

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

Canadian Immunization Guide Chapter on
Influenza and Statement on Seasonal Influenza
Vaccine for 2016-2017

PROTECTING CANADIANS FROM ILLNESS



Public Health
Agency of Canada

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Canada

PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (PHAC) 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 2016-2017* updates NACI's recommendations regarding the use of seasonal influenza vaccines.

NEW OR UPDATED INFORMATION FOR 2016-2017

Choice of vaccine product for adults ≥65 years of age (see Section V):

Fluzone® High-Dose influenza vaccine has been approved for use in Canada in adults ≥65 years of age. Fluzone® High-Dose is an inactivated trivalent influenza vaccine containing 60 µg of haemagglutinin (HA) per strain (compared to 15 µg HA per strain in a standard dose) administered as a 0.5 mL dose by intramuscular injection (refer to Appendix A for product characteristics). NACI has reviewed the available evidence and concludes that there is evidence that high dose trivalent inactivated influenza vaccine for older adults should provide superior protection compared with the standard dose intramuscular vaccine.

Adults with neurologic or neurodevelopment conditions:

Based on preliminary review of the literature and expert opinion, and consistent with other countries' recommendations, NACI now includes adults with neurologic or neurodevelopment conditions among the groups for whom influenza vaccination is particularly recommended.

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 officials in 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 the National Advisory Committee on Immunization for over 40 years.

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 user will 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

What	<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>
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<p>Who</p>	<p>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 Table 1.</p>
<p>How</p>	<p>Risks and benefits of influenza vaccine should be discussed prior to vaccination, as well as the risks of not being immunized.</p> <p><i>Dose and schedule</i> 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 Table 3). With the exception of adjuvanted trivalent inactivated influenza vaccine (ATIV) 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 <24 months of age, the dose is 0.25 mL.</p> <p><i>Contraindications and Precautions</i> 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 trivalent inactivated influenza vaccine (TIV) and quadrivalent inactivated influenza vaccine (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. Live attenuated influenza vaccine (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><i>Co-administration</i> 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>

Why	<p>Influenza occurs globally with an annual attack rate estimated at 5%–10% in adults and 20%–30% in children⁽¹⁾.</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 specific strains in the vaccine are reviewed each year by WHO and updated as necessary so that there is the greatest probability of matching circulating viruses.</p>
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EPIDEMIOLOGY

Disease Description

Influenza is a respiratory illness caused by the influenza A and B viruses and can cause mild to severe illness. Severe illness can result in hospitalization or death. Certain populations, such as young children and seniors, may be at higher risk for serious influenza complications such as viral pneumonia, secondary bacterial pneumonia and worsening of underlying medical conditions.

Infectious Agent

There are two main types of influenza virus: Types A and B. Influenza A viruses are classified into subtypes based on 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 contained in the influenza vaccine, usually requires seasonal influenza vaccines to be reformulated annually.

Transmission

Influenza is primarily transmitted by droplet 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 under 60 months of age; pregnant women; and Aboriginal Peoples.

Seasonal and Temporal Patterns

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 fall or as late as spring.

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.

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 leading causes of death in Canada⁽²⁾. Current influenza activity information can be found on the [FluWatch website](#). The FluWatch program collects data and information from various sources to provide a national picture of influenza activity. An average of 23,000 laboratory-confirmed cases of influenza is reported to the FluWatch program each year. Although the burden of influenza can vary from year to year, it is estimated that, in a given year, an average of 12,200 hospitalizations related to influenza⁽³⁾ and approximately 3,500 deaths attributable to influenza occur⁽⁴⁾.

It should be noted that the incidence of influenza is often underreported since the illness may be confused with other viral illnesses and many people with influenza-like illness do not seek medical care or have viral diagnostic testing done.

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. Provincial and territorial health authorities then determine which of the available products will be used in the individual jurisdiction's publicly-funded influenza immunization programs.

