

# An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)<sup>±</sup>

Canadian Immunization Guide Chapter on  
Influenza and Statement on Seasonal Influenza  
Vaccine for 2015-2016

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PROTECTING CANADIANS FROM ILLNESS



Public Health  
Agency of Canada

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publique du Canada

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## PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as the Agency) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency 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 the Agency's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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## **I. INTRODUCTION**

This document, the *National Advisory Committee on Immunization (NACI): Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2015-2016* updates NACI's recommendations regarding the use of seasonal influenza vaccines.

### **NEW OR UPDATED INFORMATION FOR 2015-2016**

In an effort to serve the interests of the various users of the NACI *Statement on Seasonal Influenza Vaccine* better, the format of the statement has been modified so that the information most relevant to the frontline immunizer, which is typically found in the Canadian Immunization Guide can now be found in section II (Clinical Information for Vaccine Providers), with the more detailed information following. Additionally, readers will notice a streamlining of the information, grouping relevant information together by vaccine type.

#### **Live attenuated influenza vaccine:**

Only the quadrivalent formulation of the live attenuated influenza vaccine (LAIV) [FluMist® Quadrivalent (AstraZeneca)] will be available in Canada in the 2015-16 season. The statement has been updated to reflect that the evidence supporting the use of live attenuated influenza vaccines was based on the trivalent formulation of LAIV. Based on expert opinion, the comparative efficacy data which supported the preferential recommendations for the trivalent formulation of LAIV are also applicable to the quadrivalent formulation of LAIV because the manufacturing processes and immunologic mechanism of the quadrivalent LAIV and the trivalent LAIV products are the same. This expert opinion is supported by the results of the non inferiority studies comparing trivalent and quadrivalent formulations of LAIV, which were required by regulatory bodies to authorize the use of the Q-LAIV formulation. Comparative vaccine efficacy and effectiveness data of TIV or QIV, and the quadrivalent formulation of LAIV are not available.

Decreased effectiveness of quadrivalent LAIV was observed in the United States of America with the influenza A(H1N1) strain in children during the 2013-14 influenza season. Investigations by the manufacturer have determined that this reduced effectiveness is most likely attributable to reduced stability in the A/California H1N1 vaccine strain when exposed to temperature fluctuations. NACI has reviewed the available information on this issue, including Canadian data, and concludes that this event is unlikely to occur in Canada because by contract, the contractor, (i.e., manufacturer) is required to maintain the required temperatures throughout transport from the contractor to the identified users (i.e., provincial and territorial depots) and provide evidence to that effect from the data analysis of the temperature monitoring device or carrier logs, as applicable. NACI therefore continues to recommend preferential use of LAIV in children. NACI will continue to monitor this issue and will review additional information as it arises.

#### **Choice of vaccine product for children 6-23 months (see section IV):**

Fluad Pediatric™ will be available on the Canadian market starting in the 2015-16 influenza season for use in children 6 to <24 months. Fluad Pediatric™ is an adjuvanted trivalent influenza vaccine administered as a 0.25 mL dose by intramuscular injection (refer to Appendix A for product characteristics).

NACI has reviewed the available evidence on Flud Pediatric™ and has concluded that Flud Pediatric™ may be used in children 6 to <24 months of age (NACI Recommendation Grade B).

For children 6-23 months, NACI recommends that, given the burden of influenza B disease, QIV should be used. If QIV is not available, either unadjuvanted or adjuvanted TIV should be used.

#### **Choice of vaccine product for children 2-17 years (see Section IV):**

NACI recommends LAIV use for healthy children and adolescents 2 to 17 years of age who do not have contraindications to this vaccine. There is evidence for the preferential use of LAIV in young children (younger than 6 years of age) based on superior efficacy of trivalent LAIV compared to trivalent inactivated influenza vaccine (TIV) (Grade A), with weaker evidence of superior efficacy in older children (Grade I). It is anticipated that the superior efficacy for LAIV over TIV extends beyond age 6 years, but the evidence does not indicate at which specific age the efficacies of LAIV and TIV become equivalent. Given the burden of influenza B disease in children, if LAIV is not available for those for whom it is considered superior, quadrivalent inactivated influenza vaccine (QIV) should be used. If QIV is not available, TIV should be used.

For children with underlying conditions or contraindications that preclude the use of LAIV, NACI recommends that, given the burden of influenza B disease, QIV should be used. If QIV is not available, TIV should be used. More specifically, for:

*Healthy children:* If LAIV is not available for those for whom it is considered superior, NACI recommends that QIV should be used in this age group. If QIV is not available, TIV should be used.

*Children with immune compromising conditions, which are a contraindication to LAIV:* Given the burden of influenza B disease in children, QIV should be used. If QIV is not available, TIV should be used.

*Children with severe asthma (as defined in Section II under Contraindications and Precautions) or medically attended wheezing in the previous seven days:* Given the burden of influenza B disease in children, QIV should be used. If QIV is not available, TIV should be used.

*Children with other chronic health conditions:* LAIV can be used in this group. If inactivated vaccine is being used, given the burden of influenza B disease in children, QIV should be used. If QIV is not available, TIV should be used.

NACI recommends that children with cystic fibrosis may receive LAIV if the individual is not being treated with immunosuppressive drugs, such as prolonged systemic corticosteroids, and meets the other criteria for LAIV administration.

#### **Children and adolescents with neurologic or neurodevelopment conditions:**

Following a recent publication by the Canadian Immunization Monitoring Program Active (IMPACT), NACI now includes children and adolescents with neurologic or neurodevelopment conditions, including seizure disorders, febrile seizures and isolated developmental delay, among the groups for whom influenza vaccination is particularly recommended.



**Oculo-respiratory syndrome:**

The definition for oculo-respiratory syndrome (see section II) has been updated to be consistent with the user guide for reporting of adverse events following immunization.

**Intanza®:**

Sanofi Pasteur has confirmed that Intanza® will no longer be available on the Canadian market. Consequently, information related to Intanza® has not been included in the 2015-2016 statement.

**Co-administration of LAIV with other vaccines:**

NACI recommends that LAIV 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 to avoid any possibility of immune interference. Alternatively, an inactivated influenza vaccine (TIV or QIV) may be given.

**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. 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 influenza vaccine recommendations for use in Canada are developed by the Influenza Working Group (IWG) for consideration by NACI. Recommendation development includes review of a variety of issues, including: the burden of influenza illness and the target populations for vaccination; safety, immunogenicity, efficacy, and effectiveness of influenza vaccines; vaccine schedules; 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 NACI, January 2009, CCDR.

Health care providers in Canada may offer the seasonal vaccine when it becomes available, 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 already has 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.

The decision to include specific influenza vaccines as part of publicly-funded provincial and territorial programs depends on multiple factors, such as cost-benefit evaluation and other programmatic and operational factors, for example shelf-life and implementation strategies. Not all products will be made available in all jurisdictions and availability of some products may be limited; therefore, individual provinces and territories must be consulted regarding the products available in individual jurisdictions.

## II. CLINICAL INFORMATION FOR VACCINE PROVIDERS (CANADIAN IMMUNIZATION GUIDE)

The Canadian Immunization Guide, which is written primarily for health care providers (front-line clinicians, public health practitioners) but is also used by policy makers, program planners and the general public, has been a trusted, reader-friendly summary of the vaccine statements provided by National Advisory Committee on Immunization for over 40 years.

As noted in the Introduction, the information in this section, *Clinical Information for Vaccine Providers*, replaces the influenza chapter of the Canadian Immunization Guide and is adapted for inclusion in the revised NACI Statement on Seasonal Influenza Vaccine. With a new NACI Statement on Seasonal Influenza required each year, the rationale for this format change is to allow the user to have quick access to the information that he or she requires within one document, whether it is the relevant influenza vaccine information that is written primarily for the 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.

### KEY INFORMATION

<b>What</b>	<p>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. Symptoms typically include the sudden onset of high fever, chills, sore throat, cough and myalgia. Other common symptoms include headache, loss of appetite, fatigue, and coryza. Nausea, vomiting and diarrhoea may also occur, especially in children. Most people will recover within a week or ten days, but some are at greater risk of more severe complications, such as pneumonia.</p> <p>Both inactivated and live attenuated influenza vaccines are authorized for use in Canada; some are trivalent formulations and some are quadrivalent formulations.</p> <p>Influenza vaccine is safe and well-tolerated. Influenza vaccine cannot cause influenza illness because the inactivated influenza vaccines do not contain live virus and the viruses in live attenuated influenza vaccines are weakened so that they cannot cause influenza.</p>
<b>Who</b>	Influenza vaccination is recommended for all individuals aged 6 months and older (noting product-specific age indications and contraindications), with particular focus on: people at high risk of influenza-related complications or hospitalization, including all pregnant women, people capable of transmitting influenza to those at high risk, and others listed in <b>Table 1</b> .
<b>How</b>	Risks and benefits of influenza vaccine should be discussed prior to vaccination, as well as the risks of not being immunized.

	<p><b><i>Dose and schedule</i></b></p> <p>Children who have been previously immunized with seasonal influenza vaccine and adults should receive one dose of influenza vaccine each year. Children 6 months to less than 9 years of age receiving seasonal influenza vaccine for the first time in their life should be given two doses, with a minimum interval of four weeks between doses. The route of administration and dosage varies by product (refer to <b>Table 3</b>). With the exception of adjuvanted TIV for children, (i.e., Fludac Pediatric™), the dose for intramuscular (IM) inactivated vaccines is 0.5 mL for all age groups. For Fludac Pediatric™, available for children 6 to &lt;24 months of age, the dose is 0.25 mL.</p> <p><b><i>Contraindications and Precautions</i></b></p> <p>Persons who have developed an anaphylactic reaction to a previous dose of influenza vaccine or to any of the vaccine components, with the exception of egg, or who have developed Guillain-Barré Syndrome (GBS) within six weeks of influenza vaccination, should not receive a further dose.</p> <p>NACI has concluded that egg allergic individuals may be vaccinated against influenza using inactivated TIV and QIV without a prior influenza vaccine skin test and with the full dose. The vaccine may be given in any settings where vaccines are routinely administered (see section V for details). However, immunizers administering vaccine should be prepared for and have the necessary equipment to respond to a vaccine emergency at all times. LAIV should not be given to egg allergic individuals, as egg allergy has not yet been studied for LAIV. There are additional contraindications for LAIV (see <i>Contraindications</i> in section II for details).</p> <p>Administration of the seasonal influenza vaccine should usually be postponed in persons with serious acute illnesses until their symptoms have abated. Immunization 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, inactivated vaccines can be administered or LAIV can be deferred until resolution of the illness.</p> <p><b><i>Co-administration</i></b></p> <p>All influenza vaccines, including LAIV, may be given at the same time as or at any time before or after administration of other live attenuated or inactivated vaccines (see <i>Vaccine Administration</i> below for details). For concomitant parenteral injections, different injection sites and separate needles and syringes should be used.</p>
<b>Why</b>	<p>It is estimated that between 10-20% of the population becomes infected with influenza each year.</p> <p>Vaccination is the most effective way to prevent influenza and its complications.</p> <p>Annual vaccination is required because the body's immune response from vaccination diminishes within a year. Also, because influenza viruses change often, the vaccine is reviewed each year and updated as necessary to keep up with the changing viruses.</p>



## EPIDEMIOLOGY

### Disease Description

It is estimated that between 10-20% of the population becomes infected with influenza each year<sup>(1)</sup>. Rates of influenza infection are highest in children aged 5–9 years, but rates of serious illness and death are highest in children aged <2 years, older persons (>65 years), and persons with underlying medical conditions<sup>(2)</sup>. Influenza infection not only causes primary illness but also can lead to severe secondary medical complications, including viral pneumonia, secondary bacterial pneumonia and worsening of underlying medical conditions.

### Infectious Agent

Influenza A viruses are classified into subtypes on the basis of two surface proteins: haemagglutinin (HA) and neuraminidase (NA). Three subtypes of haemagglutinin (H1, H2 and H3) and two subtypes of neuraminidase (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. Antigenic drift, which may occur in one or more influenza virus strains, usually requires seasonal influenza vaccines to be reformulated annually.

