above-mentioned contraindications, NACI also recommends that LAIV should not be given to:

- People with immune compromising conditions, due to underlying disease, therapy, or both, as the vaccine contains live attenuated virus;

- 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;
    - LAIV is not contraindicated for people with a history of stable asthma or recurrent wheeze.

- Children less than 24 months of age, due to increased risk of wheezing.

- 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;
    - Aspirin-containing products in children less than 18 years of age should be delayed for 4 weeks after receipt of LAIV.

- Pregnant women, because it is a live attenuated vaccine and there is a lack of safety data at this time;
    - LAIV is not contraindicated in breastfeeding mothers.

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, including anaphylaxis.

Precautions

NACI recommends that:

- Influenza vaccination should usually be postponed in people with serious acute illnesses until their symptoms have abated;
    - Vaccination should not be delayed because of minor acute illness, with or without fever.

- 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 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 kill the replicating vaccine virus.
    - If antiviral agents are administered within this time frame (i.e., from 48 hours before to 2 weeks after LAIV is given), revaccination should take place at least 48 hours after the antivirals are stopped, or IIV could be given at any time.

Refer to Section II.8 below for additional information on influenza vaccine-related precautions.

Simultaneous administration with other vaccines

NACI recommends that:

- All seasonal influenza vaccines, including LAIV, may be considered for administration at the same time as, or at any time before or after, administration of other live attenuated or inactivated vaccines (see Section II.6 below for details); and

- 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.

- Annual vaccination is required because the specific strains in the vaccine are reviewed each year by WHO and often changed to provide a better match against the viruses expected to circulate, and because the body's immune response to influenza vaccination is transient and unlikely to persist beyond a year.

II.2 Epidemiology

Disease description

Influenza is a respiratory illness caused by the influenza A and B viruses 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: 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.

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 droplets spread through coughing or sneezing and through direct or indirect contact with respiratory secretions. The incubation period of seasonal influenza is usually 2 days but can range from 1–4 days. 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 6–59 months of age, pregnant women, 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, the peak may occur as early as fall or as late as spring.

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. However, adults and children with chronic health conditions, adults 65 years of age and older, and children 6–59 months of age are at greater risk of more severe complications or worsening of their underlying condition.

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. For current international influenza activity information, refer to WHO's FluNet website.

National

Together, influenza and pneumonia are ranked among the top 10 leading causes of death in Canada[3]. FluWatch is Canada's national influenza surveillance system that collects data and information from various sources to provide a national picture of influenza activity. Since the 2010–2011 season, an average of 30,000 laboratory-confirmed cases of influenza are 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[4,5]. 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 influenza-like illness (ILI) do not seek medical care or have viral diagnostic testing done.

II.3 Vaccine Products Available for Use in Canada

This section describes the influenza vaccine products that are available for use in Canada for the 2019–2020 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 available products 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-recommended

antigenic strains for the Northern Hemisphere. Vaccine producers may use antigenically equivalent strains because of their growth properties.

There are two categories of influenza vaccine authorized for use in Canada: inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (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. All influenza vaccines currently authorized for use in Canada are made from influenza viruses grown in eggs.

A summary of the characteristics of influenza vaccines available in Canada can be found in Appendix A. For complete prescribing information, readers should consult the product leaflet or information contained within the product monographs available through Health Canada's Drug Product Database.

Standard-dose inactivated influenza vaccine (IIV-SD)

The standard-dose inactivated influenza vaccines (IIV-SDs) 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. These vaccines are unadjuvanted, contain 15 µg HA per strain, and are administered as a 0.5 mL dose by IM injection. Refer to Basic Immunology and Vaccinology in Part 1 of the CIG for more information about inactivated vaccines.

Both trivalent (IIV3-SD; Agriflu®, Fluviral®, and Influvac®) and quadrivalent (IIV4-SD; Afluria® Tetra, Flulaval® Tetra, and Fluzone® Quadrivalent) products are available.

Adjuvanted inactivated influenza vaccine (IIV-Adj)

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

Trivalent products (IIV3-Adj) for children 6–23 months of age (Fluad Pediatric®) and adults 65 years of age and older (Fluad®) are available.

High-dose inactivated influenza vaccine (IIV-HD)

The high-dose inactivated influenza vaccine (IIV-HD) currently authorized for use in Canada is an unadjuvanted, split virus IIV that contains 60 µg HA per strain and is administered as a 0.5 mL dose by IM injection.

A trivalent product (IIV3-HD; Fluzone® High-Dose) for adults 65 years of age and older is available.

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, as well as the health and age of the individual receiving the vaccine. Even when there is a less-than-ideal match or lower effectiveness 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, such as 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 or given through a different route of administration, 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 contraindications to the vaccine. Table 1 provides age group-specific recommendations for the age-appropriate influenza vaccine types available 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 1 provides age group-specific recommendations for the age-appropriate influenza vaccine types available in Canada.

Table 1: 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 available for use	Recommendations on choice of influenza vaccine
6–23 months	• IIV3-SD • IIV3-Adj • IIV4-SD	• Quadrivalent influenza vaccine should be used, 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 should be used.
2–17 years*	• IIV3-SD • IIV4-SD • LAIV4	• Either IIV4-SD or LAIV4 should be used in children without contraindications, including those with non-immune compromising chronic health conditions, given the burden of influenza B disease in this age group and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine. • If IIV4-SD or LAIV4 is not available, IIV3-SD should be used. • IIV4-SD should be used for children for whom LAIV is contraindicated, such as in children with: - severe asthma; - medically attended wheezing in the 7 days prior to vaccination; - current receipt of aspirin or aspirin-containing therapy; and - immune compromising conditions.

<table>
<tr><th>Recipient by age group</th><th>Vaccine types available for use</th><th colspan="2">Recommendations on choice of influenza vaccine</th></tr>
<tr><td></td><td></td><td colspan="2">• LAIV4 may be given to children with:
- stable, non-severe asthma; and
- cystic fibrosis who are not treated with immunosuppressive drugs (e.g., prolonged systemic corticosteroids).</td></tr>
<tr><td>18–59 years</td><td>• IIV3-SD
• IIV4-SD
• LAIV4</td><td colspan="2">• Any of the available influenza vaccines should be used in adults without contraindications.

• IIV should be used for adults for whom LAIV is contraindicated, such as in:
- pregnant women;
- adults with any of the chronic health conditions identified in List 1, including immune compromising conditions; and
- HCWs.</td></tr>
<tr><td>60–64 years</td><td>• IIV3-SD
• IIV4-SD</td><td colspan="2">• Any of the available influenza vaccines should be used.</td></tr>
<tr><td rowspan="2">65 years and older†</td><td rowspan="2">• IIV3-SD
• IIV3-Adj
• IIV3-HD
• IIV4-SD</td><td>Individual-level Decision-making</td><td>Public health program–level Decision-making</td></tr>
<tr><td>• When available, IIV3-HD should be used over IIV3-SD, given the burden of influenza A(H3N2) disease and the good evidence of better efficacy compared to IIV3-SD in this age group.

• There is insufficient evidence to make comparative individual-level recommendations on the use of IIV3-Adj or IIV4-SD over IIV3-SD or among IIV3-Adj, IIV3-HD, and IIV4-SD.</td><td>• Any of the available influenza vaccines should be used.
- There is insufficient evidence (cost-effectiveness assessments have not been performed) to make comparative public health program-level recommendations on the use of the available vaccines.</td></tr>
</table>

Abbreviations: HCW: health care worker; IIV: inactivated influenza vaccine; IIV3-Adj: adjuvanted trivalent inactivated influenza vaccine; IIV3-HD: high-dose trivalent inactivated influenza vaccine; IIV3-SD: standard-dose trivalent inactivated influenza vaccine; IIV4-SD: standard-dose quadrivalent inactivated influenza vaccine; LAIV4: quadrivalent live attenuated influenza vaccine.

* Refer to Table 3 of Section V.1 for a summary of vaccine characteristics of LAIV compared with IIV in children 2–17 years of age.
† Refer to Table 4 of Section V.2 for a comparison of the vaccine characteristics of influenza vaccine types available for use in adults 65 years of age and older.

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

For influenza vaccines given by the IM route, the deltoid muscle is the recommended site in adults and children 12 months of age and older, and the anterolateral thigh is the recommended site in children 6–12 months of age. For more information on vaccine administration, please refer to Vaccine Administration Practices in Part 1 of the CIG.

Table 2: Recommended dose and route of administration, by age, for influenza vaccine types available for the 2019–2020 influenza season

Age group	Influenza vaccine type (route of administration)				Number of doses required
	IIV3-SD* or IIV4-SD† (IM)	IIV3-Adj‡ (IM)	IIV3-HD§ (IM)	LAIV4‖ (intranasal)	
6–23 months	0.5 mL¶	0.25 mL	-	-	1 or 2**
2–8 years	0.5 mL	-	-	0.2 mL (0.1 mL per nostril)	1 or 2**
9–17 years	0.5 mL	-	-	0.2 mL (0.1 mL per nostril)	1
18–59 years	0.5 mL	-	-	0.2 mL (0.1 mL per nostril)	1
60–64 years	0.5 mL	-	-	-	1
65 years and older	0.5 mL	0.5 mL	0.5 mL	-	1

Abbreviations: IIV3-Adj: adjuvanted trivalent inactivated influenza vaccine; IIV3-HD: high-dose trivalent inactivated influenza vaccine; IIV3-SD: standard-dose trivalent inactivated influenza vaccine; IIV4-SD: standard-dose quadrivalent inactivated influenza vaccine; IM: intramuscular; LAIV4: quadrivalent live attenuated influenza vaccine.