The antigenic characteristics of circulating influenza virus strains provide the basis for selecting the strains included in each year's vaccine. Vaccine selection generally occurs more than six months prior to the start of the influenza season to allow time for the vaccine manufacturers to produce the required quantity of vaccine. All manufacturers that distribute influenza vaccine products in Canada confirm to Health Canada that the vaccines to be marketed in Canada for the upcoming influenza season contain the WHO-recommended

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

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.

High-dose Inactivated Influenza Vaccine

One of the trivalent products, Fluzone® High-Dose influenza vaccine, which has been approved for use in Canada in adults ≥ 65 years of age, contains 60 μg haemagglutinin (HA) per strain (compared to 15 μg HA per strain in a standard dose) and is administered as a 0.5 mL dose by intramuscular injection.

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 attenuated so that they do not cause influenza and are cold-adapted and temperature sensitive, so that they replicate in the nasal mucosa rather than the lower respiratory tract.

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 trivalent inactivated influenza vaccine (TIV), with less evidence in older children. Based on expert opinion, the comparative efficacy data that 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 quadrivalent LAIV formulation. Comparative vaccine efficacy and effectiveness data of TIV or quadrivalent inactivated influenza vaccine (QIV), and the quadrivalent formulation of LAIV are not available.

Experience with reduced effectiveness of the quadrivalent LAIV in children in 2013-14 in the USA, which the manufacturer determined was attributable to reduced stability in the A/California H1N1 vaccine strain when exposed to temperature fluctuations, emphasizes the need for ongoing monitoring of vaccine effectiveness. In accordance with usual practice, NACI continues to monitor the efficacy, effectiveness and immunogenicity of influenza vaccines and reviews additional information as it becomes available.

In older adults 65 years of age and older, given the burden of influenza A(H3N2) disease and evidence of better efficacy in this population, high dose trivalent inactivated influenza vaccine should provide superior protection compared with the standard dose intramuscular vaccine.

For a summary of efficacy studies refer to Section IV 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 who do not have contraindications to the vaccine. 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

- All pregnant women*.
- Adults 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;
- neurologic or neurodevelopment conditions**;
- morbid obesity (BMI ≥ 40);
- children and adolescents (age 6 months to 18 years) 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 ≥ 65 years of age.
- All children 6 to 59 months of age.
- Aboriginal Peoples.

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

** These include seizure disorders, febrile seizures and isolated developmental delay in children and neuromuscular, neurovascular, neurodegenerative, neurodevelopmental conditions and seizure disorders in adults, but excludes migraines and neuropsychiatric conditions without neurological conditions.

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 ≤ 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"> • TIV • QIV • ATIV 	<p>TIV, QIV and ATIV are authorized for this age group.</p> <p>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"> • TIV • QIV • LAIV 	<p>NACI recommends LAIV use for healthy children and adolescents 2 to 17 years of age who do not have contraindications to this vaccine.</p> <p>There is evidence for the preferential use of LAIV in young children (<6 years of age), with weaker evidence in older children. 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.</p> <p>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.</p> <p>LAIV is not recommended for children with immune</p>

Recipient by age group	Vaccine types available for use	Comments
		<p>compromising conditions.</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> <p>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.</p>
Adults 18-59 years of age	<ul style="list-style-type: none"> • TIV • QIV • LAIV 	<p>TIV and QIV are the recommended products for adults with chronic health conditions.</p> <p>TIV and QIV, instead of LAIV, are recommended for health care workers.</p> <p>LAIV is not recommended for adults with immune compromising conditions.</p>
Adults 60-64 years of age	<ul style="list-style-type: none"> • TIV • QIV 	
Adults 65+ years of age	<ul style="list-style-type: none"> • TIV • QIV • ATIV • High dose TIV 	<p>Given the burden of Influenza A(H3N2) disease and evidence of better efficacy in this age group, it is expected that high dose trivalent inactivated influenza vaccine should provide superior protection compared with the standard dose intramuscular vaccine for older adults.</p>
Pregnant women	<ul style="list-style-type: none"> • TIV • QIV 	<p>LAIV is not recommended because of the theoretical risk to the fetus from administering a live virus vaccine.</p>
<p>TIV: Trivalent inactivated influenza vaccine QIV: Quadrivalent inactivated influenza vaccine LAIV: Live attenuated influenza vaccine ATIV: Adjuvanted trivalent inactivated influenza vaccine</p>		