### Transmission

Influenza is primarily transmitted by droplets spread through coughing or sneezing and may also be transmitted through direct or indirect contact with contaminated respiratory secretions. The incubation period of seasonal influenza is usually two days but can range from one to four days. Adults may be able to spread influenza to others from one day before symptom onset to approximately five days after symptoms start. Children and people with weakened immune systems may be infectious for longer.

### Risk Factors

The people at greatest risk of influenza-related complications are adults and children with underlying health conditions (see **Table 1**); residents of nursing homes and other chronic care facilities; people 65 years of age and older; children 6 to 59 months of age; pregnant women; and Aboriginal Peoples.

### Seasonal and Temporal Patterns

In Canada, influenza generally occurs each year in the late fall and winter months.

### Spectrum of Clinical Illness

Symptoms typically include the sudden onset of high 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 ten days, but some - including those 65 years of age and older, young children, and

adults and children with chronic conditions - are at greater risk of more severe complications, such as pneumonia.

### **Disease Distribution: Incidence**

#### **Global**

Worldwide, annual epidemics result in an approximately one billion cases of influenza, about three to five million cases of severe illness, and about 250,000 to 500,000 deaths. For current international influenza activity information, refer to [WHO's FluNet website](#).

#### **National**

Influenza is ranked among the top 10 infectious diseases affecting the Canadian population<sup>(3)</sup>. Current influenza activity information can be found on the Agency's [FluWatch website](#). The FluWatch program collects data and information from various sources to provide a national picture of influenza activity.

Influenza activity in Canada usually is low in the spring and summer, begins to rise over the fall and peaks in the winter months. Depending on the year, the peak may occur as early as late fall or as late as early spring. It is estimated that, in a given year, an average of 12,200 hospitalizations related to influenza<sup>(4)-(6)</sup> and approximately 3,500 deaths attributable to influenza occur<sup>(7)</sup>. However, it should be noted that influenza testing is often not conducted to confirm an influenza diagnosis, and that patients may present to hospital with complications of influenza after viral shedding has been stopped. For this reason, the overall incidence of influenza may be underestimated and thus is best determined by periodic cohort studies. The rate of hospitalization and death due to influenza is best estimated by modelling of excess deaths and hospitalizations due to cardiorespiratory conditions during influenza season<sup>(8)</sup>.

## **PREPARATIONS AVAILABLE FOR USE IN CANADA**

This section describes the influenza vaccine preparations that are currently available for use in Canada. All influenza vaccines available for use in Canada have been authorized for use by Health Canada. However, not all preparations 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.

The antigenic characteristics of current and emerging influenza virus strains provide the basis for selecting the strains included in each year's vaccine. All manufacturers that distribute influenza vaccine products in Canada confirm to Health Canada that the vaccines to be marketed in Canada for the upcoming influenza season contain the WHO-recommended antigenic strains for the Northern Hemisphere. Vaccine producers may use antigenically equivalent strains because of their growth properties.

LAIV contains standardized quantities of fluorescent focus units (FFU) of live attenuated influenza virus reassortants. Inactivated seasonal influenza vaccines 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). 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<sup>(9)-(14)</sup>.

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 Health Canada's authorized product monographs available through [Health Canada's Drug Product Database](#).

### **Inactivated Influenza Vaccines**

The inactivated influenza vaccines 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. Refer to [Basic Immunology and Vaccinology](#) in Part 1 of the Canadian Immunization Guide for more information about inactivated vaccines.

Both trivalent and quadrivalent inactivated influenza vaccines are authorized for use in Canada.

### **Adjuvanted, Inactivated Influenza Vaccines**

Two of the trivalent products, Fludac® and Fludac Pediatric™, contain the adjuvant MF59, which is an oil-in-water emulsion composed of squalene as the oil phase, stabilized with the surfactants polysorbate 80 and sorbitan triolate in citrate buffer. The other inactivated products do not contain an adjuvant.

### **Live Attenuated Influenza Vaccine (LAIV)**

FluMist® Quadrivalent is a live attenuated influenza vaccine for administration by intranasal spray and authorized for use for persons 2-59 years of age. The influenza strains in FluMist® Quadrivalent are cold-adapted and temperature sensitive, so they replicate in the nasal mucosa rather than the lower respiratory tract.

## **EFFICACY, EFFECTIVENESS AND IMMUNOGENICITY**

### **Efficacy and Effectiveness**

Influenza vaccine has been shown to be efficacious, with higher efficacy demonstrated against laboratory-confirmed influenza than clinically defined outcomes.

Immunization has been shown to reduce the number of physician visits, hospitalizations and deaths in high-risk adults.

In young children, up to six years of age, there is evidence that trivalent LAIV protects better than TIV, with less evidence in older children. Based on expert opinion, the comparative efficacy data which supported the preferential recommendations for the trivalent formulation of LAIV are also applicable to the quadrivalent formulation of LAIV because the manufacturing processes and immunologic mechanism of the quadrivalent LAIV and the trivalent LAIV products are the same. This expert opinion is supported by the results of the non inferiority studies comparing trivalent and quadrivalent formulations of LAIV, which were required by regulatory bodies to authorize the use of the Q-LAIV formulation. Comparative vaccine efficacy and effectiveness data of TIV or QIV, and the quadrivalent formulation of LAIV are not available.

Reduced effectiveness of quadrivalent LAIV in children, overall and compared to inactivated vaccines, has been reported during the 2013-14 influenza season in the US against influenza A(H1N1). Investigations by the manufacturer have determined that this reduced effectiveness is most likely attributable to reduced stability in the A/California H1N1 vaccine strain when exposed to temperature fluctuations. NACI has reviewed the available information on this issue, including Canadian data, and concludes that this event is unlikely to occur in Canada because by contract, the contractor, (i.e., manufacturer) is required to maintain the required temperatures throughout transport from the contractor to the identified users (i.e., provincial and territorial depots) and provide evidence to that effect from the data analysis of the temperature monitoring device or carrier logs, as applicable. NACI therefore continues to recommend preferential use of LAIV in children. (see Section IV. Choice of Product). NACI will continue to monitor this issue and will review additional information as it arises.

For a summary of efficacy studies refer to Section V of this statement.

### Immunogenicity

The 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. Humoral antibody levels, which correlate with vaccine protection, are generally achieved by two weeks after immunization; however, there may be some protection afforded before that time.

## RECOMMENDATIONS FOR USE

### Recommended Recipients of Influenza Vaccine

Influenza vaccine is recommended for everyone 6 months of age and older without contraindications. To reduce the morbidity and mortality associated with influenza, immunization programs should focus on those at high risk of influenza-related complications, including all pregnant women, those capable of transmitting influenza to individuals at high risk of complications and others as identified in **Table 1**. Additional detail regarding the recipients identified in Table 1, including pregnant women, can be found in Section III of the statement.

**Table 1: Influenza vaccination is particularly recommended for the following groups:**

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

- Adults, including pregnant women, and children with the following chronic health conditions:
  - cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma);
  - diabetes mellitus and other metabolic diseases;
  - cancer, immune compromising conditions (due to underlying disease, therapy or both);
  - renal disease;
  - anemia or hemoglobinopathy;
  - conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration;
  - morbid obesity (BMI  $\geq 40$ );

- children and adolescents (age 6 months to 18 years) with the following conditions:
  - neurologic or neurodevelopment conditions (including seizure disorders, febrile seizures and isolated developmental delay);
  - 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.
- People  $\geq 65$  years of age.
- All children 6 to 59 months of age.
- Healthy pregnant women (the risk of influenza-related hospitalization increases with length of gestation, i.e., it is higher in the third than in the second trimester).
- Aboriginal 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 of influenza complications.
- Household contacts (adults and children) of individuals at high risk of influenza-related complications (whether or not the individual at high risk has been immunized):
  - household contacts of individuals at high risk, as listed in the section above;
  - household contacts of infants <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.
- Those providing regular child care to children  $\leq 59$  months of age, whether in or out of the home.
- Those who provide services within closed or relatively closed settings to persons at high risk (e.g., crew on a ship).

#### **Others**

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

In addition to the recipients identified in **Table 1**, influenza vaccine is also recommended for:

#### **Healthy Individuals ages 5-64 years of age**

Recent literature reviews conducted by NACI have shown that healthy individuals aged 5 to 64 years benefit from influenza vaccination.

Detailed information regarding these reviews can be found in the *Statement on Seasonal Influenza Vaccine for 2014-2015* and in each of the relevant literature reviews, available via the NACI website.

#### **Travellers**

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



is recommended for all individuals, including travellers, aged 6 months and older, with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk, and others as indicated in **Table 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 re-vaccination (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 differences between the Northern and Southern hemisphere's vaccines, and the availability of a reliable and safe vaccine at the traveller's destination. Refer to Immunization of Travellers in the Canadian Immunization Guide for additional general information.

## CHOICE OF SEASONAL INFLUENZA VACCINE

**Table 2** summarizes current recommendations by specific age and risk groups for the choice(s) of influenza vaccine currently available for use in Canada.

**Table 2: Choice of influenza vaccine for selected age and risk groups (for persons without a contraindication to the vaccine)**

Recipient by age group	Vaccine types available for use	Comments
Children 6-23 months of age	<ul style="list-style-type: none"> <li>• TIV</li> <li>• QIV</li> <li>• Adjuvanted TIV</li> </ul>	<p>TIV, QIV and adjuvanted TIV are authorized for this age group.</p> <p>For children 6-23 months, NACI recommends that, given the burden of influenza B disease, QIV should be used. If QIV is not available, either unadjuvanted or adjuvanted TIV should be used.</p>
Children 2-17 years of age	<ul style="list-style-type: none"> <li>• TIV</li> <li>• QIV</li> <li>• LAIV</li> </ul>	<p><b>**</b>For recommendations regarding use of LAIV in healthy children and adolescents 2 to 17 years of age who do not have contraindications to this vaccine, see the note below this table.</p> <p>LAIV is not recommended for children with immune compromising conditions, see below.</p> <p>LAIV, TIV or QIV can be used in children with chronic health conditions, including asthma that is not severe, and cystic fibrosis without immune suppression (see <i>Contraindications and Precautions</i> section below for definition regarding severe asthma).</p>
Adults 18-59 years of age	<ul style="list-style-type: none"> <li>• TIV</li> <li>• QIV</li> <li>• LAIV</li> </ul>	<p>TIV and QIV are the preferred products for adults with chronic health conditions.</p> <p>LAIV is not recommended for adults with</p>

Recipient by age group	Vaccine types available for use	Comments
		immune compromising conditions.
Adults 60-64 years of age	<ul style="list-style-type: none"> <li>• TIV</li> <li>• QIV</li> </ul>	
Adults 65+ years of age	<ul style="list-style-type: none"> <li>• TIV</li> <li>• QIV</li> <li>• Adjuvanted TIV</li> </ul>	
Pregnant women	<ul style="list-style-type: none"> <li>• TIV</li> <li>• QIV</li> </ul>	LAIV is not recommended because of the theoretical risk to the fetus from administering a live virus vaccine.

TIV = trivalent inactivated influenza vaccine (for IM administration); QIV = Quadrivalent inactivated influenza vaccine; LAIV = live attenuated influenza vaccine

\*\*LAIV: NACI recommends LAIV for healthy children and adolescents 2 to 17 years of age who do not have contraindications to this vaccine. There is evidence for the preferential use of LAIV in young children (younger than 6 years of age) based on superior efficacy of trivalent LAIV compared to TIV (Grade A), with weaker evidence of superior efficacy in older children (Grade I). It is anticipated that the superior efficacy for LAIV over TIV extends beyond age 6 years, but the evidence does not indicate at which specific age the efficacies of LAIV and TIV become equivalent. Given the burden of influenza B disease in children, if LAIV is not available for those for whom it is considered superior, QIV should be used. If QIV is not available, TIV should be used.

## VACCINE ADMINISTRATION

### Dose, Route of Administration and Schedule

With the variety of influenza vaccines available for use in Canada, it is important for practitioners to note the specific differences in age indications, route of administration, dosage and schedule for the products that they will be using (Table 3).

Vaccine administration practices are discussed in the [Canadian Immunization Guide](#). For influenza vaccines given by the intramuscular route, the deltoid muscle is the recommended site in adults and children ≥12 months of age and the anterolateral thigh is the recommended site in infants between 6 and 12 months of age.