* Agriflu® (6 months and older), Fluviral® (6 months and older), Influvac® (3 years and older)
† Afluria® Tetra (5 years and older), Flulaval® Tetra (6 months and older), Fluzone® Quadrivalent (6 months and older)
‡ Fluad Pediatric® (6–23 months) or Fluad® (65 years and older)
§ Fluzone® High-Dose (65 years and older)
‖ FluMist® Quadrivalent (2–59 years)
¶ 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[6,7]. 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.
** 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 2).

Serological testing

Serologic testing is not necessary 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.

Simultaneous administration with other vaccines

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 oral polio live vaccines[8-10]. No studies have been done to assess the possibility of interference between LAIV and other live vaccines, or on LAIV given before or after other live vaccines. Additional information regarding simultaneous administration with other vaccines can be found in Section IV.4 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. NACI recognizes that some vaccine providers may choose to give LAIV and other live vaccines simultaneously or separated by at least 4 weeks if a delay is chosen. Alternatively, an IIV may be given. 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.

II.7 Vaccine Safety and Adverse Events

Data from post-marketing surveillance of influenza vaccines in Canada (Canadian Adverse Events Following Immunization Surveillance System [CAEFISS]) have shown seasonal influenza vaccines to have a safe and stable profile for adverse events following immunization (AEFIs) with no unexpected events.

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[11,12] 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[13]. All single dose formulations of IIV 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. IIV3-HD tends to induce higher rates of systemic reactions post-injection compared to IIV3-SD, but most of these reactions are mild and short-lived. The most common adverse events 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 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 vaccine components. Refer to Section II.8 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, and that the risk of GBS associated with influenza illness is larger (about 17 cases per million influenza-coded health care encounters, which are a proxy for influenza illness) than that associated with influenza vaccination.

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), which is defined as the presence of bilateral red eyes and one or more associated symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness, or sore throat) that starts within 24 hours of vaccination, with or without facial edema, was found during the 2000–2001 influenza season; few cases have been reported since then. ORS is not considered to be an allergic response. People who have a recurrence of ORS upon revaccination 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 adverse events 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.

In view of the considerable morbidity and mortality associated with influenza, a diagnosis of influenza vaccine allergy 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 in one study and 45 years and older in the other) had an apparent decreased response to influenza vaccination as measured by reduced geometric mean titres (GMT)[14] or reduced VE against medically attended acute respiratory illness[15]. 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 (AEFI)

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

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. 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 adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom, or disease. In general, any serious or unexpected adverse event felt to be temporally related to vaccination should be reported. An unexpected AEFI is an event that is not listed in the approved product monograph but may be due to the vaccination, or a change in the nature, severity, specificity, or outcome of a known AEFI.

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 contraindications 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 or difference between the Northern and Southern Hemisphere vaccines, the similarity or difference 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 CIG. 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 pregnant women

NACI recommends the inclusion of all pregnant women, at any stage of pregnancy, among the particularly recommended recipients of IIV, due to the risk of influenza-associated morbidity in pregnant women[16-20], evidence of adverse neonatal outcomes associated with maternal respiratory hospitalization or influenza during pregnancy[21-24], evidence that vaccination of pregnant women protects their newborns from influenza and influenza-related hospitalization[25-28], and evidence that infants born during influenza season to vaccinated women are less likely to be premature, small for gestational age, and of low birth weight[29-32].

The safety of IIV during pregnancy has been reviewed[33]. Active studies of influenza vaccination during pregnancy have not shown evidence of harm to the mother or fetus associated with influenza immunization[34]. Although the cumulative sample size of active studies of influenza vaccination in pregnant women 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[18,19,33,35]. 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 has not revealed any safety concerns[36,37].

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.

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 human immunodeficiency virus (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) 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.

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 conditions 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[38], and influenza-attributed mortality rates increase with increased age[39].

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 the particularly recommended recipients of influenza vaccine.

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.

Indigenous peoples

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

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)[40], obesity, delayed access to health care, and increased susceptibility to disease because of poor housing and overcrowding[41-43]. 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 immunized. Immunization of care providers decreases their own risk of illness[44,45], as well as the risk of death and other serious outcomes among the individuals for whom they provide care[46-49]. Immunization of care providers and residents of nursing homes is associated with decreased risk of ILI outbreaks[50].

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

- 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; and
- Contacts, both adults and children, of individuals at high risk, whether or not the individual at high risk has been vaccinated.

Health care and other providers in facilities and community settings

This group includes HCWs, regular visitors, emergency response workers, and others who have contact with residents of 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. For the purposes of this statement, HCWs include any person, paid or unpaid, who provides services, works, volunteers, or trains in a health care setting.

Influenza immunization provides benefits to HCWs and to the patients for whom they care. NACI considers the receipt of influenza vaccination to be an essential component of the standard of care for all HCWs for the protection of their patients.

Transmission of influenza between infected HCWs and their vulnerable patients results in significant morbidity and mortality. For example, randomized controlled trials (RCTs) conducted in geriatric long-term care settings have demonstrated that vaccination of HCWs is associated with substantial decreases in morbidity[47-49] and all-cause mortality[46-49] in the residents. Therefore, HCWs should consider annual influenza vaccination included in their responsibility to provide the highest standard of care. In the absence of contraindications, refusal of HCWs to be vaccinated against influenza implies failure in their duty of care to patients.

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 immunization[51]. 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 6–59 months of age, and providers of services within closed or relatively closed settings to people at high risk (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[44,45,52-54].

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[55] 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[56].

Therefore, NACI recommends seasonal influenza vaccination for people 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[57-60]. Refer to the Statement on Seasonal Influenza Vaccine for 2013–2014 for further information informing 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 do not have contraindications to the vaccine.

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

IV. VACCINE PREPARATIONS AVAILABLE FOR USE IN CANADA: ADDITIONAL INFORMATION

The following sections describe information on the efficacy and effectiveness, immunogenicity, and safety of influenza vaccine by type in two categories: IIV and LAIV. Refer to Appendix A for a summary of the characteristics of specific influenza vaccine products available in Canada for the 2019–2020 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 monitor closely 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[61-66].

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[67,68]. 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[6,7,69]. 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, which is thought to mitigate the reduced immune response observed in the studies with the 0.25 mL dose of IIV-SDs.

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[70].

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[71-74].

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[75-78].

Standard-dose trivalent inactivated influenza vaccine (IIV3-SD)

Vaccines currently available for use:

- Agriflu® (Seqirus)
- Fluviral® (GlaxoSmithKline)
- Influvac® (BGP Pharma ULC, operating as Mylan EPD)

Efficacy and effectiveness

The NACI Literature Review on Influenza Vaccination in Healthy 5–18-Year-olds found that VE of IIV3-SD against laboratory-confirmed influenza was variable but was most frequently between 65–85%[79-97]. 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 outcome measures and the study population[98,99]. Systematic reviews have demonstrated that influenza vaccine decreases the incidence of pneumonia, hospital admissions, and deaths in the elderly[98] and reduces exacerbations in people with chronic obstructive pulmonary disease[100]. 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[101], hospitalizations for cardiac disease and stroke in adults 65 years of age and

older[102], and hospitalization and deaths in adults 18 years of age and older with diabetes mellitus[103] 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[104-108].

Immunogenicity

Both humoral and cell-mediated 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)[109]. 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 serious adverse events of note[110]. 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[111-113]. Post-vaccination fever may be observed in 12% or less of vaccinated children 1–5 years of age[89,113].

For adults, IIV3-SDs have been demonstrated to have a good safety profile with acceptable reactogenicity[110]. 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.

Adjuvanted trivalent inactivated influenza vaccine (IIV3-Adj)

Vaccines currently available 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. There remain no efficacy or effectiveness studies that compare IIV3-Adj with IIV3-HD or IIV4-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[114]. 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[115,116]. MF59 further facilitates the internalization of antigen by these dendritic cells[115,117]. 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[115].

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.

Serious adverse events 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[118]. 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[118-123]. 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[123]. 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 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 adverse events 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[121].

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 may not be initiated by the adjuvant, but by another component of the vaccine, specifically the A(H1N1) viral antigen[124]. 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 trivalent inactivated influenza vaccine (IIV3-HD)

Vaccine currently available for use:

- Fluzone® High-Dose (Sanofi Pasteur)

Efficacy and effectiveness

There is good evidence that Fluzone High-Dose (IIV3-HD) provides superior protection compared with IIV3-SD in adults 65 years of age and older. A few studies found that IIV3-HD may provide greater benefit in the very elderly (e.g., 75 years of age and older) compared to younger elderly (e.g., 65–74 years of age)[125-127]; however, additional studies are needed to validate this finding. There remain no efficacy or effectiveness studies that compare IIV3-HD with IIV3-Adj or IIV4-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-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[128-133]. Rates of seroconversion were found to be about 19% higher (ranging from 8–39%) 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[128-135]. 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[129]. In Nace et al., seroprotection was higher against A(H3N2) and B but not A(H1N1); this finding may be attributed to strain circulation during the study that made it difficult to assess seroprotection against this subtype[133].

Geometric mean titre 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[128-132,134,135]. 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.

Safety

IIV3-HD has been observed to produce a higher rate of some systemic 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. Serious adverse events were rare and similar in frequency between standard-dose and high-dose vaccines. Refer to NACI's A Review of the Literature of High Dose Seasonal Influenza Vaccine for Adults 65 Years and Older for details.