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

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 2016-2017 season

Age group	TIV without adjuvant or QIV Intramuscular [†]	MF59-adjuvanted TIV (Fluad Pediatric™ or Fluad®) Intramuscular	LAIV (FluMist®) Quadrivalent Intranasal	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 years	0.5 mL	-	0.2 mL (0.1 mL per nostril)	1
60-64 years	0.5 mL	-	-	1
≥65 years	0.5 mL	0.5 mL	-	1

[†]Influvac® ≥18 years, Fluviral® ≥6 months, Agriflu® ≥6 months, Vaxigrip® ≥6 months, Fluzone® ≥6 months, Fluzone® High-Dose ≥65 years, 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⁽⁵⁻⁷⁾. No studies have been done to assess the possibility of interference between LAIV and other live vaccines, or on LAIV given before or after other live vaccines. Additional information regarding co-administration with other vaccines can be found in section IV of this statement. 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^(8, 9). 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⁽¹⁰⁾. 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](#) in 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 high dose vaccine tends to induce higher rates of reaction post-injection compared to standard dose TIV, but these reactions are short-lived. 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 IV 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 vaccinations and that the risk of GBS associated with influenza illness is larger than that associated with influenza vaccination. Additional information regarding GBS is found in Section IV. 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 AEFIs through local public health officials (<http://www.phac-aspc.gc.ca/im/ci-rp-eng.php>) and to check for specific AEFI reporting requirements in their province or territory. In general, any serious or unexpected adverse event felt to be temporally related to vaccination should be reported. An unexpected AEFI is an event that is not listed in available product information but may be due to the immunization, or a change in the frequency of a known AEFI. For influenza vaccines, the following AEFIs are of particular interest:

- ORS
- GBS within 6 weeks following immunization

For additional information about AEFI reporting, please refer to Reporting Adverse Events Following Immunization (AEFI) in Canada (<http://www.phac-aspc.gc.ca/im/ae-fi-essi-form-eng.php>). For general vaccine safety information, refer to Vaccine Safety in Part 2 of the Canadian Immunization Guide.

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 IV – 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 immunization.
- 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.

There have been no reported or documented cases, and no theoretical or scientific basis to suggest transmission would occur between the recipient and the individual administering LAIV.

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 that could indicate a significant allergic reaction (e.g., throat constriction, difficulty swallowing) and 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 extraordinary precautions, but ensuring that the routine measures, drugs and equipment for immunization are in place. For more information regarding vaccination of egg allergic individuals, please see Section IV 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 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.

Based on preliminary review of the literature and expert opinion, and consistent with other countries' recommendations, NACI now includes adults with neurologic or neurodevelopment conditions among the groups for whom influenza vaccination is particularly recommended. This replaces and includes the previous recommendation for people with conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration.

From the preliminary review, it was noted that the odds ratios for influenza complications in patients with neurologic conditions in comparison to those without in the reviewed studies ranged from 1.57 (pneumonia; 95% CI, 1.05 to 2.36) to 19.11 (ICU admission; 95% CI, 3.92 to 93.22) and 22.2 (hospitalization; 95% CI, 2.6 to 186.0)⁽¹¹⁻¹³⁾. The conditions identified as risk factors in the studies reviewed include neuromuscular, neurovascular, neurodegenerative, neurodevelopmental conditions and seizure disorders.

International bodies including the Centers for Disease Control and Prevention (United States)⁽¹⁴⁾, the Joint Committee on Vaccination and Immunisation (United Kingdom)⁽¹⁵⁾ and the Australian Technical Advisory Group on Immunization⁽¹⁶⁾ all have listed both children and adults with neurological conditions as a high risk group for influenza complications.