**Table 3: Influenza vaccine: Recommended dosage and route, by age, for the 2015-2016 season**

Age group	TIV without adjuvant or QIV IM <sup>†</sup>	MF59-adjuvanted TIV (Fluad Pediatric™ or Fluad®) IM	LAIV (FluMist®) Quadrivalent) IN	Number of doses required
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	0.5 mL	-	0.2 mL (0.1 mL per	1

years			nostril)	
60-64 years	0.5 mL	-	-	1
≥65 years	0.5 mL	0.5 mL	-	1

TIV=Trivalent inactivated influenza vaccine, QIV=Quadrivalent inactivated influenza vaccine, LAIV = Live attenuated influenza vaccine, IM=Intramuscular, IN = intranasal

†Influvac® ≥18 years, Fluviral® ≥6 months, Agriflu® ≥6 months, Vaxigrip® ≥6 months, Fluzone® ≥6 months, Flulaval® Tetra ≥6 months and Fluzone® Quadrivalent ≥6 months.

\*This information differs from the product monograph. As noted in the preamble of this statement, *recommendations for use and other information in this statement may differ from that set out in the product monographs/leaflets of the Canadian manufacturers.*

\*\*Children 6 months to less than 9 years of age who have never received the seasonal influenza vaccine require two doses of influenza vaccine, with a minimum interval of four weeks between doses. Eligible children <9 years of age who have properly received one or more doses of seasonal influenza vaccine in the past should receive one dose per influenza vaccination season thereafter.

### Booster Doses and Re-Immunization

Booster doses are not required within the same influenza season.

### 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 Canadian Immunization Guide for additional information.

### Co-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 trivalent LAIV concomitantly with measles, mumps, rubella (MMR), measles, mumps, rubella, varicella (MMRV) or oral polio live vaccines<sup>(15)-(17)</sup>. 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. 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 to avoid any possibility of immune interference. Alternatively, an inactivated influenza vaccine (TIV or QIV) 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 the Canadian Immunization Guide.

When multiple injections are given at one 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 cm. A separate needle and syringe should be used for each injection.

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

## VACCINE SAFETY AND ADVERSE EVENTS

Data from post marketing surveillance of influenza vaccines in Canada (CAEFISS) have shown seasonal influenza vaccines to have a safe and stable Adverse Events Following Immunization (AEFI) profile with no unexpected events.

All influenza vaccines currently authorized for use in Canada are considered safe for use in persons with latex allergies. The multi-dose formulations of inactivated influenza vaccine that are authorized for use in Canada contain minute quantities of thimerosal, which is used as a preservative<sup>(18)(19)</sup>. Large cohort studies of health databases have demonstrated that there is no association between childhood vaccination with thimerosal-containing vaccines and neurodevelopmental outcomes, including autistic-spectrum disorders<sup>(20)</sup>. Despite the absence of data indicating any associated risk, influenza vaccine manufacturers in Canada are currently working towards production and marketing of thimerosal-free influenza vaccines. All single dose formulations of inactivated vaccine and LAIV are thimerosal-free. Refer to Vaccine Safety Part 2 of the Canadian Immunization Guide for additional information.

### Common Adverse Events

With IM administered influenza vaccines, injection site reactions are common but are generally classified as mild and transient. Adjuvanted TIV tends to produce more extensive injection site reactions than non-adjuvanted TIV, but these reactions are also generally mild and resolve spontaneously within a few days. The most common adverse events experienced by recipients of trivalent LAIV are nasal congestion and runny nose, which are also expected for the quadrivalent formulation. Additional information can be found in the relevant subsections of Section V of the Statement.

### Less Common and Serious or Severe Adverse Events

Serious adverse events are rare following immunization 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 Contraindications and Precautions below for additional information.

### Other Reported Adverse Events and Conditions

#### Guillain-Barré Syndrome (GBS)

Recent studies suggest that the absolute risk of GBS in the period following seasonal and A(H1N1)pdm09 influenza vaccination is about one excess case per 1 million vaccines and that the risk of GBS associated with influenza infection is larger than that associated with influenza vaccination. Additional information regarding GBS is found in Section V. Information regarding vaccinating individuals who have experienced GBS is provided under Precautions below.

**Oculo-respiratory syndrome (ORS)**

Oculo-respiratory syndrome (ORS), which is defined as the presence of bilateral red eyes plus one or more respiratory symptoms (cough, wheeze, chest tightness, difficulty breathing, difficulty swallowing, hoarseness or sore throat) that starts within 24 hours of vaccination, with or without facial oedema, was found during the 2000-2001 influenza season; few cases have been reported since then. ORS is not considered to be an allergic response.

Persons who have a recurrence of ORS upon revaccination do not necessarily experience further episodes with future vaccinations. 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. Refer to Contraindications and Precautions below for additional information.

**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 through local public health officials any serious or unexpected adverse event felt to be temporally related to vaccination. An unexpected AEFI is an event that is not listed in available product information but may be due to the immunization, or a change in the frequency of a known AEFI. The following AEFIs are of particular interest:

- ORS
- GBS within 6 weeks following immunization

Refer to Vaccine Safety in Part 2 of the Canadian Immunization Guide, the national Adverse Events Following Immunization Report Form and the User Guide to the Completion and Submission of the AEFI Reports for additional information about AEFI reporting.

**CONTRAINDICATIONS AND PRECAUTIONS****Contraindications**

Influenza vaccine should not be given to:

- people who have had an anaphylactic reaction to a previous dose; or
- people who have had an anaphylactic reaction to any of the vaccine components, with the exception of egg (Refer to Section V – Additional vaccine safety considerations).

Refer to Contents of Immunizing Agents Available for Use in Canada in Part 1 of the Canadian Immunization Guide for a list of all vaccines authorized for use in Canada and their contents and to Vaccine Safety in Part 2 of the Canadian Immunization Guide for information regarding the management of adverse events, including anaphylaxis.

**Additional LAIV – Specific contraindications and precautions**

LAIV is contraindicated for:

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



- Individuals with severe asthma, as defined as currently on oral or high dose inhaled glucocorticosteroids or active wheezing, or those with medically attended wheezing in the 7 days prior to vaccination.
- Children and adolescents, 2 to 17 years of age currently receiving aspirin or aspirin-containing therapy because of the association of Reye's syndrome with aspirin and wild-type influenza infection. It is recommended that aspirin-containing products in children less than 18 years of age be delayed for four 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. However, it is not contraindicated in breastfeeding mothers.
- Persons with immune compromising conditions, due to underlying disease, therapy, or both, as the vaccine contains live attenuated virus.

As a precautionary measure, LAIV recipients should avoid close association with persons with severe immune compromising conditions (e.g., bone marrow transplant recipients requiring isolation) for at least two weeks following vaccination, because of the theoretical risk for transmitting a vaccine virus and causing infection.

### Precautions

#### Allergic reactions to previous vaccine doses

Expert review of the risks and benefits 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 which could indicate a significant allergic reaction (e.g., throat constriction, difficulty swallowing) that raise concern regarding the safety of re-immunization. This advice may be obtained from local medical officers of health or other 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 skin testing, from an allergy or immunology 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.

#### Oculo-respiratory syndrome (ORS)

Individuals who have experienced ORS without lower respiratory tract symptoms may be safely re-immunized with influenza vaccine. Persons 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 IgE-mediated hypersensitivity immune response should seek advice.

#### Guillain-Barré syndrome (GBS)

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 persons known to have had GBS within six 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.

**Severe acute illness with or without fever**

Administration of seasonal influenza vaccine should usually be postponed in persons with serious acute illness until their symptoms have abated. Immunization 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, inactivated vaccines can be administered or LAIV may be deferred until resolution of the illness.

**Administration of influenza vaccine to egg allergic persons**

All influenza vaccine products authorized for use in Canada are manufactured by a process involving chicken eggs, which may result in the vaccine's containing trace amounts of residual egg protein. Egg allergic individuals may be vaccinated against influenza using inactivated TIV or QIV, 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 immunization setting. For more information regarding vaccination of egg allergic individuals, please see Section V of this statement. Data are not currently available to support vaccination of egg allergic individuals with LAIV.

**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. It is recommended that LAIV not be administered until 48 hours after antiviral agents active against influenza (oseltamivir and zanamivir) are stopped, and that antiviral agents, unless medically indicated, not be administered until two weeks after receipt of LAIV so that the antiviral agents do not kill the replicating virus. If antiviral agents are administered within this time frame (i.e., from 48 hours before to two weeks after LAIV is given), revaccination should take place at least 48 hours after the antivirals are stopped.

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

### **III. SPECIFICALLY RECOMMENDED RECIPIENTS: ADDITIONAL INFORMATION**

**Table 1** in section II lists the groups for which influenza vaccination is particularly recommended. Additional information regarding these specifically recommended recipients is provided below.

#### **PEOPLE AT HIGH RISK OF INFLUENZA-RELATED COMPLICATIONS OR HOSPITALIZATION**

**Adults (including pregnant women) and children with chronic health conditions as noted in Table 1.**

A number of chronic health conditions, as noted **Table 1**, are associated with increased risk of influenza-related complications and influenza can lead to exacerbation of the chronic disease. Influenza vaccination can induce protective antibody levels in a substantial proportion of adults and children with immune compromising conditions, including transplant recipients, those with proliferative diseases of the hematopoietic and lymphatic systems, and HIV-infected persons.

Vaccine efficacy may be lower in persons with immune compromising conditions than in healthy adults.

As of 2015-16, **children and adolescents with neurologic or neurodevelopment conditions** (including seizure disorders, febrile seizures and isolated developmental delay) have been included in this high risk group. A recent publication by the Canadian Immunization Monitoring Program Active (IMPACT) has documented that the burden of influenza infection in hospitalized children with neurological and neurodevelopment conditions, even those whose conditions do not obviously compromise respiratory function, is significant<sup>(21)</sup>. Over five years (2004-2009) of seasonal influenza surveillance, 1991 children were hospitalized with influenza, 293 of whom had neurologic or neurodevelopment conditions. These 293 cases were further analyzed to determine if they would have been considered high risk for influenza based on any other vaccine indication. One hundred and fifteen did not have airway compromise or another vaccine indication. This latter group presented with seizures more frequently than those with neurologic and neurodevelopment conditions and a vaccine indication (41.7% vs. 26.4%;  $P = 0.006$ ) and required intensive care unit admission (20.9% vs. 11.8%;  $P = 0.02$ ) and mechanical ventilation (14.8% vs. 4.5%;  $P < 0.001$ ) more often than children without neurologic or neurodevelopment condition but with a vaccine indication. The pre-existing neurologic and neurodevelopment conditions included those with isolated seizure disorders including febrile seizures and isolated developmental delay. Children with neurologic and neurodevelopment conditions have therefore been added to the list of conditions at high risk of influenza-related complications or hospitalization for whom vaccine is particularly recommended. In light of these findings in the paediatric population, NACI will be further assessing the information available for adults with neurological conditions. However, it is important to note that NACI already recommends influenza vaccine for everyone 6 months of age and older without contraindications.

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

Such residents often have one or more chronic medical conditions and live in institutional environments that may facilitate the spread of influenza.

### People ≥65 years of age

Admissions attributable to influenza in this age group are estimated at 125 to 228 per 100 000 healthy persons<sup>(22)</sup>, and mortality rates increase with increased age<sup>(8)</sup>.

### All Children 6 to 59 months of age

On the basis of existing data, NACI recommends the inclusion of all children 6 to 59 months of age among the specifically recommended recipients of influenza vaccine. For additional details on children 24-59 months, please see the Statement on Seasonal Influenza Vaccine for 2012-2013 and for children 6 to 23 months please see the Statement on Seasonal Influenza Vaccine for 2011-2012.

### Pregnant Women

NACI recommends the inclusion of all pregnant women, at any stage of pregnancy, among the specifically recommended recipients of inactivated influenza vaccine due to the risk of influenza-associated morbidity in pregnant women<sup>(23)-(27)</sup>, evidence of adverse neonatal outcomes associated with maternal respiratory hospitalization or influenza during pregnancy<sup>(28)-(31)</sup>, evidence that vaccination of pregnant women protects their newborns from influenza and influenza-related hospitalization<sup>(32)-(35)</sup>, and evidence that infants born during

influenza season to vaccinated women are less likely to be premature, small for gestational age, and low birth weight<sup>(36)-(39)</sup>.