Standard-dose quadrivalent inactivated influenza vaccine (IIV4-SD)

Vaccines currently available for use:

- Afluria® Tetra (Seqirus)
- Flulaval® Tetra (GlaxoSmithKline)
- Fluzone® Quadrivalent (Sanofi Pasteur)

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[136]. No literature was found in this review on efficacy or effectiveness directly comparing trivalent and quadrivalent formulations.

Immunogenicity

In this same review of the literature, 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 Committee for Medicinal Products for Human Use (CHMP) and Centre for Biologics Evaluation and Research (CBER) criteria for evaluation of influenza vaccine immunogenicity, including those 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[137].

Safety

As IIV4-SD has higher antigenic content than IIV3-SD, increased reactogenicity may be a concern for the quadrivalent vaccine. However, 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[138].

IV.2 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 available 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's 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 of America found low effectiveness of LAIV against circulating post-2009 pandemic A(H1N1), or 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)[139].

This finding led to the manufacturer replacing the A(H1N1)pdm09 component of LAIV with a new strain. 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[140]. 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[141-143].

Safety

The most common adverse events 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[140]. This finding is expected to be the same for recipients of LAIV4; however, pre-licensure clinical studies for LAIV4 were conducted in adults and children 2 years of age and older.

Studies on LAIV3 have shown that vaccine virus can be recovered by nasal swab in children and adults following immunization (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.

IV.3 Schedule

The first time that children 6 months to less than 9 years of age receive seasonal influenza immunization, a two-dose schedule is required to achieve protection[144-146]. Several studies have looked at whether these two initial doses need to be given in the same season[63,64,147]. 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[63,64].

However, seroprotection rates to the B component were considerably reduced 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[62,64]. Issues related to effective prime-boost when there is a major change in influenza B lineage across sequential seasons require further evaluation[148].

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.4 Simultaneous Administration 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[149]. 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[150-153].

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[8-10]. 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, 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. NACI recognizes that some vaccine providers may choose to give LAIV and other live vaccines simultaneously or separated by at least 4 weeks as a professional preference. Alternatively, an inactivated influenza vaccine may be given.

IV.5 Additional Vaccine Safety Considerations

Influenza vaccine is safe and well tolerated. Contraindications, precautions, and common adverse events 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 appropriate product, including 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 adverse events. 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[154].

The attributable risk of GBS in the period following seasonal and monovalent 2009 pandemic influenza vaccination is about one excess case per million vaccinations[155,156]. 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[156].

This finding shows 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[157-160].

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 available influenza vaccines. This section provides more details for these recommendations.

V.1 Children

Burden of disease in children

The proportion of disease burden due to influenza B infection is higher in children compared to other age groups. Canadian surveillance data from 2001–2002 to 2012–2013 has shown that influenza B strains accounted for 17% of laboratory-confirmed tests for influenza. Children less than 24 months of age comprise approximately 2% of the Canadian population[161].

Using case-based laboratory data from 2001–2012, children 0–23 months of age averaged (excluding 2009) 10.8% of reported influenza B cases (range: 8.3–13.7%). With respect to severe outcomes (e.g., hospitalization, ICU 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)[162].

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

In the NACI Literature Review on Quadrivalent Influenza Vaccines, a review of B lineage antigens included in the Canadian influenza vaccines and the circulating strains each season indicates a match in 5 of the 12 seasons from 2001–2002 through to 2012–2013, a moderate match (about 50% from each lineage) in 1 season, and a mismatch in remaining 6 influenza seasons (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 available 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 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

Three types of influenza vaccine are available for use in children 2–17 years of age: IIV3-SD, IIV4-SD, 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 either IIV4-SD or LAIV4 should be used in children without contraindications. If IIV4-SD or LAIV4 is not available, IIV3-SD 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, with the exception of those with severe asthma (as defined as currently on oral or high-dose inhaled glucocorticosteroids), those with medically attended wheezing in the 7 days prior to vaccination, and those with immune compromising conditions, all of whom should receive IIV. If IIV is used, NACI recommends that a quadrivalent vaccine should be used. If a quadrivalent vaccine is not available, a trivalent vaccine should be used.

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

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

Summary of vaccine characteristics for decision making

IIV (IIV3-SD and IIV4-SD) and LAIV (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 3 below, may be considered in making a decision on the preferred vaccine option(s) for use by an individual or a public health program.

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

Considerations*	LAIV† compared with IIV‡
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 RCTs, 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 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, as well as those currently receiving aspirin or aspirin-containing therapy.
Administration	Delivery of LAIV as a nasal spray may be preferable for children who are averse to receiving the vaccine by needle injection.

Abbreviations: IIV3-SD: standard-dose trivalent inactivated influenza vaccine; IIV4-SD: standard-dose quadrivalent inactivated influenza vaccine; LAIV3: trivalent live attenuated influenza vaccine; LAIV4: quadrivalent live attenuated influenza vaccine.

* NACI has not assessed the comparative cost-effectiveness of available influenza vaccine types for children 2–17 years of age.
† 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.
‡ Both trivalent and quadrivalent IIV-SD (IIV3-SD and IIV4-SD) are available for use in Canada for the 2019–2020 influenza season.

V.2 Adults

Burden of disease in adults

A study focusing on estimates of deaths associated with influenza in the United States of America 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)[163]. The study also states that deaths among persons 65 years of age and older accounted for 87.9% of the overall estimated average annual influenza-associated deaths with underlying pneumonia and influenza causes.

When influenza-related deaths were estimated using underlying respiratory and circulatory causes, 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 underlying medical cause. 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[164].

Canadian surveillance data show that hospitalization rates among adults 65 years of age and older were higher during the 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 A(H3N2) circulation predominated and in which there was a vaccine mismatch with the circulating A(H3N2) strain.

Similar to the hospitalization rates, death rates among seniors were highest in the 2014–2015 season compared to the previous five seasons and compared to the previous A(H3N2) season in 2012–2013. Death 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 prevalence of positive cases in younger age groups.

Adults 18–59 years of age

Three types of influenza vaccine are available for use in adults 18–59 years of age: IIV3-SD, IIV4-SD, and LAIV4.

NACI recommends that any of the available influenza vaccines should be used in adults without contraindications. IIV should be used for pregnant women, adults with any of the chronic health conditions identified in List 1, and HCWs.

Adults 60–64 years of age

Two types of influenza vaccine are available for use in adults 60–64 years of age: IIV3-SD and IIV4-SD.

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

Adults 65 years of age and older

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

Recommendation for individual-level decision making

NACI concludes that, given the burden of disease associated with influenza A(H3N2) and the good evidence of better efficacy compared to IIV3-SD in this age group, when available, IIV3-HD should be used over IIV3-SD.

There is insufficient evidence to make comparative recommendations on the use of IIV3-Adj or IIV4-SD over IIV3-SD or among IIV3-Adj, IIV3-HD, and IIV4-SD.

Recommendation for public health program-level decision making

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

IIV3-HD is expected to provide superior protection compared to IIV3-SD; however, with cost-effectiveness assessments having been outside the scope of the evidence review and without data on the relative efficacy and effectiveness between IIV3-HD, IIV3-Adj, and IIV4-SD, there is insufficient evidence to make a comparative recommendation on the use of these vaccines at the programmatic level.

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

Summary of vaccine characteristics for decision making

There are four types of inactivated influenza vaccines (IIV3-SD, IIV3-Adj, IIV3-HD, and IIV4-SD) authorized for use in Canada for adults 65 years of age and older. The comparison of vaccine characteristics across vaccine types, in Table 4 below, may be considered in making a decision on the preferred vaccine option(s) for use by an individual or a public health program. Due to a lack of available data directly comparing the performance of IIV3-Adj, IIV3-HD, and IIV4-SD, considerations for these vaccines in Table 4 are compared to IIV3-SD for which comparative data on efficacy, effectiveness, and/or immunogenicity with each of IIV3-Adj, IIV3-HD, and IIV4-SD are available.

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

Considerations*	Influenza vaccine type compared with IIV3-SD		
	IIV3-Adj	**IIV3-HD**	**IIV4-SD**
Efficacy and effectiveness	Insufficient evidence compared with IIV3-SD.	Superior protection compared with IIV3-SD, particularly in influenza A(H3N2)-dominant seasons.**	Additional protection against the influenza B strain not contained in IIV3.
	Insufficient head-to-head studies directly comparing efficacy and effectiveness of IIV3-Adj, IIV3-HD, and IIV4-SD.		
Immunogenicity	Non-inferior immune response compared to IIV3-SD. Superiority to IIV3-SD has not been consistently demonstrated.	Generally better immune response compared to IIV3-SD.	Non-inferior immune response to the strains contained in IIV3-SD with better immune response to the additional B strain.
	Insufficient head-to-head studies comparing immunogenicity data of IIV3-Adj, IIV3-HD, and IIV4-SD.		
Contraindications	Same contraindications as IIV3-SD.***		
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. Serious adverse events were comparable to IIV3-SD and were uncommon.	Higher rate of some systemic reactions than IIV3-SD; most systemic reactions were mild and transient. Serious adverse events were rare and similar in frequency to IIV3-SD.	Pre-licensure clinical trials and post-marketing surveillance showed a similar safety profile to IIV3.

Abbreviations: IIV3-Adj: adjuvanted trivalent inactivated influenza vaccine; IIV3-HD: high-dose trivalent inactivated influenza vaccine; IIV3-SD: standard-dose trivalent inactivated influenza vaccine; IIV4-SD: standard-dose quadrivalent inactivated influenza vaccine.