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 the high risk group for whom influenza vaccine is particularly recommended. Supporting this inclusion is a recent publication by the Canadian Immunization Monitoring Program Active (IMPACT) that 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⁽¹⁷⁾. Over five years (2004-2009) of seasonal influenza surveillance, 1991 children were hospitalized with influenza, 293 of whom had neurologic or neurodevelopment conditions. The pre-existing neurologic and neurodevelopment conditions included isolated seizure disorders including febrile seizures and isolated developmental delay. 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. 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.

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⁽¹⁸⁾, and mortality rates increase with increased age⁽¹⁹⁾.

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⁽²⁰⁻²⁴⁾, evidence of adverse neonatal outcomes associated with maternal respiratory hospitalization or influenza during pregnancy⁽²⁵⁻²⁸⁾, evidence that vaccination of pregnant women protects their newborns from influenza and influenza-related hospitalization⁽²⁹⁻³²⁾ 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⁽³³⁻³⁶⁾.

The safety of inactivated influenza vaccine during pregnancy has been reviewed⁽³⁷⁾. Active studies of influenza vaccination during pregnancy have not shown evidence of harm to the mother or fetus associated with influenza immunization⁽³⁸⁾. 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^(22, 23, 37, 39). 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^(40, 41).

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)⁽⁴²⁾, obesity, delayed access to health care and increased susceptibility to disease because of poor housing and overcrowding⁽⁴³⁻⁴⁵⁾. 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⁽⁴⁶⁻⁵²⁾. Immunization of care providers and residents is associated with decreased risk of ILI outbreaks⁽⁵³⁾. 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.

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^(48, 51, 54) and all-cause mortality^(47, 48, 50, 51, 54) in the residents. Therefore, HCWs should consider annual influenza vaccination included in their responsibility to provide the highest standard of care. In the absence of contraindications, refusal of HCWs to be 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 for two reasons. Firstly and most importantly, most comparative studies in persons 18 to 59 years of age have found that TIV was more efficacious⁽⁵⁵⁾. Secondly, as noted in section II, 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.

As noted in the PHAC *Guidance: Infection Prevention and Control Measures for Healthcare Workers in Acute Care and Long-term Care Settings: Seasonal Influenza*, all healthcare organizations should have a written plan for managing an influenza outbreak in their facilities⁽⁵⁶⁾. Inherent in such plans should be policies and programs to optimize staff influenza immunization⁽⁵⁷⁾. As part of outbreak management, the above mentioned PHAC guidance suggests consideration of chemoprophylaxis for all unvaccinated HCWs, unless contraindications exist. Guidelines regarding the use of antiviral medications for prophylaxis can be found in the Association of Medical Microbiology and Infectious Disease Canada (AMMI Canada) guideline, *The use of antiviral drugs for influenza: A foundation document for practitioners*⁽⁵⁸⁾.

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. Household contacts of infants <6 months of age (who are also 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 would also be included in this group.

They also include those who provide 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. Those who provide essential community services, 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^(51, 59-61).

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

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)⁽⁶²⁻⁶⁵⁾. 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*, and *Appendix 1: Evidence Review on Occupational Exposure of Swine and Poultry Workers*.

Although seasonal influenza immunization will not prevent avian influenza infection, some countries⁽⁶⁶⁾ and provinces, have recommended influenza immunization on a yearly basis for poultry workers based on the rationale that preventing infection with human influenza strains may reduce the theoretical potential for human-avian re-assortment of genes should such workers become co-infected with human and avian influenza viruses⁽⁶⁷⁾.

Direct contact may be defined as sufficient contact with infected poultry to allow transmission of an avian virus to the exposed person. The relevant individuals include those performing the cull, as well as others who may be directly exposed to the avian virus, such as supervising veterinarians and inspectors. It is 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 [Human Health Issues related to Avian Influenza in Canada](#).

IV. 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

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⁽⁶⁸⁻⁷³⁾.

Trivalent Inactivated Influenza Vaccines: Unadjuvanted: IM administered (TIV), standard dose

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⁽⁷⁴⁾. 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%⁽⁷⁵⁻⁹³⁾. Efficacy against serologically-confirmed influenza (rise in antibody titres from post-vaccine levels) ranged from 54% to 63% and efficacy against clinical illness ranged between 33% and 36%⁽⁹⁴⁻⁹⁶⁾. Vaccine efficacy against clinical 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^(75, 77, 79, 83, 87, 97).