The safety of inactivated influenza vaccine during pregnancy has been reviewed<sup>(40)</sup>. Active studies of influenza vaccination during pregnancy have not shown evidence of harm to the mother or fetus associated with influenza immunization<sup>(41)</sup>. 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 inactivated influenza vaccine in pregnancy over several decades<sup>(23)(24)(40)(42)</sup>. Surveillance following the use of both adjuvanted and unadjuvanted pH1N1 vaccine in >100,000 pregnant women in Canada and >488,000 pregnant women in Europe has not revealed any safety concerns<sup>(43)(44)</sup>.

For further details on influenza immunization in pregnancy and other evidence reviewed to inform this recommendation, see the *Statement on Seasonal Influenza Vaccine for 2011-2012* and the *Statement on Seasonal Influenza Vaccine for 2012-2013*.

### Aboriginal Peoples

Based on the body of evidence indicating a higher rate of influenza-associated hospitalization and death among Aboriginal Peoples, NACI recommends the inclusion of Aboriginal Peoples among specifically recommended recipients of influenza vaccine.

It has been proposed that the increased risk of severe influenza outcomes in the Aboriginal populations is a consequence of multiple factors, including high prevalence of chronic health conditions (e.g., diabetes, chronic lung disease, end-stage kidney disease)<sup>(45)</sup>, obesity, delayed access to health care and increased susceptibility to disease because of poor housing and overcrowding<sup>(46)-(48)</sup>. For further details on the evidence reviewed to inform this recommendation, see the *Statement on Seasonal Influenza Vaccine for 2011-2012*.

## 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 person has been immunized. Immunization of care providers decreases their own risk of illness, as well as the risk of death and other serious outcomes among the patients for whom they provide care<sup>(49)-(55)</sup>. Immunization of care providers and residents is associated with decreased risk of ILI outbreaks<sup>(56)</sup>. Individuals who are more likely to transmit influenza to those at risk of medical complications or hospitalization due to influenza include the following groups:

### Health Care and other Providers in Facilities and Community Settings

This group includes health care workers (HCWs), regular visitors, emergency response workers, those who have contact with residents of continuing care or long-term care facilities or residences, those who provide home care for persons in high-risk groups 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 vaccination provides benefits to HCWs and to the patients for whom they care. NACI considers the provision of influenza vaccination to be an essential component of the standard of care for all HCWs for the protection of their patients. This standard applies to any person, paid or unpaid, who provides services, works, volunteers or trains in a health care setting.

Transmission of influenza between infected HCWs and their vulnerable patients results in significant morbidity and mortality. Randomized controlled trials conducted in geriatric long-term care settings have demonstrated that vaccination of HCWs is associated with substantial decreases in morbidity<sup>(50)(53)(57)</sup> and mortality<sup>(49)(50)(52)(53)(57)</sup> in the residents. Therefore, HCWs should consider it their responsibility to provide the highest standard of care, which includes annual influenza vaccination. In the absence of contraindications, refusal of HCWs to be immunized against influenza implies failure in their duty of care to patients.

NACI recommends that TIV or QIV, instead of LAIV, should be used for HCWs providing care to individuals with immune compromising conditions, unless the HCW will only accept LAIV. If a HCW or other person receives LAIV and is providing care to individuals with severe immune compromising conditions (defined as hospitalized and requiring care in a protected environment), they should wait two weeks following receipt of LAIV before continuing to provide care to such individuals.

To protect vulnerable patients during influenza outbreaks, HCWs with confirmed or presumed influenza and unvaccinated HCWs who are not receiving antiviral prophylaxis should be excluded from direct patient contact. Health care organizations should have policies in place to deal with this issue.

**Household contacts, both adults and children, of individuals at high risk of influenza complications, whether or not the individual at high risk has been immunized**

These individuals include household contacts of individuals at high risk of influenza-related complications or hospitalization, as listed earlier, including household contacts of those ≤59 months of age, and household contacts of infants <6 months of age (who are at high risk of complications from influenza but for whom influenza vaccine is not authorized); and members of a household expecting a newborn during the influenza season.

They also include those providing regular child care to children ≤59 months of age, whether in or out of the home, and

those who provide services within closed or relatively closed settings to persons at high risk (e.g., crews on ships).

## 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 epidemics. Employers and their employees, including healthy working adults, should consider yearly influenza immunization, as this intervention has been shown to decrease work absenteeism due to respiratory and related illnesses.

**People in direct contact during culling operations involving poultry infected with avian influenza or swine workers**

NACI recommends immunization against seasonal influenza for people in direct contact with poultry infected with an avian influenza during culling operations as these individuals may be



at increased risk of avian influenza infection because of exposure during the culling operation (see below)<sup>(58)-(61)</sup>. However, NACI has concluded that there is insufficient evidence at this time to specifically recommend routine influenza immunization for swine workers. Information informing this recommendation can be found in the *Statement on Seasonal Influenza Vaccine for 2013-2014*.

Although seasonal influenza immunization will not prevent avian influenza infection, some countries<sup>(62)</sup> and provinces, have recommended influenza immunization on a yearly basis for these workers based on the rationale that preventing infection with human influenza strains may reduce the theoretical potential for human-avian re-assortment of genes should such workers become co-infected with human and avian influenza viruses<sup>(63)</sup>. It should be noted that vaccination with seasonal influenza vaccine will not produce protective antibodies against the human vaccine strains for approximately 14 days.

Direct involvement 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 essential that biosecurity measures such as personal protective equipment and antivirals be used. For further information regarding recommendations during a domestic avian influenza outbreak, see the Agency guidance at [http://www.phac-aspc.gc.ca/publicat/daio-enia/pdf/nat-ai-guide-2006\\_e.pdf](http://www.phac-aspc.gc.ca/publicat/daio-enia/pdf/nat-ai-guide-2006_e.pdf).

## IV. CHOICE OF PRODUCT

With the recent availability of a number of new vaccines, some of which are designed to enhance immunogenicity in specific age groups, the choice of product is no longer straightforward. **Table 2** in section II summarizes NACI's current recommendations for the choice(s) of currently available influenza vaccines in specific age and risk groups. More details along with brief supporting rationale are outlined here. Further detail for the trivalent formulation of FluMist®, and Fludac® can be found in supplementary NACI statements for each product<sup>(64)(65)</sup>. Further detail regarding quadrivalent influenza vaccines can be found in the *Statement on Seasonal Influenza Vaccine for 2014-2015* and in the literature review regarding quadrivalent influenza vaccines, available via the NACI website.

## PAEDIATRIC CONSIDERATIONS

The first time that children <9 years of age receive seasonal influenza immunization, a two-dose schedule is required to achieve protection<sup>(66)-(68)</sup>. Several studies have looked at whether these two initial doses need to be given in the same season<sup>(11)(12)(69)</sup>. Englund et al. reported similar immunogenicity in children 6-23 months of age whether two doses were given in the same or separate seasons when there was no change, or only minor vaccine strain change, in vaccine formulation between seasons<sup>(11)(12)</sup>. 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<sup>(10)(12)</sup>. Issues related to effective prime-boost when there is a major change in influenza B lineage across sequential seasons requires further evaluation<sup>(70)</sup>. 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.

Published and unpublished evidence suggest 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<sup>(71)(72)</sup>. 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.

In choosing a vaccine product for the paediatric age group, it is important to consider the following:

- the burden of influenza B disease in the paediatric population being cared for;
- the potential for mismatch between the predominant circulating strain of influenza B and the vaccine strain given historical trends; and
- the efficacy, immunogenicity and safety profile of the vaccine.

With the availability of QIV, it is important to evaluate the burden of influenza B to consider the impact of protection from having both B lineage strains in the vaccine. Canadian surveillance data from 2001-02 to 2012-13 has shown that influenza B strains accounted for 17% of laboratory-confirmed tests for influenza. Previously, in anticipation of QIV's entrance to the Canadian market, NACI had assessed that the burden of influenza B is highest in people less than 20 years of age. Children <24 months of age make up approximately 2% of the Canadian population<sup>(73)</sup>. Using case-based laboratory data from 2001 to 2012, children 0-23 months of age averaged (excluding 2009) 10.8% of reported influenza B cases (range 8.3 % to 13.7%). With respect to severe outcomes (e.g., hospitalization, ICU admission and death), influenza B was confirmed in 15.1% to 58.2% of paediatric influenza-associated hospitalizations (children ≤16 years of age) reported by IMPACT between 2004/05 and 2012/13 (excluding the 2009-2010 pandemic season). The proportion of hospitalizations due to influenza B relative to all influenza hospitalizations has been generally similar to the proportion of influenza B detections 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% of the characterized B strains were of the opposite lineage to the antigen in that season's vaccine).

### Children 6 to 23 months of age

There are three types of vaccine authorized for use in this age group: TIV, QIV and adjuvanted TIV (ATIV).

### Choice of vaccine product for children 6 to 23 months of age

ATIV has recently been made available for use in children 6-23 months. There is currently insufficient efficacy data on ATIV compared to unadjuvanted TIV or QIV to determine the relative clinical benefit of ATIV. There is limited but consistent evidence that ATIV is more immunogenic than unadjuvanted TIV against influenza A types. In particular, a single dose of ATIV is more immunogenic than a single dose of unadjuvanted TIV. However, two doses of ATIV are still necessary to achieve a satisfactory immune response against influenza B. Safety data showed ATIV was more reactogenic than unadjuvanted TIV, with recipients

experiencing 10-15% more solicited local and systemic reactions. However, most reactions were mild and resolved quickly. (See Section V. Vaccine preparations available for use in Canada for more information on ATIV.)

For children 6-23 months, NACI recommends that given the burden of influenza B disease, QIV should be used. If QIV is not available, either unadjuvanted or adjuvanted TIV should be used.

### Children 2 to 17 years of age

There are three types of vaccine authorized for use in this age group: TIV, QIV and LAIV.

#### Choice of vaccine product for children 2 to 17 years

NACI recommends LAIV use for healthy children and adolescents 2 to 17 years of age who do not have contraindications to this vaccine. There is evidence for the preferential use of LAIV in young children (younger than 6 years of age) based on superior efficacy of trivalent LAIV compared to TIV (Grade A), with weaker evidence of superior efficacy in older children (Grade I).

Based on expert opinion, the comparative efficacy data which supported the preferential recommendations for the trivalent formulation of LAIV are also applicable to the quadrivalent formulation of LAIV because the manufacturing processes and immunologic mechanism of the quadrivalent LAIV and the trivalent LAIV products are the same. This expert opinion is supported by the results of the non inferiority studies comparing trivalent and quadrivalent formulations of LAIV, which were required by regulatory bodies to authorize the use of the Q-LAIV formulation. Comparative vaccine efficacy and effectiveness data of TIV or QIV, and the quadrivalent formulation of LAIV are not available. It is anticipated that the superior efficacy for LAIV over TIV extends beyond age 6 years, but the evidence does not indicate at which specific age the efficacies of LAIV and TIV become equivalent. Given the burden of influenza B disease in children, if LAIV is not available for those for whom it is considered superior, QIV should be used. If QIV is not available, TIV should be used.

For children with underlying conditions or contraindications that preclude the use of LAIV, NACI also recommends that, given the burden of influenza B disease, QIV should be used. If QIV is not available, TIV should be used. More specifically, for:

- *Healthy children:* if LAIV is not available for those for whom it is considered superior, NACI now recommends that QIV should be used in this age group. If QIV is not available, TIV should be used.
- *Children with immune compromising conditions, which are a contraindication to LAIV:* Given the burden of influenza B disease in children, QIV should be used. If QIV is not available, TIV should be used.
- *Children with severe asthma (as defined in Section II under Contraindications and Precautions) or medically attended wheezing in the previous seven days:* Given the burden of influenza B disease in children, QIV should be used. If QIV is not available, TIV should be used.
- *Children with other chronic health conditions:* LAIV can be used in this group. If inactivated vaccine is being used, given the burden of influenza B disease in children, QIV should be used. If QIV is not available, TIV should be used.

### Healthy children and adolescents 2-17 years of age

With respect to the live attenuated influenza vaccine, NACI recommends its use for healthy children and adolescents 2 to 17 years of age who do not have contraindications to this vaccine.