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

** The burden of influenza A(H3N2) disease is higher in adults 65 years of age and older compared to younger age groups.

*** Influenza vaccines are contraindicated in people who have had an anaphylactic reaction to any of the vaccine components, with the exception of egg. Please note that not all vaccines listed contain the same components.

Adults with chronic health conditions

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

Pregnant women

NACI recommends that any age-appropriate IIV, but not LAIV, should be offered to pregnant women.

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

Health care workers

NACI recommends that any age-appropriate IIV, 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[140]. 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.

APPENDIX A: CHARACTERISTICS OF INFLUENZA VACCINES AVAILABLE FOR USE IN CANADA, 2019–2020*

Characteristic	Product name (manufacturer)								
	Agriflu® (Seqirus)	**Fluviral® (GSK)**	**Influvac® (BGP Pharma ULC)**	**Fluad Pediatric® and Fluad® (Seqirus)**	**Fluzone® High-Dose (Sanofi Pasteur)**	**Afluria® Tetra (Seqirus)**	**Flulaval® Tetra (GSK)**	**Fluzone® Quadrivalent (Sanofi Pasteur)**	**FluMist® Quadrivalent (AstraZeneca)**
Vaccine type	IIV3-SD (subunit inactivated, trivalent)	IIV3-SD (split virus inactivated, trivalent)	IIV3-SD (subunit inactivated, trivalent)	IIV3-Adj (adjuvanted, subunit inactivated, trivalent)	IIV3-HD (high-dose, split virus inactivated, trivalent)	IIV4-SD (split virus inactivated, quadrivalent)	IIV4-SD (split virus inactivated, quadrivalent)	IIV4-SD (split virus inactivated, quadrivalent)	LAIV4 (live attenuated, quadrivalent)
Route of administration	IM	IM	IM†	IM	IM	IM	IM	IM	Intranasal
Authorized ages for use	6 months and older	6 months and older	3 years and older	**Pediatric:** 6–23 months **Adult:** 65 years and older	65 years and older	5 years and older	6 months and older	6 months and older	2–59 years
Antigen content for each vaccine strain	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	**Pediatric:** 7.5 µg HA /0.25 mL dose **Adult:** 15 µg HA /0.5 mL dose	60 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	$10^{6.5\text{-}7.5}$ FFU of live attenuated reassortants /0.2 mL dose (given as 0.1 mL in each nostril)
Adjuvant	None	None	None	MF59	None	None	None	None	None

Characteristic	Product name (manufacturer)								
	Agriflu® (Seqirus)	**Fluviral® (GSK)**	**Influvac® (BGP Pharma ULC)**	**Fluad Pediatric® and Fluad® (Seqirus)**	**Fluzone® High-Dose (Sanofi Pasteur)**	**Afluria® Tetra (Seqirus)**	**Flulaval® Tetra (GSK)**	**Fluzone® Quadrivalent (Sanofi Pasteur)**	**FluMist® Quadrivalent (AstraZeneca)**
Formats available	5 mL multi-dose vial Single dose pre-filled syringe without a needle	5 mL multi-dose vial	Single dose pre-filled syringe with Luer tip	Single dose pre-filled syringe without a needle	Single dose pre-filled syringe	5 mL multi-dose vial Single dose pre-filled syringe without attached needle	5 mL multi-dose vial Single dose pre-filled syringe	5 mL multi-dose vial Single dose vial Single-dose pre-filled syringe without attached needle	Single use pre-filled glass sprayer
Post-puncture shelf life for multi-dose vials	28 days	28 days	Not applicable	Not applicable	Not applicable	Not available‡	28 days	Up to expiry date indicated on vial label	Not applicable
Thimerosal	Yes (multi-dose vial only)	Yes	No	No	No	Yes (multi-dose vial only)	Yes (multi-dose vial only)	Yes (multi-dose vial only)	No
Antibiotics (traces)	Kanamycin and neomycin	None	Gentamicin	Kanamycin and neomycin	None	Neomycin and polymixin B	None	None	Gentamicin
Egg protein (traces)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviations: FFU: fluorescent focus units; HA: hemagglutinin; IIV3-Adj: adjuvanted trivalent inactivated influenza vaccine; IIV3-HD: high-dose trivalent inactivated influenza vaccine; IIV3-SD: standard-dose trivalent inactivated influenza vaccine; IIV4-SD: standard-dose quadrivalent inactivated influenza vaccine; IM: intramuscular; LAIV4: quadrivalent live attenuated influenza vaccine; NA: neuraminidase.

* 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.
† Refer to product monograph for alternate route(s) of administration.
‡ Information not available at time of writing; refer to product monograph.

LIST OF ABBREVIATIONS

AEFI	Adverse event following immunization
BMI	Body mass index
CI	Confidence interval
FFU	Fluorescent focus units
GBS	Guillain-Barré syndrome
GMT	Geometric mean titre
GMTR	Geometric mean titre rise
HA	Hemagglutinin
HCW	Health care worker
HIV	Human immunodeficiency virus
Ig	Immunoglobulin
IIV	Inactivated influenza vaccine
IIV3	Trivalent inactivated influenza vaccine (formerly “TIV)”
IIV3-Adj	Adjuvanted trivalent inactivated influenza vaccine (formerly “ATIV” or “adjuvanted TIV”)
IIV3-HD	High-dose trivalent inactivated influenza vaccine (formerly “high-dose TIV”)
IIV3-SD	Standard-dose trivalent inactivated influenza vaccine
IIV4	Quadrivalent inactivated influenza vaccine (formerly “QIV”)
IIV4-SD	Standard-dose quadrivalent inactivated influenza vaccine
ILI	Influenza-like illness
IM	Intramuscular
LAIV	Live attenuated influenza vaccine
LAIV3	Trivalent live attenuated influenza vaccine (formerly “trivalent LAIV”)
LAIV4	Quadrivalent live attenuated influenza vaccine (formerly “quadrivalent LAIV”)
MMR	Measles, mumps and rubella

MMRV	Measles, mumps, rubella, and varicella
NA	Neuraminidase
NACI	National Advisory Committee on Immunization
ORS	Oculorespiratory syndrome
PHAC	Public Health Agency of Canada
RCT	Randomized controlled trial
VE	Vaccine effectiveness
WHO	World Health Organization

ACKNOWLEDGMENTS

This statement was prepared by: Dr. L. Zhao, Ms. K. Young, Dr. R. Stirling, Dr. I. Gemmill, and approved by NACI.

Influenza Working Group Members: Dr. I. Gemmill (Chair), Dr. C. Bancej, Ms. L. Cochrane, Dr. N. Dayneka, Dr. L. Grohskopf, Dr. D. Kumar, Dr. J. Langley, Dr. M. Lavoie, Ms. A. Lebans, Dr. J. McElhaney, Dr. A. McGeer, Dr. D. Moore, Dr. B. Warshawsky, and Dr. J. Xiong.

NACI Members: Dr. C. Quach (Chair), Dr. W. Vaudry (Vice-Chair), Dr. N. Dayneka, Dr. P. De Wals, Dr. S. Deeks, Dr. V. Dubey, Dr. R. Harrison, Dr. M. Lavoie, Dr C. Rotstein, Dr. M. Salvadori, Dr. B. Sander, Dr. N. Sicard, and Dr. R. Warrington.

Liaison Representatives: Dr. J. Brophy (Canadian Association for Immunization Research and Evaluation), Dr. E. Castillo (Society of Obstetricians and Gynaecologists of Canada), Dr. A. Cohn (Centers for Disease Control and Prevention, United States), Ms. T. Cole (Canadian Immunization Committee), Dr. J. Emili (College of Family Physicians of Canada), Dr. K. Klein (Council of Chief Medical Officers of Health), Dr. C. Mah (Canadian Public Health Association), Dr. D. Moore (Canadian Paediatric Society), and Dr. A. Pham-Huy (Association of Medical Microbiology and Infectious Disease Canada).

Ex-Officio Representatives: Dr. (LCdr) K. Barnes (National Defence and the Canadian Armed Forces), Ms. E. Henry (Centre for Immunization and Respiratory Infectious Diseases [CIRID], Public Health Agency of Canada [PHAC]), Dr. G. Coleman (Biologics and Genetic Therapies Directorate, Health Canada [HC]), Dr. J. Gallivan (Marketed Health Products Directorate, HC), Ms. J. Pennock (CIRID, PHAC), Dr. G. Poliquin (National Microbiology Laboratory, PHAC), and Dr. T. Wong (First Nations and Inuit Health Branch, Indigenous Services Canada).

NACI gratefully acknowledges the contribution of: Dr. M. Doll, Ms. A. Fleurant, Ms. A. House, Ms. M. Laplante, and Dr. M. Tunis.