In a systematic review of healthy adults, inactivated influenza vaccine efficacy against laboratory-confirmed influenza was estimated to be 62% (95% CI [52%,69%]) and vaccine effectiveness against influenza-like illness was estimated at 16% (95% CI [9%, 23%]) when the vaccine strain matched the circulating strains⁽⁹⁸⁾. Two other studies found somewhat lower vaccine efficacy at 55% (95% CI [41%, 65%]) in the 2006-07 season⁽⁹⁹⁾ and 68% (95% CI [46%, 81%]) in the 2007-08 season⁽¹⁰⁰⁾. 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^(98, 101, 102).

In the elderly, vaccine effectiveness is about half of that in healthy adults and varies depending on the outcome measures and the study population^(94, 103). Systematic reviews have demonstrated that the influenza vaccine decreases the incidence of pneumonia, hospital admissions and deaths in the elderly⁽⁹⁴⁾ and reduces exacerbations in persons with chronic obstructive pulmonary disease⁽¹⁰⁴⁾.

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⁽¹⁰⁵⁾, hospitalizations for cardiac disease and stroke in the elderly⁽¹⁰⁶⁾, and hospitalization and deaths in persons with diabetes mellitus 18 years of age and older⁽¹⁰⁷⁾ during influenza epidemics. 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⁽¹⁰⁸⁻¹¹²⁾.

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⁽¹¹³⁾. 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 (lower 95% CI >0%) against

medically attended laboratory-confirmed 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.

Because of changes in the circulating influenza virus from year to year and waning immunity in vaccine recipients, annual influenza vaccination is recommended. Although NACI is aware of some recent studies that suggest that vaccine induced protection may be greater in individuals who have no recent vaccine history, optimal protection against influenza season after season is best achieved through annual influenza immunization^(114, 115). NACI will continue to monitor this issue.

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

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)⁽¹¹⁶⁾. 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.

Considerations related to immunogenicity studies in the pediatric population

Some studies have shown there may be immunogenicity differences between influenza vaccine products in young children⁽¹¹⁷⁻¹²⁰⁾. However, the use of a 0.5 mL vaccine dose of unadjuvanted TIV 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. No correlate has ever been identified or clinically validated in the pediatric population, and there remains a need to better define immunological correlates of protection.

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 pediatric population can be used for influenza immunization of children, noting the preferential recommendations outlined in Table 2.

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⁽¹²¹⁾.

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⁽¹²²⁻¹²⁵⁾.

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⁽¹²⁶⁻¹²⁹⁾.

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⁽¹³⁰⁻¹³²⁾. Post-vaccination fever may be observed in 12% or less of immunized children 1 to 5 years of age^(85, 132).

In adults 60 years and older, common local reactions to influenza vaccines without adjuvant that are injected intramuscularly include redness, swelling, pain, and induration. These reactions last 2-3 days and rarely interfere with normal activities. Systemic reactions common to adults 60 years and older who receive influenza vaccines include headache, malaise, myalgia, fatigue, arthralgia, and fever.

Trivalent Inactivated Influenza Vaccines: Unadjuvanted: IM administered (TIV), high dose

Vaccines currently available for use

- Fluzone® High-Dose (Sanofi Pasteur)

Efficacy and Effectiveness

Two randomized controlled trials and one retrospective cohort study have measured the relative efficacy of Fluzone® High-Dose compared to a standard dose TIV in adults 65 years and older. Relative efficacy of high dose versus standard dose vaccine against laboratory confirmed symptomatic influenza was 12.5% (95% CI: -141, 66) in one randomized controlled trial during a predominantly A(H1N1) season with vaccine strain mismatch⁽¹³³⁾, and 24% (95% CI: 10, 36) in a second larger trial conducted over 2 seasons⁽¹³⁴⁻¹³⁶⁾. In a retrospective cohort study of medicare beneficiaries in the United States, conducted using administrative data, Fluzone® High-Dose was estimated to be 22% (95% CI: 15, 29) more effective than standard dose vaccine in preventing symptomatic influenza, and 22% (95% CI: 16, 27) more effective than standard dose vaccine in preventing hospital admission due to influenza⁽¹³⁷⁾.