As previously noted, there is evidence for the preferential use of LAIV in young children (younger than 6 years of age) based on superior efficacy of trivalent LAIV compared to TIV (Grade A), with weaker evidence of superior efficacy in older children (Grade I). It is anticipated that the superior efficacy of LAIV over TIV extends beyond age 6 years, but the evidence does not indicate at which specific age the efficacies of LAIV and TIV become equivalent. Based on expert opinion, this is expected to apply to quadrivalent LAIV as well. Given the burden of influenza B disease in children, if LAIV is not available for those for whom it is considered superior, QIV should be used. If QIV is not available, TIV should be used.

Two studies have directly compared the efficacy of LAIV and TIV in younger children (up to age 5 and 6) and one study has compared the efficacy of LAIV and TIV in asthmatic children 6 to 17 years of age<sup>(74)-(76)</sup>. NACI recognizes that there are differences in levels of evidence for younger and older children. There is more evidence that directly compares TIV and LAIV efficacy and that shows superior efficacy of LAIV in children younger than 6 years of age than in older children. Also, for children under 6 years of age, the evidence for the superiority of LAIV is of higher quality and the estimate of efficacy is higher, compared to the one study performed on children 6 to 17 years old.

The study by Fleming et al. (2006) looking at 2229 asthmatic children 6-17 years of age (mean age 11) showed superior efficacy of LAIV over TIV in this age group<sup>(74)</sup>. These results seem to have been mostly driven by influenza B and were not significant for the H3N2 strain. Although the study has limitations, such as the fact that the study population was asthmatic and so may not be generalizable to all children, its strengths include a randomized design and culture confirmed outcome.

It is hypothesized that as children get older, they are more likely to have had previous influenza infection, which might interfere with the immune response elicited to LAIV. It is not known at what age LAIV efficacy is no longer superior to TIV in children, and may vary from person to person, depending on their experience with various influenza viruses. In adults, comparative efficacy trials of LAIV and TIV have shown either no difference or superior efficacy of TIV. More evidence is needed that directly compares the efficacy and effectiveness of LAIV and TIV or QIV, especially in children over 6 years old and NACI considers this a research priority.

NACI also acknowledges that LAIV offers other advantages to children, including needle-free administration. Also, as a live, replicating whole virus formulation administered intranasally, it elicits mucosal immunity which may more closely mimic natural infection and contribute to the superior efficacy compared to TIV.

### Children with immune compromising conditions

NACI recommends against LAIV for individuals with immune compromising conditions. (NACI Recommendation Grade D). Given the burden of influenza B disease in children, QIV should be used. If QIV is not available, TIV should be used.

Live vaccines are generally contraindicated in people with immune compromising conditions, with some exceptions. NACI concludes that there is insufficient evidence supporting the use of LAIV in those with immune compromising conditions, in terms of both safety and effectiveness. The trivalent formulation of LAIV has been administered to approximately 170 children and adults with mild to moderate immune suppression due to HIV infections and 10 children with mild to moderate immune suppression due to cancer. Although these small studies demonstrated a similar safety profile to healthy individuals, based on expert opinion, NACI concludes that the use of LAIV in this population is contraindicated.

### Children with asthma

NACI recommends that LAIV can be used in children 24 months and older with stable, non-severe asthma. (NACI Recommendation Grade B).

LAIV should not be used in those with severe asthma (as defined as currently on oral or high dose inhaled glucocorticosteroids or active wheezing) and those with medically attended wheezing in the 7 days prior to vaccination.

A study of trivalent LAIV found increased rates of wheezing in children 6-23 months of age when compared to TIV<sup>(77)</sup>. Children 2 years of age and older and adolescents with asthma who received LAIV in clinical trials showed that there was no significant difference between LAIV and TIV in the exacerbation of asthma post-vaccination. Several studies demonstrated that the trivalent LAIV is well tolerated in asthmatics, and it has been demonstrated to have a higher relative efficacy compared to TIV with matched and mismatched strains<sup>(74)</sup>. NACI's review of current evidence on the use of LAIV in children 2 years of age and over with asthma and wheezing supports the use of LAIV in stable, non-severe asthmatics; however, NACI recommends against LAIV in those with severe asthma or medically attended wheezing in the previous seven days. Given the burden of influenza B disease in children, QIV should be used. If QIV is not available, TIV should be used.

### Children with other chronic health conditions

NACI recommends that LAIV can be used in children with chronic health conditions (excluding those with immune compromising conditions and severe asthma, as defined above). (NACI Recommendation Grade B).

A limited number of immunogenicity and efficacy studies have been conducted in this population. Based on expert review, it is expected that LAIV should be as immunogenic and efficacious in immune competent children with chronic health conditions as it is in healthy children.

At this time, there is insufficient evidence to recommend LAIV preferentially over inactivated vaccines in children with chronic health conditions. If inactivated vaccine is being used, given the burden of influenza B disease in children, QIV should be used. If QIV is not available, TIV should be used.

A Canadian study conducted by Boikos et al. (2014) during the 2012-13 season followed a cohort of 168 participants, 2-18 years of age with cystic fibrosis for 56 days following administration of trivalent LAIV to evaluate the safety of LAIV in this population (see Appendix B for evidence table)<sup>(78)</sup>. Individuals were excluded if they were using systemic corticosteroids, considered immunosuppressed, or had nasal polyps or rhinorrhea considered significant enough (by vaccinator) to prevent LAIV from reaching the nasal mucosa. Overall, LAIV was



found to be well-tolerated by the study participants. When comparing the at-risk period (0-28 days post receipt of LAIV) to the non at-risk period (29-56 days post LAIV), there was no significant increase in the rate of incident respiratory deteriorations [incident rate ratio (IRR): 0.72 (95% CI: 0.11, 4.27)] or all-cause hospitalizations was observed [IRR: 1.16 (95% CI: 0.30, 4.81)]. At least one solicited adverse event was reported in the first week following vaccination by 64% of participants. The most frequent symptoms reported included fever, runny nose, nasal congestion, headaches, and tiredness. Thirteen cases of wheezing were reported [RR: 4.33 (95% CI: 1.26, 14.93)], with the greatest incidence occurring during the day of vaccination. Of 15 participants who reported redness in both eyes, 13 were reported during the first three days post-vaccination, and all reports of facial swelling (n=10) also occurred during the same time period. Most of these symptoms occurred within 24 hours of vaccination and were compatible with oculo-respiratory syndrome.

Cystic fibrosis is considered a hyper-inflammatory disorder, and unless treated with immunosuppressive drugs, such as prolonged systemic corticosteroids, children with cystic fibrosis are not considered immunosuppressed, and may receive LAIV. The findings in the study by Boikos et al. (2014) provide reassurance that LAIV is safe for use in this population.

NACI recommends that children with cystic fibrosis may receive LAIV if the individual is not being treated with immunosuppressive drugs, such as prolonged systemic corticosteroids, and meets the other criteria for LAIV administration.

## ADULTS

### Adults 18-59 years of age

There are three types of vaccine available for use in adults 18-59 years of age: TIV, QIV and LAIV. For healthy adults in this age group, NACI considers all three types of vaccine to be acceptable choices (unless contraindicated).

For adults in this age group with chronic health conditions, TIV or QIV may be used.

Additional information can be found in the NACI statement: *Recommendations on the use of live, attenuated influenza vaccine (FluMist®): Supplemental Statement on Seasonal Influenza Vaccine for 2011-2012.*

### Adults 60-64 years of age

The vaccines available for use in adults 60-64 years of age, with or without chronic health conditions, are TIV and QIV.

### Adults ≥65 years of age

Three types of vaccine are available for use in adults ≥65 years of age: TIV, QIV and MF59-adjuvanted TIV.

### Pregnant women

TIV and QIV are available for use in pregnant women. Due to a lack of safety data at this time, LAIV, which is a live attenuated vaccine, should not be administered to pregnant women, but it can be administered to breastfeeding women.



## **V. VACCINE PREPARATIONS AVAILABLE FOR USE IN CANADA**

The following sections describe, by vaccine type, relevant information including efficacy and effectiveness, immunogenicity and safety related to influenza vaccines currently available for use.

Key relevant details and differences between vaccine products are highlighted in **Appendix A**.

### **INACTIVATED INFLUENZA VACCINES**

#### **Trivalent Inactivated Influenza Vaccines: Unadjuvanted: IM administered (TIV)**

Vaccines currently available for use

- Agriflu® (Novartis)
- Fluviral® (GlaxoSmithKline)
- Fluzone® (Sanofi Pasteur)
- Influvac® (BGP Pharma ULC, Note: products may still be labeled *Abbott*)
- Vaxigrip® (Sanofi Pasteur)

#### **Efficacy and Effectiveness**

Multiple studies have shown that influenza vaccine is efficacious with higher efficacy demonstrated against laboratory-confirmed influenza than clinically defined outcomes<sup>(79)</sup>. In healthy children (equal to or younger than 16 or 18 years old, depending on the study), a systematic review and meta-analyses showed that the efficacy of influenza vaccine against laboratory confirmed influenza ranged from 59% to 82%; similarly, a 2013 literature review looking at influenza vaccine effectiveness, immunogenicity and safety in healthy 5-18 year olds found that vaccine efficacy against laboratory confirmed influenza was variable but most frequently between 65-85%<sup>(80)-(98)</sup>. Efficacy against serologically-confirmed influenza ranged from 54% to 63% and efficacy against clinical illness ranged between 33% and 36%<sup>(99)-(101)</sup>. Vaccine efficacy against influenza-like illness was generally not well demonstrated in the studies included in the 2013 literature review in healthy children, although one of the six studies assessing this suggested vaccine efficacy of 68-85% against this outcome<sup>(81)(82)(84)(88)(92)(102)</sup>.

In a systematic review of healthy adults, inactivated influenza vaccine efficacy against laboratory-confirmed influenza was estimated to be 80% (95% CI [56%,91%]) and vaccine effectiveness against influenza-like illness was estimated at 30% (95% CI [17%, 41%]) when the vaccine strain matched the circulating strains and circulation was high<sup>(99)</sup>. Two other studies found somewhat lower vaccine efficacy at 55% (95% CI [41%, 65%]) in the 2006-07 season<sup>(103)</sup> and 68% (95% CI [46%, 81%]) in the 2007-08 season<sup>(104)</sup>. Vaccine efficacy of 50% in healthy adults (95% CI [27%, 65%]) has been identified during select seasons of vaccine mismatch, although mismatch is a relative term and the amount of cross-protection is expected to vary<sup>(105)-(107)</sup>.

In the elderly, vaccine effectiveness is about half of that in healthy adults and varies depending on the outcome measures and the study population<sup>(108)(109)</sup>. Systematic reviews have demonstrated that the influenza vaccine decreases the incidence of pneumonia, hospital

admissions and deaths in the elderly<sup>(108)</sup> and reduces exacerbations in persons with chronic obstructive pulmonary disease<sup>(110)</sup>.

In observational studies, immunization has been shown to reduce the number of physician visits, hospitalizations and deaths in high-risk persons 18 to 64 years of age<sup>(111)</sup>, hospitalizations for cardiac disease and stroke in the elderly<sup>(112)</sup>, and hospitalization and deaths in persons with diabetes mellitus 18 years of age and older<sup>(113)</sup>. Observational studies that use non-specific clinical outcomes and that do not take into account differences in functional status or health-related behaviours should be interpreted with caution<sup>(114)-(118)</sup>.

Vaccine efficacy may be lower in certain populations (e.g., persons with immune compromising conditions, elderly persons) than in healthy adults. However, the possibility of lower efficacy should not preclude immunization in those at high risk of influenza-associated morbidity, since vaccinated individuals are still more likely to be protected compared to those who are unvaccinated.

In a 2012 systematic review and meta-analysis conducted by Osterholm et al. on influenza vaccine efficacy and effectiveness, efficacy of TIV in adults was found to be lower than was found in other literature<sup>(119)</sup>. The included studies in 18-64 year olds covered nine influenza seasons and had a random-effects pooled vaccine efficacy of 59% (95% CI [51, 67]). The authors found no papers that met their inclusion criteria for TIV efficacy in children or in older adults. These authors found vaccine effectiveness was variable for seasonal influenza with six of 17 analyses in nine studies showing significant protection against medically attended influenza in the outpatient or inpatient setting. The author's conclusions in this review may be subject to interpretation because of the restrictive inclusion criteria that were used to select evidence for this review. The NACI methodology uses broader inclusion criteria for available evidence, and thus, interpretation of evidence may vary from other reviews.