REFERENCES

1. World Health Organization. Influenza (seasonal): fact sheet N°211. 2014. Accessed: 9 October 2018. Available from: http://www.who.int/mediacentre/factsheets/fs211/en/

2. Moriarty LF, Omer SB. Infants and the seasonal influenza vaccine. A global perspective on safety, effectiveness, and alternate forms of protection. Hum Vaccin Immunother. 2014;10(9):2721-8

3. Statistics Canada. The 10 leading causes of death, 2011. 2014. Accessed: 9 October 2018. Available from: http://www.statcan.gc.ca/pub/82-625-x/2014001/article/11896-eng.htm

4. Schanzer DL, McGeer A, Morris K. Statistical estimates of respiratory admissions attributable to seasonal and pandemic influenza for Canada. Influenza Other Respir Viruses. 2013;7(5):799-808

5. Schanzer DL, Sevenhuysen C, Winchester B, Mersereau T. Estimating influenza deaths in Canada, 1992-2009. PLoS One. 2013;8(11):e80481

6. Langley JM, Vanderkooi OG, Garfield HA, Hebert J, Chandrasekaran V, Jain VK, Fries L. Immunogenicity and safety of 2 dose levels of a thimersol-free trivalent seasonal influenza vaccine in children aged 6-35 months. J Ped Infect Dis. 2012;1(1):55-8

7. Skowronski DM, Hottes TS, Chong M, De Serres G, Scheifele DW, Ward BJ, Halperin SA, Janjua NZ, Chan T, Sabaiduc S, Petric M. Randomized controlled trial of dose response to influenza vaccine in children aged 6 to 23 months. Pediatrics. 2011;128(2):e276-89

8. Breiman RF, Brooks WA, Goswami D, Lagos R, Borja-Tabora C, Lanata CF, Londoño JA, Lum LC, Rappaport R, Razmpour A, Walker RE. A multinational, randomized, placebo-controlled trial to assess the immunogenicity, safety, and tolerability of live attenuated influenza vaccine coadministered with oral poliovirus vaccine in healthy young children. Vaccine. 2009;27(40):5472-9

9. Lum LC, Borja-Tabora CF, Breiman RF, Vesikari T, Sablan BP, Chay OM, Tantracheewathorn T, Schmitt HJ, Lau YL, Bowonkiratikachorn P, Tam JS. Influenza vaccine concurrently administered with a combination measles, mumps, and rubella vaccine to young children. Vaccine. 2010;28(6):1566-74

10. Nolan T, Bernstein DI, Block SL, Hilty M, Keyserling HL, Marchant C, Marshall H, Richmond P, Yogev R, Cordova J, Cho I. Safety and immunogenicity of concurrent administration of live attenuated influenza vaccine with measles-mumps-rubella and varicella vaccines to infants 12 to 15 months of age. Pediatrics. 2008;121(3):508-16

11. National Advisory Committee on Immunization. Statement on thimerosal. Can Commun Dis Rep. 2003;29(ACS-1):1-12

12. National Advisory Committee on Immunization. Thimerosal: updated statement. an Advisory Committee Statement (ACS). Can Commun Dis Rep. 2007;33(ACS-6):1-13

13. Gerber JS, Offit PA. Vaccines and autism: a tale of shifting hypotheses. Clin Infect Dis. 2009;48(4):456-61

14. Black S, Nicolay U, Del Giudice G, Rappuoli R. Influence of statins on influenza vaccine response in elderly individuals. J Infect Dis. 2016;213(8):1224-8

15. Omer SB, Phadke VK, Bednarczyk RA, Chamberlain AT, Brosseau JL, Orenstein WA. Impact of statins on influenza vaccine effectiveness against medically attended acute respiratory illness. J Infect Dis. 2016;213(8):1216-23

16. Louie JK, Acosta M, Jamieson DJ, Honein MA. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. N Engl J Med. 2010;362(1):27-35

17. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, Louie J, Doyle TJ, Crockett M, Lynfield R, Moore Z. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA. 2010;303(15):1517-25

18. Mak TK, Mangtani P, Leese J, Watson JM, Pfeifer D. Influenza vaccination in pregnancy: current evidence and selected national policies. Lancet Infect Dis. 2008;8(1):44-52

19. McNeil S, Halperin B, MacDonald N. Influenza in pregnancy: the case for prevention. Adv Exp Med Biol. 2009;634:161-83

20. Rasmussen SA, Jamieson DJ, Bresee JS. Pandemic influenza and pregnant women. Emerg Infect Dis. 2008;14(1):95-100

21. Centers for Disease Control and Prevention. Maternal and infant outcomes among severely ill pregnant and postpartum women with 2009 pandemic influenza A (H1N1)--United States, April 2009-August 2010. MMWR Morb Mortal Wkly Rep. 2011;60(35):1193-6

22. Pierce M, Kurinczuk J, Spark P, Brocklehurst P, Knight M. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. BMJ. 2011;342:d3214

23. Goldenberg R, Culhane J, Iams J, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75-84

24. McNeil SA, Dodds LA, Fell DB, Allen VM, Halperin BA, Steinhoff MC, MacDonald NE. Effect of respiratory hospitalization during pregnancy on infant outcomes. Am J Obstet Gynecol. 2011;204(6 Suppl 1):S54-7

25. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, Omer SB, Shahid NS, Breiman RF, Steinhoff MC. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med. 2008;359(15):1555-64

26. Poehling K, Szilagyi P, Staat M, Snively BM, Payne DC, Bridges CB, Chu SY, Light LS, Prill MM, Finelli L, Griffin MR. Impact of maternal immunization on influenza hospitalizations in infants. Obstet Gynecol. 2011;204(6 Suppl 1):S141-8

27. Eick AA, Uyeki TM, Klimov A, Hall H, Reid R, Santosham M, O'Brien KL. Maternal influenza vaccination and effect on influenza virus infection in young infants. Arch Pediatr Adolesc Med. 2011;165(2):104-11

28. France EK, McClure D, Hambidge S, Hambidge S, Xu S, Yamasaki K, Shay D, Weintraub E, Fry AM, Black SB, Shinefield HR. Impact of maternal influenza vaccination during pregnancy on the incidence of acute respiratory illness visits among infants. Arch Pediatr Adolesc Med. 2006;160(12):1277-83

29. Steinhoff M, Omer S, Roy E, El Arifeen S, Raqib R, Dodd C, Breiman RF, Zaman K. Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial. CMAJ. 2012;184(6):645-53

30. Fell DB, Sprague AE, Liu N, Yasseen III AS, Wen SW, Smith G, Walker MC. H1N1 influenza vaccination during pregnancy and fetal and neonatal outcomes. Am J Public Health. 2012;102(6):e33-40

31. Omer S, Goodman D, Steinhoff M, et al. Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study. PLoS Med. 2011;8(5):e1000441

32. Dodds L, MacDonald N, Scott J, Rochat R, Klugman KP, Stoll BJ, Ramakrishnan U. The association between influenza vaccine in pregnancy and adverse neonatal outcomes. J Obstetr Gynecol Can. 2012;34(8):714-20

33. Tamma PD, Ault KA, del Rio C, Steinhoff MC, Halsey NA, Omer SB. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol. 2009;201(6):547-52

34. MacDonald NE, Riley LE, Steinhoff MC. Influenza immunization in pregnancy. Obstet Gynecol. 2009;114(2 Pt 1):365-8

35. Moro PL, Broder K, Zheteyeva Y, Walton K, Rohan P, Sutherland A, Guh A, Haber P, DeStefano F, Vellozzi C. Adverse events in pregnant women following administration of trivalent inactivated influenza vaccine and live attenuated influenza vaccine in the Vaccine Adverse Event Reporting System, 1990-2009. Am J Obstet Gynecol. 2011;204(2):146e1-7

36. Public Health Agency of Canada. Vaccine surveillance report—adverse events following immunization. Ottawa: Public Health Agency of Canada. 2010

37. European Medicines Agency. Fifteenth pandemic pharmacovigilance update. London: European Medicines Agency. 2010. Accessed: 9 October 2018. Available from: https://www.ema.europa.eu/documents/report/fifteenth-pandemic-pharmacovigilance-update_en.pdf

38. Simonsen L, Fukuda K, Schonberger LB, Cox NJ. The impact of influenza epidemics on hospitalizations. J Infect Dis. 2000;181(3):831-7

39. Schanzer DL, Tam TW, Langley JM, Winchester BT. Influenza-attributable deaths, Canada 1990-1999. Epidemiol Infect. 2007;135(7):1109-16

40. Centers for Disease Control and Prevention. Deaths related to 2009 pandemic influenza A (H1N1) among American Indian/Alaska Natives - 12 states, 2009. MMWR Morb Mortal Wkly Rep. 2009;58(48):1341-4

41. National Center for Education Statistics. Individuals, families and children in poverty. Status and trends in the education of American Indians and Alaska Natives. Washington, DC: US Department of Education. 2008. Accessed: 9 October 2018. Available from: http://nces.ed.gov/pubs2008/nativetrends/ind_1_6.asp

42. Indigenous and Northern Affairs Canada. Highlights from the report of the Royal Commission on Aboriginal Peoples - people to people, nation to nation. 2010. Accessed: 9 October 2018. Available from: http://www.aadnc-aandc.gc.ca/eng/1100100014597/1100100014637

43. Clark M, Riben P, Nowgesic E. The association of housing density, isolation and tuberculosis in Canadian First Nations communities. Int J Epidemiol. 2002;31(5):940-5

44. Saxen H, Virtanen M. Randomized, placebo-controlled double blind study on the efficacy of influenza immunization on absenteeism of health care workers. Pediatr Infect Dis J. 1999;18(9):779-83

45. Wilde JA, McMillan JA, Serwint J, Butta J, O'Riordan MA, Steinhoff MC. Effectiveness of influenza vaccine in health care professionals: a randomized trial. JAMA. 1999;281(10):908-13

46. Carman WF, Elder AG, Wallace LA, McAulay K, Walker A, Murray GD, Stott DJ. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. Lancet. 2000;355(9198):93-7

47. Hayward AC, Harling R, Wetten S, Johnson AM, Munro S, Smedley J, Murad S, Watson JM. Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. BMJ. 2006;333(7581):1241