There are preliminary indications that there may be an age effect in those ≥65 years of age, where individuals who are older or more susceptible to influenza infection may be better protected by the high dose vaccine. In a supplementary analysis conducted using data from the large efficacy trial mentioned above⁽¹³⁴⁾, vaccine effectiveness estimates were higher in

individuals 75 years and older, and in those with two or more high-risk comorbidities⁽¹³⁶⁾. Although the difference in estimates was not statistically significant, this trial was also not powered to adequately address the supplementary analysis. In the study by Izurieta et al., the relative vaccine effectiveness of high dose vaccine compared to standard dose TIV was 36% (95%CI: 13, 54) in adults 85 years and older, although the difference between overall estimate and the age-stratified estimate was not statistically significant. Additional studies are needed to explore this further.

Immunogenicity

Five studies compared the rates of seroconversion for study participants receiving high dose and standard dose TIV among those 65 years of age and older⁽¹³⁸⁻¹⁴³⁾. Rates of seroconversion were about 19% higher (ranging from 8-39% higher) for those receiving the higher dose vaccine - across all three strains in the vaccines and in the studies. Similarly, rates of seroconversion were higher for those receiving the high compared to standard dose vaccines for participants 75 years and older and for a cohort of participants with underlying cardiopulmonary disease.

Six studies reported higher rates of seroprotection for older adults receiving high dose TIV compared to those vaccinated with standard dose TIV^(133, 135, 138-143). Seroprotection was significantly higher for all three strains in the vaccine in three of five studies assessing significance. There were different results in the remaining studies. In the study by Couch et al. (2007), seroprotection was higher only against A(H1N1), possibly attributed to the fact that 78% of participants were vaccinated against the same influenza strains within 6 months prior to the study⁽¹³⁹⁾. In Nace et al. (2015), seroprotection was higher against A(H3N2) and B but not A(H1N1); this finding may be attributed to strain circulation during the study that made it difficult to assess seroprotection against this subtype⁽¹⁴³⁾.

Geometric mean titre ratios (GMTR) of participants' responses to the high versus the standard dose influenza vaccines were reported in several studies and were calculated for those that provided group-specific post-vaccination titres for each of the vaccines^(133, 135, 138-142). Seroresponse to the B strains in the vaccines was about 1.5 times greater (1.3-1.7) in the high dose TIV recipients than the standard dose TIV recipients. The GMTR of the A strains was about 1.8 times higher for those receiving high dose TIV compared to the standard dose TIV; ranging from 1.6-2.3.

Safety

High dose TIV has been observed to produce a higher rate of some systemic reactions than the comparator standard dose TIV. Studies have reported higher rates of malaise⁽¹³⁸⁾, myalgia^(138, 141), and moderate to severe fever⁽¹³⁸⁾. Most systemic reactions were mild and resolved within three days⁽¹³⁸⁾. Serious adverse events were similar in frequency between the standard dose and high dose vaccine^(133, 135, 138, 139).

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 3-8 years of age, in comparison to children who received hepatitis A vaccine⁽¹⁴⁴⁾. 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 also 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 Committee for Medicinal Products for Human Use (CHMP) and Centre for Biologics Evaluation Research (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⁽¹⁴⁵⁾.

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

- Fludac® (Novartis)
- Fludac Pediatric™ (Novartis)

1. Fludac® (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⁽¹⁴⁶⁾. However, this study was not designed to estimate vaccine effectiveness against laboratory-confirmed outcomes.

A few observational studies suggest that Fludac® may be effective at reducing the risk of hospitalization for influenza and influenza 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⁽¹⁴⁷⁻¹⁵²⁾.