NACI continues to encourage high quality research on influenza vaccine efficacy and effectiveness as it constitutes critical information to make influenza immunization recommendations and data are still lacking on several topics of relevance.

### **Immunogenicity**

Intramuscular administration of TIV results in the production of circulating IgG antibodies to the viral haemagglutinin and neuraminidase proteins, as well as a more limited cytotoxic T lymphocyte response. 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)<sup>(120)</sup>. Repeated annual administration of influenza vaccine has not been demonstrated to impair the immune response of the recipient to influenza virus.

### **Considerations related to immunogenicity studies in the paediatric population**

Some studies have shown there may be immunogenicity differences between influenza vaccine products in young children<sup>(71)(121)-(123)</sup>. However, the use of a 0.5 mL vaccine dose generated a more comparable immune response than a 0.25 mL dose in children <24 months and in unprimed children.

Overall, the clinical implications of these findings are unclear as vaccine effectiveness was not studied and could be unaffected even where immunogenicity is lower. As well, there are no established licensing criteria for immunogenicity in young children as there is generally insufficient information on immunity in this age group. All four studies that were reviewed with respect to differing immunologic responses between products used licensing criteria for adults, which have not similarly been proven to correlate with 50% efficacy in children. It is important to note that NACI recommends the use of a 0.5 mL dose for all recipients of the unadjuvanted inactivated influenza vaccine, including young children, which is thought to mitigate the reduced immune response observed in the studies with the 0.25 mL dose. Due to insufficient information, there is no change in product recommendations at this time and all products authorized for use in the paediatric population can be used for influenza immunization of children.

### **Considerations related to the elderly and those with immune compromising conditions**

Although the initial antibody response in elderly recipients 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 the elderly than in younger age groups<sup>(124)</sup>.

Influenza vaccination can induce protective antibody levels in a substantial proportion of adults and children with immune compromising conditions, including transplant recipients, those with proliferative diseases of the haematopoietic and lymphatic systems, and HIV-infected patients<sup>(125)-(128)</sup>.

Most studies have shown that administration of a second dose of influenza vaccine in the same season to elderly individuals or other individuals who may have an altered immune response does not result in a clinically significant antibody boost<sup>(128)-(132)</sup>.

### **Safety**

Healthy adults receiving TIV show no increase in the frequency of fever or other systemic symptoms compared with those receiving placebo. TIV is safe and well tolerated in healthy children. Mild injection site reactions, primarily soreness at the vaccination site, occur in 7% or less of healthy children who are less than 3 years of age. Post-vaccination fever may be observed in 12% or less of immunized children 1 to 5 years of age.

### **Quadrivalent Inactivated Influenza Vaccines: Unadjuvanted: IM administered (QIV)**

Vaccines Currently Available for use

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

### **Efficacy and Effectiveness**

In a Literature Review on Quadrivalent Influenza Vaccines conducted by NACI, to date, only one study has measured QIV efficacy. In that study, vaccine effectiveness was estimated at 59% in children 3-7 years of age, in comparison to children who received hepatitis A vaccine<sup>(133)</sup>. No literature was found on head to head efficacy or effectiveness studies directly comparing trivalent and quadrivalent formulations, for either inactivated or live attenuated formulations.

### Immunogenicity

In this same review of the literature, NACI reviewed the immunogenicity data for QIV produced by manufacturers who supplied influenza vaccine in Canada at the time of the literature review: GlaxoSmithKline, Astra Zeneca 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 H3N2, 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 it. These findings were consistent across age groups and different types of trivalent vaccines (inactivated and LAIV).

In some of the unpublished data from manufacturers that were submitted to NACI, the H3N2 or H1N1 immune response in QIV recipients was different compared to TIV recipients. For example, in a study in 6-35 month olds by one manufacturer, the seroconversion and seroprotection rates for H1N1 and H3N2 were much higher in QIV recipients compared to TIV recipients. Of note, the QIV and TIV products in this study were manufactured by different processes. In another study, by a different manufacturer, in adults 65 years and older, the H1N1 seroconversion rate was statistically inferior in QIV recipients compared to TIV recipients. The H1N1 GMTs were slightly lower in the QIV recipients compared to the TIV recipients; however this result was statistically non inferior. These results were not further explained by the investigators. The number of patients in these studies is relatively small and the clinical significance of these results is unknown. As previously mentioned, comparative vaccine efficacy and effectiveness data of TIV and QIV are not available.

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 criteria in the CHMP and CBER guidelines, including those for the 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. This cross protection against infection with one lineage provided by immunization against the other lineage is uncertain, however, and it is expected to be low<sup>(134)</sup>.

### Safety

The QIV Phase III trials generally showed similar and expected rates of adverse events between the trivalent and quadrivalent formulations. Most of these studies included a limited number of patients. As the quadrivalent formulations have a higher antigenic content than the trivalent vaccine, Phase IV trials and post-marketing surveillance will need to monitor whether increased reactogenicity will be a concern for the quadrivalent vaccine.

### Trivalent Inactivated Influenza Vaccine: Adjuvanted: IM administered (adjuvanted TIV)

Vaccines currently available for use

- Flud® (Novartis)
- Flud Pediatric™ (Novartis)

#### 1. Flud® (Novartis)

### Efficacy and Effectiveness

A phase III, randomized, observer-blinded study comparing the safety and immunogenicity of a MF59 adjuvanted influenza vaccine with unadjuvanted influenza vaccine in adults ≥65 years

of age noted no significant difference in the clinical effectiveness between adjuvanted and unadjuvanted TIV in terms of ILI<sup>(135)</sup>. However, this study was not designed to estimate vaccine effectiveness against laboratory-confirmed outcomes.

A few observational studies suggest that Flud® may be effective at reducing the risk of hospitalization for influenza and its complications in the elderly, compared to unvaccinated individuals and those who received unadjuvanted trivalent inactivated subunit vaccine. However, these studies have significant methodological limitations that make their interpretation difficult<sup>(65)(136)-(140)</sup>.

A Canadian observational study performed in British Columbia by Van Buynder et al. evaluated the comparative effectiveness of Flud® to TIV in reducing laboratory confirmed influenza in the elderly<sup>(141)</sup>. In the first year of the study (2011-2012 season), elderly people in three health authorities were included in a community-based case control study. Participants were included if they were 65 or older, had ILI and were swabbed and tested for influenza. The participants included elderly in long term care, as well as individuals in the community. Influenza testing was carried out as part of routine clinical care. Cases had a positive test for influenza, whereas controls had negative tests. The choice of product was determined by external factors such as geographic location and vaccine availability, and these factors were not controlled. There were a total of 84 cases and 198 controls, which the authors acknowledged was a very small sample size and was attributable to the low level of influenza activity in the community that year. The results showed that in a variety of multivariate analyses, Flud® effectiveness was 58% (95% CI: 5-82) and TIV effectiveness was 24% (95% CI: -129% to 75 %) (personal communication, P Van Buynder, December 2013). The study did not evaluate protection against hospitalization. As this study continued for a second year, further results will be discussed once published. The methodological limitations of this study should be taken into consideration when interpreting the results.

### Immunogenicity

The mechanism of action of MF59 is not fully determined and has primarily been studied using in vitro and mouse models. From these studies, it appears that MF59 may act differently from aluminum-based adjuvants. These studies show that MF59 acts in the muscle fibres to create a local immune-stimulatory environment at the injection site<sup>(142)</sup>. MF59 allows for an increased influx of phagocytes (e.g., macrophages and monocytes) to the site of injection. The recruited phagocytes are further stimulated by MF59, thereby increasing the production of chemokines to attract more innate immune cells and inducing differentiation of monocytes into dendritic cells<sup>(143)(144)</sup>. MF59 further facilitates the internalization of antigen by these dendritic cells<sup>(144)(145)</sup>. The overall higher number of cells available locally increases the likelihood of interaction between an antigen presenting cell and the antigen, leading to more efficient transport of antigen to the lymph nodes, with resulting improved T cell priming<sup>(144)</sup>.

There is evidence from randomized controlled trials that Flud® induces higher immunogenicity and broader cross-reactivity in adults 65 years of age and older as compared to the unadjuvanted subunit vaccines. In the recent Frey et al (2014) study, adjuvanted subunit TIV elicited a significantly higher antibody response than unadjuvanted subunit TIV, especially against A/H3N2, although superiority by pre-defined criteria was not formally met<sup>(135)</sup>. Similar but less consistent results have been shown in terms of improvement in antibody response relative to split-virus vaccine, which is the type of influenza vaccine used most often in Canada. The studies which compare Flud® to split-virus vaccine generally compared it to a vaccine called Mutagrip®, which is not available in Canada. The one study that compared Flud® to Vaxigrip® found similar seroprotection and seroconversion rates for

H3N2 and a higher immune response for H1N1 and B for Flud® recipients <75 years of age<sup>(146)</sup>. For those 75 years of age and older, higher seroprotection and seroconversion rates were noted for all three strains in those receiving Flud®. In a randomized clinical trial comparing Intanza® (intradermal TIV) to Flud® in participants aged 65 years and older, non-inferiority of the intradermal vaccine compared with the adjuvanted vaccine was demonstrated for the A/H1N1 and B strains with the haemagglutination inhibition assay (HAI) method and for all three strains with the single radial haemolysis (SRH) method<sup>(147)</sup>.

A Canadian study conducted by the Public Health Agency of Canada/CIHR Influenza Research Network (PCIRN) looked at the immunogenicity of Flud® (Adjuvanted Trivalent Inactivated Vaccine: ATIV), Intanza 15® (TIV-ID) and Agriflu® (sub-unit TIV) in ambulatory seniors (≥65 years) living in the community<sup>(143)</sup>. This randomized controlled study comprised 911 participants. For the B strain (Brisbane), the baseline antibody titres were too high for meaningful response assessments post immunization. For H1N1, seroprotection rates were significantly higher after ATIV than after the other vaccines when measured by HAI, but not by SRH. For H3N2, seroprotection rates were significantly higher after ATIV than after other vaccines by both HAI and SRH, while rates did not differ significantly between TIV-ID and the sub-unit TIV. In the microneutralization (MN) assay, titers ≥40 to H3N2 were achieved more frequently after ATIV than after the other vaccines. GMTs were highest after ATIV for both A viruses. When immune responses were compared using criteria for licensing influenza vaccines in seniors, all 3 vaccines met the seroprotection criterion for each virus (both HAI and SRH assays). By HAI, ATIV and TIV-ID met the seroconversion and GM fold increase criteria for the A viruses. TIV did not meet the seroconversion criterion for H3N2. By SRH assay, the GM fold increase criterion was not met for any virus after TIV-ID or TIV but it was met for the A viruses after ATIV. While statistically significant, the differences in seroprotection rates and GMT ratios after ATIV or TIV were of modest magnitude. Whether this would result in greater protection against infection is not yet certain.

Six months after vaccination, residual seroprotection rates to the A viruses did not differ significantly among the 3 groups, but only ATIV recipients had rates over 60% for each virus, meeting international immunogenicity criteria.

The implication of these immunogenicity findings with regard to clinical efficacy is unknown and requires further study.

### **Safety**

MF59-adjuvanted TIV produces injection site reactions (pain, erythema and induration) significantly more frequently than unadjuvanted vaccines, but they are classified as mild and transient. Systemic reactions (myalgia, headache, fatigue and malaise) are comparable or more frequent with Flud® compared to unadjuvanted vaccines and are rated as mild to moderate and transient.

## **2. Flud Pediatric™ (Novartis)**

### **Efficacy and Effectiveness**

In a *Literature Review on Pediatric Flud® Influenza Vaccine Use in Children 6-72 Months of Age* conducted by NACI, only a single efficacy trial of ATIV in children aged 6 to <72 months was identified<sup>(148)</sup>. However, there were several considerations regarding the applicability of this trial. Firstly, the European Medicines Agency identified a number of critical issues related to trial management, quality of data, and data handling for this study at some of the trial sites during a Good Clinical Practice inspection conducted as part of the authorization process in



Europe<sup>(149)</sup>. As evidenced in the product monograph, efficacy data from the efficacy trial, although available, were not considered in granting product authorization in Canada.