48. Potter J, Stott DJ, Roberts MA, Elder AG, O'donnell B, Knight PV, Carman WF. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. J Infect Dis. 1997;175(1):1-6

49. Lemaitre M, Meret T, Rothan-Tondeur M, Belmin J, Lejonc JL, Luquel L, Piette F, Salom M, Verny M, Vetel JM, Veyssier P. Effect of influenza vaccination of nursing home staff on mortality of residents: a cluster-randomized trial. J Am Geriatr Soc. 2009;57(9):1580-6

50. Shugarman LR, Hales C, Setodji CM, Bardenheier B, Lynn J. The influence of staff and resident immunization rates on influenza-like illness outbreaks in nursing homes. J Am Med Dir Assoc. 2006;7(9):562-7

51. Accreditation Canada. Infection prevention and control standards. 9th ed. Ottawa: Accreditation Canada. 2013

52. Grotto I, Mandel Y, Green MS, Varsano N, Gdalevich M, Ashkenazi I, Shemer J. Influenza vaccine efficacy in young, healthy adults. Clin Infect Dis. 1998;26(4):913-7

53. Leighton L, Williams M, Aubery D, Parker SH. Sickness absence following a campaign of vaccination against influenza in the workplace. Occup Med (Lond). 1996;46(2):146-50

54. Nichol KL, Lind A, Margolis KL, Murdoch M, McFadden R, Hauge M, Magnan S, Drake M. The effectiveness of vaccination against influenza in healthy, working adults. N Engl J Med. 1995;333(14):889-93

55. Department of Health (UK). Flu vaccination for poultry workers. London: Department of Health. 2007

56. Gray GC, Trampel DW, Roth JA. Pandemic influenza planning: shouldn't swine and poultry workers be included? Vaccine. 2007;25(22):4376-81

57. Bridges CB, Lim W, Hu-Primmer J, Sims L, Fukuda K, Mak KH, Rowe T, Thompson WW, Conn L, Lu X, Cox NJ. Risk of influenza A (H5N1) infection among poultry workers, Hong Kong, 1997-1998. J Infect Dis. 2002;185(8):1005-10

58. Puzelli S, Di Trani L, Fabiani C, Campitelli L, De Marco MA, Capua I, Aguilera JF, Zambon M, Donatelli I. Serological analysis of serum samples from humans exposed to avian H7 influenza viruses in Italy between 1999 and 2003. J Infect Dis. 2005;192(8):1318-22

59. Tweed SA, Skowronski DM, David ST, Larder A, Petric M, Lees W, Li Y, Katz J, Krajden M, Tellier R, Halpert C. Human illness from avian influenza H7N3, British Columbia. Emerg Infect Dis. 2004;10(12):2196-9

60. Skowronski DM, Li Y, Tweed SA, Tam TW, Petric M, David ST, Marra F, Bastien N, Lee SW, Krajden M, Brunham RC. Protective measures and human antibody response during an avian influenza H7N3 outbreak in poultry in British Columbia, Canada. CMAJ. 2007;176(1):47-53

61. Heckler R, Baillot A, Engelmann H, Neumeier E, Windorfer A. Cross-protection against homologous drift variants of influenza A and B after vaccination with split vaccine. Intervirology. 2007;50(1):58-62

62. Walter EB, Neuzil KM, Zhu Y, Fairchok MP, Gagliano ME, Monto AS, Englund JA.. Influenza vaccine immunogenicity in 6- to 23-month-old children: are identical antigens necessary for priming? Pediatrics. 2006;118(3):e570-8

63. Englund JA, Walter EB, Fairchok MP, Monto AS, Neuzil KM. A comparison of 2 influenza vaccine schedules in 6- to 23-month-old children. Pediatrics. 2005;115(4):1039-47

64. Englund JA, Walter EB, Gbadebo A, Monto AS, Zhu Y, Neuzil KM. Immunization with trivalent inactivated influenza vaccine in partially immunized toddlers. Pediatrics. 2006;118(3):e579-85

65. Levandowski RA, Gross PA, Weksler M, Staton E, Williams MS, Bonelli J. Cross-reactive antibodies induced by a monovalent influenza B virus vaccine. J Clin Microbiol. 1991;29(7):1530-2

66. Levandowski RA, Regnery HL, Staton E, Burgess BG, Williams MS, Groothuis JR. Antibody responses to influenza B viruses in immunologically unprimed children. Pediatrics. 1991;88(5):1031-6

67. McLean HQ, Thompson MG, Sundaram ME, Kieke BA, Gaglani M, Murthy K, Piedra PA, Zimmerman RK, Nowalk MP, Raviotta JM, Jackson ML. Influenza vaccine effectiveness in the United States during 2012-2013: variable protection by age and virus type. J Infect Dis. 2015;211(10):1529-40

68. McLean HQ, Thompson MG, Sundaram ME, Meece JK, McClure DL, Friedrich TC, Belongia EA. Impact of repeated vaccination on vaccine effectiveness against influenza A(H3N2) and B during 8 seasons. Clin Infect Dis. 2014;59(10):1375-85

69. Pavia-Ruz N, Angel Rodriguez Weber M, Lau YL, Nelson EA, Kerdpanich A, Huang LM, Silas P, Qaqundah P, Blatter M, Jeanfreau R, Lei P. A randomized controlled study to evaluate the immunogenicity of a trivalent inactivated seasonal influenza vaccine at two dosages in children 6 to 35 months of age. Hum Vaccin Immunother. 2013;9(9):1978-88

70. Skowronski DM, Tweed SA, De Serres G. Rapid decline of influenza vaccine-induced antibody in the elderly: is it real, or is it relevant? J Infect Dis. 2008;197(4):490-502

71. Anema A, Mills E, Montaner J, Brownstein JS, Cooper C. Efficacy of influenza vaccination in HIV-positive patients: a systematic review and meta-analysis. HIV Med. 2008;9(1):57-61

72. Cooper C, Hutton B, Fergusson D, Mills E, Klein MB, Boivin G, Halperin S. A review of influenza vaccine immunogenicity and efficacy in HIV-infected adults. Canadian Journal of Infectious Diseases and Medical Microbiology. 2008;19(6):419-23

73. Scharpé J, Evenepoel P, Maes B, Bammens B, Claes K, Osterhaus AD, Vanrenterghem Y, Peetermans WE. Influenza vaccination is efficacious and safe in renal transplant recipients. Am J Transplant. 2008;8(2):332-7

74. Manuel O, Humar A, Chen MH, Chernenko S, Singer LG, Cobos I, Kumar D. Immunogenicity and safety of an intradermal boosting strategy for vaccination against influenza in lung transplant recipients. Am J Transplant. 2007;7(11):2567-72

75. Buxton JA, Skowronski DM, Ng H, Marion SA, Li Y, King A, Hockin J. Influenza revaccination of elderly travelers: antibody response to single influenza vaccination and revaccination at 12 weeks. J Infect Dis. 2001;184(2):188-91

76. Ljungman P, Nahi H, Linde A. Vaccination of patients with haematological malignancies with one or two doses of influenza vaccine: a randomised study. Br J Haematol. 2005;130(1):96-8

77. McElhaney JE, Hooton JW, Hooton N, Bleackley RC. Comparison of single versus booster dose of influenza vaccination on humoral and cellular immune responses in older adults. Vaccine. 2005;23(25):3294-300

78. Gross PA, Weksler ME, Quinnan GV, Douglas RG, Gaerlan PF, Denning CR. Immunization of elderly people with two doses of influenza vaccine. J Clin Microbiol. 1987;25(9):1763-5

79. Cowling BJ, Fang VJ, Nishiura H, Chan KH, Ng S, Ip DK, Chiu SS, Leung GM, Peiris JM. Increased risk of noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine. Clin Infect Dis. 2012;54(12):1778-83

80. Cowling BJ, Ng S, Ma ES, Fang VJ, So HC, Wai W, Cheng CK, Wong JY, Chan KH, Ip DK, Chiu SS. Protective efficacy against pandemic influenza of seasonal influenza vaccination in children in Hong Kong: a randomized controlled trial. Clin Infect Dis. 2012;55(5):695-702

81. Fujieda M, Maeda A, Kondo K, Kaji M, Hirota Y. Inactivated influenza vaccine effectiveness in children under 6 years of age during the 2002-2003 season. Vaccine. 2006;24(7):957-63

82. Katayose M, Hosoya M, Haneda T, Yamaguchi H, Kawasaki Y, Sato M, Wright PF. The effectiveness of trivalent inactivated influenza vaccine in children over six consecutive influenza seasons. Vaccine. 2011;29(9):1844-9

83. Kawai N, Ikematsu H, Iwaki N, Satoh I, Kawashima T, Tsuchimoto T, Kashiwagi S. A prospective, Internet-based study of the effectiveness and safety of influenza vaccination in the 2001-2002 influenza season. Vaccine. 2003;21(31):4507-13

84. Kawai S, Nanri S, Ban E, Inokuchi M, Tanaka T, Tokumura M, Kimura K, Sugaya N. Influenza vaccination of schoolchildren and influenza outbreaks in a school. Clin Infect Dis. 2011;53(2):130-6

85. Kwong JC, Ge H, Rosella LC, Guan J, Maaten S, Moran K, Johansen H, Guttmann A. School-based influenza vaccine delivery, vaccination rates, and healthcare use in the context of a universal influenza immunization program: an ecological study. Vaccine. 2010;28(15):2722-9

86. Kwong JC, Maaten S, Upshur RE, Patrick DM, Marra F. The effect of universal influenza immunization on antibiotic prescriptions: an ecological study. Clin Infect Dis. 2009;49(5):750-6

87. Loeb M, Russell ML, Moss L, Fonseca K, Fox J, Earn DJ, Aoki F, Horsman G, Van Caeseele P, Chokani K, Vooght M. Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial. JAMA. 2010;303(10):943-50

88. Maeda T, Shintani Y, Miyamoto H, Kawagoe H, Nakano K, Nishiyama A, Yamada Y. Prophylactic effect of inactivated influenza vaccine on young children. Pediatr Int. 2002;44(1):43-6

89. Neuzil KM, Dupont WD, Wright PF, Edwards KM. Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985 to 1990: the pediatric experience. Pediatr Infect Dis J. 2001;20(8):733-40

90. Nicholls S, Carroll K, Crofts J, Ben-Eliezer E, Paul J, Zambon M, Joseph CA, Verlander NQ, Goddard NL, Watson JM. Outbreak of influenza A (H3N2) in a highly-vaccinated religious community: a retrospective cohort study. Commun Dis Public Health. 2004;7(4):272-7

91. Ochiai H, Fujieda M, Ohfuji S, Fukushima W, Kondo K, Maeda A, Nakano T, Kamiya H, Hirota Y, Influenza Vaccine Epidemiology Study Group. Inactivated influenza vaccine effectiveness against influenza-like illness among young children in Japan--with special reference to minimizing outcome misclassification. Vaccine. 2009;27(50):7031-5

92. Pebody RG, Andrews N, Fleming DM, McMenamin J, Cottrell S, Smyth B, Durnall H, Robertson C, Carman W, Ellis J, Sebastian-Pillai P. Age-specific vaccine effectiveness of seasonal 2010/2011 and pandemic influenza A(H1N1) 2009 vaccines in preventing influenza in the United Kingdom. Epidemiol Infect. 2013;141(3):620-30

93. Reichert TA, Sugaya N, Fedson DS, Glezen WP, Simonsen L, Tashiro M. The Japanese experience with vaccinating schoolchildren against influenza. N Engl J Med. 2001;344(12):889-96

94. Treanor JJ, Talbot HK, Ohmit SE, Coleman LA, Thompson MG, Cheng PY, Petrie JG, Lofthus G, Meece JK, Williams JV, Berman L. Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. Clin Infect Dis. 2012;55(7):951-9

95. Yamaguchi S, Ohfuji S, Hirota Y. Influenza vaccine effectiveness in primary school children in Japan: a prospective cohort study using rapid diagnostic test results. J Infect Chemother. 2010;16(6):407-13

96. Belongia EA, Kieke BA, Donahue JG, Coleman LA, Irving SA, Meece JK, Vandermause M, Lindstrom S, Gargiullo P, Shay DK. Influenza vaccine effectiveness in Wisconsin during the 2007-08 season: comparison of interim and final results. Vaccine. 2011;29(38):6558-63

97. Charu V, Viboud C, Simonsen L, Sturm-Ramirez K, Shinjoh M, Chowell G, Miller M, Sugaya N. Influenza-related mortality trends in Japanese and American seniors: evidence for the indirect mortality benefits of vaccinating schoolchildren. PloS One. 2011;6(11):e26282

98. Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev. 2010(2):CD004876

99. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. JAMA. 1994;272(21):1661-5

100. Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006(1):CD002733

101. Hak E, Buskens E, van Essen GA, de Bakker DH, Grobbee DE, Tacken MA, van Hout BA, Verheij TJ. Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions: the PRISMA study. Arch Intern Med. 2005;165(3):274-80

102. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. N Engl J Med. 2003;348(14):1322-32

103. Looijmans-Van den Akker I, Verheij TJ, Buskens E, Nichol KL, Rutten GE, Hak E. Clinical effectiveness of first and repeat influenza vaccination in adult and elderly diabetic patients. Diabetes Care. 2006;29(8):1771-6

104. Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. Int J Epidemiol. 2006;35(2):337-44

105. Jackson LA, Nelson JC, Benson P, Neuzil KM, Reid RJ, Psaty BM, Heckbert SR, Larson EB, Weiss NS. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. Int J Epidemiol. 2006;35(2):345-52

106. Simonsen L. Commentary: Observational studies and the art of accurately measuring influenza vaccine benefits. Int J Epidemiol. 2007;36(3):631-2

107. Simonsen L, Viboud C, Taylor RJ. Effectiveness of influenza vaccination. N Engl J Med. 2007;357(26):2729-30

108. Orenstein EW, De Serres G, Haber MJ, Shay DK, Bridges CB, Gargiullo P, Orenstein WA. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. Int J Epidemiol. 2007;36(3):623-31

109. Thomas PG, Keating R, Hulse-Post DJ, Doherty PC. Cell-mediated protection in influenza infection. Emerg Infect Dis. 2006;12(1):48-54

110. Trombetta CM, Gianchecchi E, Montomoli E. Influenza vaccines: evaluation of the safety profile. Hum Vaccin Immunother. 2018;14(3):657-70

111. Edwards KM, Dupont WD, Westrich MK, Plummer Jr WD, Palmer PS, Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. J Infect Dis. 1994;169(1):68-76

112. Gonzalez M, Pirez MC, Ward E, Dibarboure H, Garcia A, Picolet H. Safety and immunogenicity of a paediatric presentation of an influenza vaccine. Arch Dis Child. 2000;83(6):488-91

113. Piedra PA, Glezen WP, Mbawuike I, Gruber WC, Baxter BD, Boland FJ, Byrd RW, Fan LL, Lewis JK, Rhodes LJ, Whitney SE. Studies on reactogenicity and immunogenicity of attenuated bivalent cold recombinant influenza type A (CRA) and inactivated trivalent influenza virus (TI) vaccines in infants and young children. Vaccine. 1993;11(7):718-24

114. Mosca F, Tritto E, Muzzi A, Monaci E, Bagnoli F, Iavarone C, O'Hagan D, Rappuoli R, De Gregorio E. Molecular and cellular signatures of human vaccine adjuvants. Proc Natl Acad Sci U S A. 2008;105(30):10501-6

115. Calabro S, Tortoli M, Baudner B, Pacitto A, Cortese M, O'Hagan DT, De Gregorio E, Seubert A, Wack A. Vaccine adjuvants alum and MF59 induce rapid recruitment of neutrophils and monocytes that participate in antigen transport to draining lymph nodes. Vaccine. 2011;29(9):1812-23

116. Seubert A, Monaci E, Pizza M, O'Hagan DT, Wack A. The adjuvants aluminum hydroxide and MF59 induce monocyte and granulocyte chemoattractants and enhance monocyte differentiation toward dendritic cells. J Immunol. 2008;180(8):5402-12

117. O'Hagan DT, Rappuoli R, De Gregorio E, Tsai T, Del Giudice G. MF59 adjuvant: the best insurance against influenza strain diversity. Expert Rev Vaccines. 2011;10(4):447-62

118. Vesikari T, Knuf M, Wutzler P, Karvonen A, Kieninger-Baum D, Schmitt HJ, Baehner F, Borkowski A, Tsai TF, Clemens R. Oil-in-water emulsion adjuvant with influenza vaccine in young children. N Engl J Med. 2011;365:1406-16

119. Vesikari T, Groth N, Karvonen A, Borkowski A, Pellegrini M. MF59®-adjuvanted influenza vaccine (FLUAD®) in children: safety and immunogenicity following a second year seasonal vaccination. Vaccine. 2009;27:6291-5

120. Vesikari T, Pellegrini M, Karvonen A, Groth N, Borkowski A, O'Hagan DT, Podda A. Enhanced immunogenicity of seasonal influenza vaccines in young children using MF59 adjuvant. Pediatr Infect Dis J. 2009;28:563-71

121. Della Cioppa G, Vesikari T, Sokal E, Lindert K, Nicolay U. Trivalent and quadrivalent MF59®-adjuvanted influenza vaccine in young children: a dose- and schedule-finding study. Vaccine. 2011;29:8696-704

122. Zedda L, Forleo-Neto E, Vertruyen A, Raes M, Marchant A, Jansen W, Clouting H, Arora A, Beatty ME, Galli G, Del Giudice G. Dissecting the immune response to MF59-adjuvanted and nonadjuvanted seasonal influenza vaccines in children less than three years of age. Pediatr Infect Dis J. 2015;34(1):73-8

123. Nolan T, Bravo L, Ceballos A, Mitha E, Gray G, Quiambao B, Patel SS, Bizjajeva S, Bock H, Nazaire-Bermal N, Forleo-Neto E. Enhanced and persistent antibody response against

homologous and heterologous strains elicited by a MF59-adjuvanted influenza vaccine in infants and young children. Vaccine. 2014;32(46):6146-56

124. Vaarala O, Vuorela A, Partinen M, Baumann M, Freitag TL, Meri S, Saavalainen P, Jauhiainen M, Soliymani R, Kirjavainen T, Olsen P. Antigenic differences between AS03 adjuvanted influenza A (H1N1) pandemic vaccines: implications for Pandemrix-associated narcolepsy risk. PLoS One. 2014;9(12):e114361

125. DiazGranados CA, Dunning AJ, Robertson CA, Talbot HK, Landolfi V, Greenberg DP. Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty. Vaccine. 2015;33(36):4565-71

126. Izurieta HS, Thadani N, Shay DK, Lu Y, Maurer A, Foppa IM, Franks R, Pratt D, Forshee RA, MaCurdy T, Worrall C. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. Lancet Infect Dis. 2015;15(3):293-300