Secondly, the unadjuvanted TIV comparator in this trial was shown, in an unrelated study, to generate a lower immune response compared to another unadjuvanted TIV product during the 2006/07 season<sup>(122)(150)</sup>. It is not clear what implication this has on clinical protection. Finally, the study administered 0.25 mL doses of the comparator vaccine for children <36 months, which is lower than the dose of 0.5 mL of unadjuvanted influenza vaccine that is recommended for this age group in Canada.

A reanalysis was conducted excluding the affected trial sites, and there was no notable change from the original findings<sup>(151)</sup>. After reviewing this information, NACI continues to believe that the concerns with the trial identified above should be taken into account when assessing the results of the study.

### **Immunogenicity**

In children, there is limited but consistent evidence that ATIV is more immunogenic than comparable unadjuvanted TIVs against influenza A types<sup>(148)(152)-(156)</sup>. In particular, a single dose of ATIV is more immunogenic than a single dose of unadjuvanted TIV. However, two doses of ATIV are still necessary to achieve a satisfactory immune response against influenza B.

Almost all of the studies included in *Literature Review on Pediatric Fluad® Influenza Vaccine Use in Children 6-72 Months of Age* used vaccine formulations of 0.25 mL in children 6-35 months of age, both for the adjuvanted vaccine and the comparator unadjuvanted influenza vaccine. One study employed a dose-ranging factorial design comparing adjuvanted and unadjuvanted versions of seasonal TIV and QIV administered to children 6-36 months old<sup>(154)</sup>. Immunogenicity data was presented for 0.25 mL ATIV (n=27) and 0.5 mL unadjuvanted TIV or QIV, reported jointly as a single group (n=50). The 0.25 mL ATIV generated a better immune response after the first and second dose when compared to the first and second dose of unadjuvanted 0.5 mL TIV/QIV. Additional data provided by the authors separating unadjuvanted TIV (n=22) and QIV (n=28), showed a similar or better immune response for QIV compared to TIV. It should be noted that participants receiving ATIV were, on average, older than those in the unadjuvanted TIV and QIV groups (which may lead to an enhanced immune response) and the findings are based on small sample sizes.

NACI recommends 0.5 mL dosage of unadjuvanted TIV or QIV in all age groups. While there is some indication of how ATIV at 0.25 mL dose would compare to unadjuvanted TIV or QIV at 0.5 mL dose immunologically in the 6 to <24 month age group, it is unclear whether the stronger humoral immune response induced by ATIV in one trial with a very limited number of participants translates into an appreciable advantage in terms of preventing influenza or its complications.

### **Safety**

The safety data in children are consistent with what is known about ATIV's safety profile in adults. In the paediatric trials, ATIV was more reactogenic than unadjuvanted TIV, with recipients experiencing 10-15% more solicited local and systemic reactions<sup>(157)</sup>. However, most reactions were mild and resolved quickly.

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 H1N1 pandemic that has been associated with an increased risk of narcolepsy. A study published in December 2014 comparing two adjuvanted H1N1 vaccine products has suggested that the underlying immune mediated mechanism may not be initiated by the adjuvant, but by another component of the vaccine, specifically the H1N1 viral antigen<sup>(158)</sup>. 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.

One study employed a dose-ranging factorial design and included both adjuvanted and unadjuvanted versions of seasonal TIV and QIV administered to children 6-36 months old<sup>(154)</sup>. Overall, there was no indication of an increasing risk of adverse events associated with increasing MF59 dose, antigen dose, or the addition of a second B strain. However, reactogenicity of 15µg formulations were slightly higher for both adjuvanted and unadjuvanted vaccines compared to the 7.5µg formulations.

## LIVE ATTENUATED INFLUENZA VACCINE (LAIV)

Vaccines currently available for use

- Flumist® Quadrivalent (AstraZeneca) live attenuated vaccine

*Note: The statement has been updated to reflect that the evidence supporting the use of live attenuated influenza vaccines was based on the trivalent formulation. Based on expert opinion, the comparative efficacy data which supported the preferential recommendations for the trivalent formulation of LAIV are also applicable to the quadrivalent formulation of LAIV because the manufacturing processes and immunologic mechanism of the quadrivalent LAIV and the trivalent LAIV products are the same. This expert opinion is supported by the results of the non inferiority studies comparing trivalent and quadrivalent formulations of LAIV, which were required by regulatory bodies to authorize the use of the Q-LAIV formulation. Comparative vaccine efficacy and effectiveness data of TIV or QIV, and the quadrivalent formulation of LAIV are not available.*

### Efficacy and Effectiveness

A number of studies (LAIV versus placebo and LAIV versus TIV) have been conducted in children and adults. Two studies have directly compared the efficacy of LAIV and TIV in younger children (up to age 5 and 6) and one study has compared the efficacy of LAIV in asthmatic children 6 to 17 years of age<sup>(74)-(76)</sup>. NACI recognizes that there are differences in levels of evidence for younger and older children. There is more evidence that directly compares TIV and LAIV efficacy and that shows superior efficacy of LAIV in children younger than 6 years of age than in older children. Also, for children under 6 years of age, the evidence for the superiority of LAIV is of higher quality and the estimate of efficacy is higher compared to the study performed on children 6 to 17 years old. In contrast to children, most comparative studies in persons 18 to 59 years of age have found that LAIV and TIV had similar efficacy or that TIV was more efficacious<sup>(64)</sup>. Further details regarding the recommendation rationale for LAIV are found in section IV.

Comparative vaccine efficacy and effectiveness data of TIV or QIV, and the quadrivalent formulation of LAIV are not available.

Reduced effectiveness of LAIV (quadrivalent formulation) in children, overall and compared to inactivated vaccines, was reported during the 2013-14 influenza season in the US against

influenza A(H1N1). Investigations by the manufacturer have determined that this reduced effectiveness is most likely attributable to reduced stability of the hemagglutinin stalk sequence for the A/California H1N1 vaccine strain. Thermal stability tests have shown that the reduced stability likely resulted in strain degradation when experiencing deviations in temperature during storage or transport. The manufacturer has indicated that the A/California H1N1 strain used in this LAIV formulation will be replaced in the 2015/16 influenza season with a more thermal stable strain. Undocumented deviations in temperature during storage or transport from the manufacturer to the provincial and territorial depots are unlikely to occur in Canada as, by contract, the contractor, (i.e., manufacturer) is required to maintain the required temperatures throughout transport from the contractor to the identified users (i.e., provincial and territorial depots) and provide evidence to that effect from the data analysis of the temperature monitoring device or carrier logs, as applicable.

Based on information from the Canadian Sentinel Influenza Vaccine Effectiveness Surveillance Network, a similar problem was not seen in Canada with the trivalent LAIV, but this observation must be interpreted with caution due to the small number of LAIV recipients available for analysis. This issue continues to be monitored by NACI.

NACI has reviewed the available information on this issue, including Canadian data, and continues to recommend preferential use of LAIV in children (see Section IV. Choice of Product). LAIV will continue to be monitored to assess whether the issues with low vaccine effectiveness have been fully addressed with the proposed change to the vaccine strain.

### **Immunogenicity**

LAIV (FluMist® Quadrivalent), 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 an HAI antibody response after the administration of trivalent LAIV is predictive of protection. However, efficacy studies have shown protection in the absence of a significant antibody response<sup>(64)</sup>. In these studies, LAIV has generally been shown to be equally, if not more immunogenic, than TIV for all three strains in children, whereas TIV was typically more immunogenic in adults than LAIV. Greater rates of seroconversion to LAIV occurred in baseline seronegative individuals compared to baseline seropositive individuals in both child and adult populations, because pre-existing immunity may interfere with response to a live vaccine. For further details consult the rationale below and the NACI supplemental statement for FluMist®.

The quadrivalent formulation of LAIV has shown non-inferiority compared to the trivalent formulation in both children and adults. The immune response to the B strain found only in the quadrivalent formulation was better in children who received the quadrivalent vaccine<sup>(159)-(161)</sup>.

### **Safety**

The most common adverse events experienced by recipients of trivalent LAIV are nasal congestion and runny nose, which are also expected for quadrivalent formulation. In a large efficacy trial, wheezing occurred in recipients of trivalent LAIV vaccine at rates above those in TIV recipients only in children <24 months of age<sup>(64)</sup>. This is expected to be the same for recipients of the quadrivalent LAIV.

Studies on the trivalent formulation of FluMist® have shown that vaccine virus can be recovered by nasal swab in children and adults following vaccination (i.e., “shedding”). The frequency of shedding decreases with increasing age and time since vaccination. Shedding is generally below the levels needed to transmit infection, although in rare instances, shed vaccine viruses can be transmitted from vaccine recipients to unvaccinated persons. For more detailed information on LAIV and viral shedding, consult the [NACI supplemental statement for FluMist®](#).

## CO-ADMINISTRATION WITH OTHER VACCINES

NACI has reviewed the potential for immune interference when live vaccines are administered sequentially within a short time period (less than 4 weeks). In general, NACI recommends that two live parenteral vaccines be administered either on the same day or at least four weeks apart<sup>(162)</sup>. This is based largely on a single study from 1965 that demonstrated immune interference between smallpox vaccine and measles vaccine administered 9 to 15 days apart. Subsequent studies have revealed conflicting results on immune interference between live vaccines<sup>(163)-(166)</sup>.

A literature search was conducted for clinical data on immune interference between LAIV and other live attenuated vaccines (oral or parenteral) administered within 4 weeks. No studies were found. Three studies included data on concomitant administration of LAIV with MMR, varicella and oral polio vaccines<sup>(15)-(17)</sup>. Although the impact on vaccine efficacy was not evaluated, none found evidence of clinically significant immune interference. One study reported a statistically significant but not clinically meaningful decrease in seroresponse rates to rubella antigen.

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 (i) the inhibitory and immunomodulatory effects of systemic and locally produced cytokines on B- and on viral replication and T-cell response (ii) immunosuppression induced by certain viruses (such as measles); and (iii) 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 to avoid any possibility of immune interference. Alternatively, an inactivated influenza vaccine (TIV or QIV) may be given.

Research on immunogenicity and efficacy following concomitant and non-concomitant administration of LAIV and parenteral live vaccines is encouraged, to determine the optimal timing for vaccine administration.

## 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

Regarding administration of influenza vaccine to egg allergic persons, after careful review, NACI has concluded that egg allergic individuals may be vaccinated against influenza using TIV 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 immunization setting. Based on expert opinion, informed by the understanding that QIV manufacturing processes are similar to those of TIV and by information regarding the egg albumin content of the current vaccines, similar recommendations have been made for QIV. Waiting period post immunization would be as recommended in the [Canadian Immunization Guide](#). As with all vaccine administration, immunizers should have the necessary equipment and be prepared to respond to a vaccine emergency at all times.

Supporting this change in recommendation is work done by DesRoches et al. (2012)<sup>(167)</sup> and Greenhawt et al. (2012)<sup>(168)</sup>. DesRoches et al. conducted two studies, a prospective cohort study (2010/2011 and 2011/2012 flu seasons) in 5 Canadian hospitals, and a retrospective cohort study (2007/2008, 2008/2009 and 2009/2010 flu seasons) based out of one Canadian hospital. Recruitment included patients with egg-allergy, including severe allergy defined as the occurrence of anaphylaxis or cardiorespiratory symptoms upon egg ingestion. For both studies, patients were examined immediately before vaccination with Fluviral® and remained under observation for 60 minutes post-vaccination before being re-examined. Over the 5 influenza seasons, 457 doses of the seasonal TIV were administered to 367 patients, among whom 132 (153 doses) had a history of severe egg-allergy. Four patients reported mild allergic-like symptoms after previous influenza vaccination (1 urticaria, 2 vomiting, and 1 eczema), but none experienced an adverse event when given the current vaccine. While 13 patients developed mild allergic-like symptoms in the 24 hours following vaccination, none of the 367 patients developed anaphylaxis.