127. Richardson DM, Medvedeva EL, Roberts CB, Linkin DR. Comparative effectiveness of high-dose versus standard-dose influenza vaccination in community-dwelling veterans. Clin Infect Dis. 2015;61(2):171-6

128. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis. 2009;200(2):172-80

129. Couch RB, Winokur P, Brady R, Belshe R, Chen WH, Cate TR, Sigurdardottir B, Hoeper A, Graham IL, Edelman R, He F. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. Vaccine. 2007;25(44):7656-63

130. Keitel WA, Atmar RL, Cate TR, Petersen NJ, Greenberg SB, Ruben F, Couch RB. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. Arch Intern Med. 2006;166(10):1121-7

131. Sanofi Pasteur. Study of Fluzone® influenza virus vaccine 2011-2012 formulation (intramuscular route) among adults. 2013. Accessed: 9 October 2018. Available from: https://www.clinicaltrials.gov/ct2/show/study/NCT01430819

132. Tsang P, Gorse GJ, Strout CB, Sperling M, Greenberg DP, Ozol-Godfrey A, DiazGranados C, Landolfi V. Immunogenicity and safety of Fluzone intradermal and high-dose influenza vaccines in older adults >65 years of age: a randomized, controlled, phase II trial. Vaccine. 2014;32(21):2507-17

133. Nace DA, Lin CJ, Ross TM, Saracco S, Churilla RM, Zimmerman RK. Randomized, controlled trial of high-dose influenza vaccine among frail residents of long-term care facilities. J Infect Dis. 2015;211(12):1915-24

134. DiazGranados CA, Dunning AJ, Jordanov E, Landolfi V, Denis M, Talbot HK. High-dose trivalent influenza vaccine compared to standard dose vaccine in elderly adults: safety, immunogenicity and relative efficacy during the 2009-2010 season. Vaccine. 2013;31(6):861-6

135. DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, Pollak R, Christoff J, Earl J, Landolfi V, Martin E. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med. 2014;371(7):635-45

136. Jain VK, Rivera L, Zaman K, Espos Jr RA, Sirivichayakul C, Quiambao BP, Rivera-Medina DM, Kerdpanich P, Ceyhan M, Dinleyici EC, Cravioto A. Vaccine for prevention of mild and moderate-to-severe influenza in children. N Engl J Med. 2013;369(26):2481-91

137. Belshe RB. The need for quadrivalent vaccine against seasonal influenza. Vaccine. 2010;28(Suppl 4):D45-53

138. Haber P, Moro PL, Lewis P, Woo EJ, Jankosky C, Cano M. Post-licensure surveillance of quadrivalent inactivated influenza (IIV4) vaccine in the United States, Vaccine Adverse Event Reporting System (VAERS), July 1, 2013−May 31, 2015. Vaccine. 2016;34(22):2507-12

139. Grohskopf LA, Sokolow LZ, Fry AM, Walter EB, Jernigan DB. Update: ACIP recommendations for the use of quadrivalent live attenuated influenza vaccine (LAIV4) - United States, 2018-19 influenza season. MMWR Morb Mortal Wkly Rep. 2018;67(22):643-5

140. National Advisory Committee on Immunization. Recommendations on the use of live, attenuated influenza vaccine (FluMist®): supplemental statement on seasonal influenza vaccine 2011-2012. Can Commun Dis Rep. 2011;37(ACS-7):1-77

141. Block SL, Falloon J, Hirschfield JA, Krilov LR, Dubovsky F, Yi T, Belshe RB. Immunogenicity and safety of a quadrivalent live attenuated influenza vaccine in children. Pediatr Infect Dis J. 2012;31(7):745-51

142. Block SL, Yi T, Sheldon E, Dubovsky F, Falloon J. A randomized, double-blind noninferiority study of quadrivalent live attenuated influenza vaccine in adults. Vaccine. 2011;29(50):9391-7

143. MedImmune. A randomized, partially blind active controlled study to evaluate the immunogenicity of MEDI8662 in adults 18-49 years of age. 2011. Accessed: 9 October 2018. Available from: https://clinicaltrials.gov/ct2/show/results/NCT00952705

144. Ritzwoller DP, Bridges CB, Shetterly S, Yamasaki K, Kolczak M, France EK. Effectiveness of the 2003-2004 influenza vaccine among children 6 months to 8 years of age, with 1 vs 2 doses. Pediatrics. 2005;116(1):153-9

145. Neuzil KM, Jackson LA, Nelson J, Klimov A, Cox N, Bridges CB, Dunn J, DeStefano F, Shay D. Immunogenicity and reactogenicity of 1 versus 2 doses of trivalent inactivated influenza vaccine in vaccine-naive 5-8-year-old children. J Infect Dis. 2006;194(8):1032-9

146. Shuler CM, Iwamoto M, Bridges CB, Marin M, Neeman R, Gargiullo P, Yoder TA, Keyserling HL, Terebuh PD. Vaccine effectiveness against medically attended, laboratory-confirmed influenza among children aged 6 to 59 months, 2003-2004. Pediatrics. 2007;119(3):e587-95

147. Allison MA, Daley MF, Crane LA, Marin M, Neeman R, Gargiullo P, Yoder TA, Keyserling HL, Terebuh PD. Influenza vaccine effectiveness in healthy 6- to 21-month-old children during the 2003-2004 season. J Pediatr. 2006;149(6):755-62

148. Skowronski DM, Hottes TS, De Serres G, Ward BJ, Janjua NZ, Sabaiduc S, Chan T, Petric M. Influenza B/Victoria antigen induces strong recall of B/Yamagata but lower B/Victoria response in children primed with two doses of B/Yamagata. Pediatr Infect Dis J. 2011;30(10):833-9

149. Public Health Agency of Canada. Canadian Immunization Guide: Part 1 - Key Immunization Information: Timing of Vaccine Administration. 2017. Accessed: 9 October 2018. Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-1-key-immunization-information/page-10-timing-vaccine-administration.html

150. Nascimento Silva JR, Camacho LAB, Siqueira MM, Freire MDS, Castro YP, Maia MDLS, Yamamura AMY, Martins RM, Leal MDLF. Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps and rubella. Vaccine. 2011;29(37):6327-34

151. Stefano I, Sato HK, Pannuti CS, Omoto TM, Mann G, Freire MS, Yamamura AM, Vasconcelos PF, Oselka GW, Weckx LW, Salgado MF. Recent immunization against measles does not interfere with the sero-response to yellow fever vaccine. Vaccine. 1999;17(9-10):1042-6

152. Tauraso NM, Myers MG, Nau EV, O'Brien TC, Spindel SS, Trimmer RW. Effect of interval between inoculation of live smallpox and yellow-fever vaccines on antigenicity in man. J Infect Dis. 1972;126(4):362-71

153. Verstraeten T, Jumaan AO, Mullooly JP, Seward JF, Izurieta HS, DeStefano F, Black SB, Chen RT. A retrospective cohort study of the association of varicella vaccine failure with asthma, steroid use, age at vaccination, and measles-mumps-rubella vaccination. Pediatrics. 2003;112(2):e98-103

154. Institute of Medicine of the National Academies. Immunization safety review: influenza vaccines and neurological complications. Washington, DC: National Academy of Sciences. 2008

155. Centers for Disease Control and Prevention. Preliminary results: surveillance for Guillain-Barré syndrome after receipt of influenza A (H1N1) 2009 monovalent vaccine - United States, 2009-2010. MMWR Morb Mortal Wkly Rep. 2010;59(21):657-61

156. Kwong JC, Vasa PP, Campitelli MA, Hawken S, Wilson K, Rosella LC, Stukel TA, Crowcroft NS, McGeer AJ, Zinman L, Deeks SL. Risk of Guillain-Barré syndrome after seasonal influenza vaccination and influenza health-care encounters: a self-controlled study. Lancet Infect Dis. 2013;13(9):769-76

157. Sivadon-Tardy V, Orlikowski D, Porcher R, Sharshar T, Durand MC, Enouf V, Rozenberg F, Caudie C, Annane D, Van Der Werf S, Lebon P. Guillain-Barre syndrome and influenza virus infection. Clin Infect Dis. 2009;48(1):48-56

158. Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenza like illness using the United Kingdom General Practice Research Database. Am J Epidemiol. 2009;169(3):382-8

159. Tam CC, O'Brien SJ, Petersen I, Islam A, Hayward A, Rodrigues LC. Guillain-Barre syndrome and preceding infection with campylobacter, influenza and Epstein-Barr virus in the general practice research database. PLoS One. 2007;2(4):e344

160. Andrews N, Stowe J, Al-Shahi Salman R, Miller E. Guillain-Barre syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: self-controlled case series. Vaccine. 2011;29(45):7878-82

161. Statistics Canada. Table 051-0001 - Estimates of population, by age group and sex for July 1, Canada, provinces and territories, annual (persons unless otherwise noted), CANSIM (database). 2014 Accessed: 9 October 2018. Available from: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo10a-eng.htm

162. Tran D, Vaudry W, Moore D, Bettinger JA, Halperin SA, Scheifele DW, Jadvji T, Lee L, Mersereau T. Hospitalization for Influenza A Versus B. Pediatrics. 2016;138(3):e20154643

163. Centers for Disease Control and Prevention. Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. MMWR Morb Mortal Wkly Rep. 2010;59(33):1057-62

164. Cromer D, van Hoek AJ, Jit M, Edmunds WJ, Fleming D, Miller E. The burden of influenza in England by age and clinical risk group: a statistical analysis to inform vaccine policy. J Infect. 2014;68(4):363-71