DesRoches et al. also conducted a literature review on egg allergic patients who had been vaccinated. A total of 26 studies were found, representing 4729 doses of influenza vaccine administered to 4172 patients with egg allergy, of which 513 patients had been identified as having severe egg allergy. None of the 4172 patients experienced anaphylaxis post influenza immunization. For the 597 doses administered to the 513 patients with a history of severe allergic reaction to egg, the 95% CI of the risk of anaphylaxis was 0% to 0.62%<sup>(167)</sup>. Greenhawt et al. (2012), using inclusion criteria of a history of a severe reaction, including anaphylaxis, to the ingestion of egg and a positive skin test result or evidence of serum specific IgE antibody to egg, conducted a 2-phase multi-centre study in which phase 1 consisted of a randomized, prospective, double-blind, placebo control trial of TIV to egg allergic children, using a 2-step approach in which group A received 0.1 mL of influenza vaccine, followed in 30 minutes if there was no reaction, with the remainder of an age-appropriate dose. Group B, by contrast, received an injection of normal saline followed in 30 minutes if there was no reaction with the full 100% of the age-appropriate dose. Phase II was a retrospective analysis of single dose versus divided doses administration of TIV in eligible study participants who declined participation in the RCT. All participants in both phases received TIV without developing an allergic reaction<sup>(168)</sup>.

Data are not currently available to support this recommendation for LAIV.

### **Guillain-Barré syndrome (GBS)**

Recent studies suggest that the absolute risk of GBS in the period following seasonal and A(H1N1)pdm09 influenza vaccination is about one excess case per 1 million vaccines. 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 reject a causal relation between GBS in adults and seasonal influenza vaccination<sup>(169)</sup>. More recent studies suggest that the absolute risk of GBS in the period following seasonal and A(H1N1)pdm09 influenza vaccination is about one excess case per 1 million vaccines<sup>(170)(171)</sup>, which is consistent with a 2013 study by Kwong et al<sup>(172)</sup>.

This self-controlled study, which explored the risk of GBS after seasonal influenza vaccination and after influenza health-care encounters (a proxy for influenza illness), found the attributable risks were 1.03 GBS admissions per million vaccinations, compared with 17.2 GBS admissions per million influenza-coded health-care encounters. These observations demonstrate that both influenza vaccines and influenza illness are associated with small attributable risks of GBS, although the risk associated with influenza infection is larger than that associated with vaccination. Kwong 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 remained high for up to four 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<sup>(173)-(177)</sup>.

Refer to Contraindications and Precautions in Section II for additional information.



## LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices (US)
AEFI	Adverse event following immunization
AMMI	Association of Medical Microbiology and Infectious Disease
ATIV	Adjuvanted trivalent inactivated vaccine
BMI	Body mass index
CAEFISS	Canadian Adverse Events Following Immunization Surveillance System
CBER	Centre for Biologics Evaluation Research
CCDR	Canada Communicable Disease Report
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Harmonization of Medicinal Products
CI	Confidence interval
CIHR	Canadian Institutes of Health Research
CIRID	Centre for Immunization and Respiratory Infectious Diseases
FFU	Fluorescent focus units
GBS	Guillain-Barré syndrome
GM	Geometric mean
GMT	Geometric mean titre
HA	Haemagglutinin
HAI	Hemagglutination inhibition assay
HCW	Health care worker
HIV	Human immunodeficiency virus
ICU	Intensive care unit
ID	Intradermal
IgE	Immune globulin E
IgG	immune globulin G
ILI	Influenza-like illness
IM	Intramuscular
IMPACT	Immunization Monitoring Program, ACTive
IWG	Influenza Working Group
LAIV	Live attenuated influenza vaccine
MAARI	Medically attended acute respiratory illness
mL	Millilitre
MN	Microneutralization
NA	Neuraminidase
NACI	National Advisory Committee on Immunization
NML	National Microbiology Laboratory
ORS	Oculo-respiratory syndrome
PCIRN	Public Health Agency of Canada/CIHR Influenza Research Network
pH1N1	Pandemic H1N1 2009
PHAC	Public Health Agency of Canada
QIV	Quadrivalent inactivated influenza vaccine
SRH	Single radial haemolysis
TIV	Trivalent inactivated influenza vaccine
TIV-ID	Trivalent inactivated influenza vaccine administered intradermally
µg	Microgram
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event Reporting System (US)

VE Vaccine efficacy  
WHO World Health Organization

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## APPENDICES

Appendix A: Characteristics of influenza vaccines available for use in Canada, 2015-2016\*

Manufacturer and Product name	BGP Pharma ULC (Abbott)  Influvac®	GSK  Fluviral®	Novartis  Agriflu®	Novartis  Fluad Pediatric™ and Fluad®	Sanofi Pasteur  Vaxigrip®	Sanofi Pasteur  Fluzone®	AstraZeneca  FluMist® Quadrivalent	GSK  Flulaval® Tetra	Sanofi Pasteur  Fluzone® Quadrivalent
Vaccine preparations	TIV	TIV	TIV	TIV	TIV	TIV	LAIV	QIV	QIV
Vaccine type	Inactivated – surface antigen subunit	Inactivated - split virus	Inactivated - subunit	Inactivated - subunit	Inactivated - split virus	Inactivated - split virus	Live attenuated	Inactivated - split virus	Inactivated - split virus
Route of administration	IM	IM	IM	IM	IM	IM	Intranasal spray	IM	IM
Authorized ages for use	≥18 years	≥6 months	≥6 months	Pediatric: 6-23 months  Adult: ≥65 years	≥6 months	≥6 months	2-59 years	≥6 months	≥6 months
Antigen content (each of strains)	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	Pediatric: 7 µg HA /0.25 mL dose  Adult: 15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	10 <sup>6.5-7.5</sup> FFU of live attenuated reassortants /0.2 mL dose given as 0.1 mL in each nostril	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose
Adjuvant	No	No	No	MF59 (oil-in-water emulsion)	No	No	No	No	No
Formats available	Single dose pre-filled syringes with luer tip	5 mL multidose vial	5 mL multi-dose vial, single dose pre-filled syringes without a needle	Single dose pre-filled syringes without a needle	5 mL multi-dose vial, single dose ampoule, single-dose pre-filled syringes	5 mL multi-dose vial, single dose ampoule, single-dose pre-filled syringes	Prefilled single use glass sprayer	5 mL multidose vial	5 mL multi-dose vial, single dose vials, single-dose pre-filled syringes without

Manufacturer and Product name	BGP Pharma ULC (Abbott) Influvac®	GSK Fluviral®	Novartis Agriflu®	Novartis Fluad Pediatric™ and Fluad®	Sanofi Pasteur Vaxigrip®	Sanofi Pasteur Fluzone®	AstraZeneca FluMist® Quadrivalent	GSK Flulaval® Tetra	Sanofi Pasteur Fluzone® Quadrivalent
					with or without a needle	without a needle			attached needle
Post puncture shelf life for multi-dose vials	n/a	28 days	28 days	n/a	7 days	28 days	n/a	28 days	Up to expiry date indicated on vial label
Thimerosal	No	Yes	Yes - multi-dose vials only	No	Yes - multi-dose vials only	Yes - multi-dose vials only	No	Yes	Yes - multi-dose vials only
Antibiotics (traces)	Gentamicin	None	Kanamycin Neomycin	Kanamycin Neomycin	Neomycin	None	Gentamicin	None	None
Other clinically relevant non-medicinal ingredients*	Egg protein Chicken protein Formaldehyde CTAB Polysorbate 80	Egg protein α-tocopheryl hydrogen succinate Polysorbate 80 Formaldehyde Ethanol Sodium deoxycholate Sucrose	Egg protein Formaldehyde Polysorbate 80 CTAB	Egg protein Formaldehyde Polysorbate 80 CTAB	Egg protein Formaldehyde Triton X-100	Egg protein Formaldehyde Triton X-100 Gelatin Sucrose	Egg protein Gelatin hydrolysate Sucrose Arginine Monosodium glutamate	Egg protein α-tocopheryl hydrogen succinate Polysorbate 80 Formaldehyde Ethanol Sodium deoxycholate Sucrose	Egg protein Formaldehyde Triton X-100 Sucrose

\*Full details of the composition of each vaccine authorized for use in Canada and a brief description of its manufacturing process can be found in the product monograph.

## Appendix B: Evidence table for LAIV and children with cystic fibrosis

Study	Vaccine	Study Design	Participants	Summary of Key Findings Using Text or Data	Quality and level of evidence
Boikos C, De Serres G, Lands LC, et al. Safety of live-attenuated influenza vaccination in cystic fibrosis. <i>Pediatrics</i> . (2014) 134(4):e983-e991.	<b>Name:</b> Flumist®  <b>Admin:</b> Intranasal  <b>Season:</b> 2012-13	<p>Prospective cohort, comparing at-risk period (days 0-28) and non-at-risk period (days 29-56); self-controlled</p> <p>Followed up for 56 days after first dose of LAIV</p>	<p><b>Age:</b> 2-18 years of age</p> <p><b>Country:</b> Canada</p> <p><b>Number of participants:</b> 168</p> <p><b>Inclusion Criteria:</b> Children with CF from three participating CF clinics across Quebec</p> <p><b>Exclusion criteria:</b> On systemic corticosteroids; medically attending wheezing episode in 7 days before vaccination; patients &lt;2 years; with nasal polyps or rhinorrhea considered to significant (by vaccinator) to allow LAIV to reach nasal mucosa; considered immunosuppressed</p> <p>Only 2 individuals required and received a 2 dose schedule of LAIV</p>	<p><b>Primary outcome:</b> Respiratory deteriorations resulting in an unscheduled medical visit or hospital admission</p> <p><b>Secondary outcome:</b> Incident oral antibiotic use for respiratory complaints (proxy for respiratory deteriorations), all-cause hospitalizations, occurrence of respiratory and/or systemic adverse events for the 56 days after LAIV administration</p> <p><b>Findings</b></p> <p><u>Primary outcome:</u></p> <ul style="list-style-type: none"> <li>No significant difference in rate of incident respiratory deteriorations or all-cause hospitalizations during at-risk period compared with non-at-risk period</li> <li>7 respiratory deteriorations requiring hospitalization reported (3 during at-risk and 4 during non-at-risk period) ; influenza not detected in any of the events</li> </ul> <p><u>Secondary outcomes:</u></p> <ul style="list-style-type: none"> <li>2 oral antibiotic treatments initiated during at-risk period compared to 6 during non-at-risk period for respiratory complaints</li> <li>11 all-cause hospitalizations reported (6 during at-risk and 5 during non-at-risk period)</li> </ul> <p><u>Reported solicited symptoms during at-risk period</u></p> <ul style="list-style-type: none"> <li>64% of participants experienced at least 1 solicited symptom in the first week following vaccination</li> <li>None of solicited symptoms required hospitalization (except respiratory deteriorations)</li> <li>1 unscheduled medical visit for joint pain that started 8 days post-vaccination</li> <li>Compared to non-at-risk period, largest relative risks seen for: <ul style="list-style-type: none"> <li>Joint pain: 21 cases (13%), RR: 10.50 (95% CI: 2.5, 44.08)</li> <li>Muscle aches: 29 cases (17%), RR: 9.67 (3, 31.12)</li> <li>Vomiting: 23 cases (14%), RR: 7.67 (2.35, 25.05)</li> </ul> </li> </ul>	II-2 Fair

<b>Study</b>	<b>Vaccine</b>	<b>Study Design</b>	<b>Participants</b>	<b>Summary of Key Findings Using Text or Data</b>	<b>Quality and level of evidence</b>
				<ul style="list-style-type: none"> <li>• Most common symptoms included runny nose (44%), nasal congestion (40%), fever (38%), headache (33%), and tiredness (32%) <ul style="list-style-type: none"> <li>○ 42/64 febrile cases occurred on day 4 post vaccination</li> <li>○ Majority of febrile episodes (58/92) lasted only 1 day</li> </ul> </li> <li>• Participants &lt;9 yrs more likely to have runny nose and vomiting than participants ≥9yrs</li> <li>• Wheezing more likely to be reported during at-risk period: 13 cases, RR: 4.33 (1.26, 14.93); greatest incidence during day of vaccination, and no wheezing reported beyond first week</li> <li>• Only redness in both eyes, difficulty breathing, difficulty swallowing, and facial swelling reported during the at-risk period <ul style="list-style-type: none"> <li>○ During the first 3 days post-vaccination 13/15 participants reported redness in both eyes, and 10/10 participants reported facial swelling; most occurred within 24 hours of vaccination and compatible with oculorespiratory syndrome</li> </ul> </li> </ul>	



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