A Canadian observational study performed in British Columbia by Van Buynder et al. evaluated the comparative effectiveness of Fludac® to TIV in reducing laboratory confirmed influenza in the elderly⁽¹⁵³⁾. During the 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, Fludac® effectiveness was 58% (95% CI: 5-82), with a relative effectiveness of 63% (95% CI: 4-86) when compared to TIV. The study did not evaluate protection against hospitalization. The authors identify a number of limitations to this study, including the small sample size and low influenza activity in the community that year and note that repeated studies in subsequent years are necessary to confirm findings and look for potential strain variation not assessable due to a relatively homogenous strain year.

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⁽¹⁵⁴⁾. 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^(155, 156). MF59 further facilitates the internalization of antigen by these dendritic cells^(155, 157). 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⁽¹⁵⁵⁾.

There is evidence from randomized controlled trials that Fludac® 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⁽¹⁴⁶⁾. 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 Fludac® to split-virus vaccine generally compared it to a vaccine called Mutagrip®, which is not available in Canada. The one study that compared Fludac® to Vaxigrip® found similar seroprotection and seroconversion rates for H3N2 and a higher immune response for H1N1 and B for Fludac® recipients <75 years of age⁽¹⁵⁸⁾. For those 75 years of age and older, higher seroprotection and seroconversion rates were noted for all three strains in those receiving Fludac®. In a randomized clinical trial comparing Intanza® (an intradermal TIV product) to Fludac® 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, but not the A/H3N2 strain, with the haemagglutination inhibition assay (HAI) method and for all three strains with the single radial haemolysis (SRH) method⁽¹⁵⁹⁾.

A Canadian study conducted by the Public Health Agency of Canada/CIHR Influenza Research Network (PCIRN) looked at the immunogenicity of Fludac® (Adjuvanted Trivalent Inactivated Vaccine: ATIV), Intanza 15® (TIV-ID) and Agriflu® (sub-unit TIV) in ambulatory seniors (≥65 years) living in the community⁽¹⁵⁶⁾. 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 compared to 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⁽¹⁶⁰⁾. However, there were several considerations regarding the applicability of this trial in the Canadian context. Firstly, the European Medicines Agency (EMA) 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, which could impact the estimate of ATIV vaccine efficacy⁽¹⁶¹⁾. The original study authors conducted a reanalysis of vaccine efficacy excluding data from one of the audited trial sites, and reported no notable change from the original findings⁽¹⁶²⁾. However, the auditors were of the opinion that the deficiencies identified in the audited site were of a nature that they could have occurred in other study sites not subject to audit. As a result, despite the company's reanalysis of the data, there remained concerns with the conduct of the study which could have impacted upon the accuracy of the estimate of vaccine efficacy.

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^(119, 163). 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.

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 both influenza A and B^(160, 164-168). In particular, a single dose of ATIV is more immunogenic than a single dose of unadjuvanted TIV, and has been shown in one study to produce greater geometric mean titres than two doses of unadjuvanted TIV against influenza A⁽¹⁶⁸⁾. However, similar to unadjuvanted TIV, ATIV generally induced a weaker hemagglutination inhibition response against B strains compared to A strains and therefore 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 Flud® 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 both seasonal TIV and QIV administered to children 6-36 months old⁽¹⁶⁶⁾. 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 inactivated influenza vaccine 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 pediatric trials, ATIV was more reactogenic than unadjuvanted TIV, with recipients experiencing 10-15% more solicited local and systemic reactions⁽¹⁶⁹⁾. 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 vaccine that has been associated with an increased risk of narcolepsy. A study published in December 2014 comparing two AS03 adjuvanted H1N1 vaccine products (Pandemrix and Arepanrix) has suggested that the underlying immune mediated mechanism may not be initiated by the adjuvant, but by another component of the vaccine, specifically the H1N1 viral antigen⁽¹⁷⁰⁾. 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⁽¹⁶⁶⁾. 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 15 µg formulations were slightly higher for both adjuvanted and unadjuvanted vaccines compared to the 7.5 µg formulations.

LIVE ATTENUATED INFLUENZA VACCINE (LAIV)

LAIV contains standardized quantities of fluorescent focus units (FFU) of live attenuated influenza virus reassortants. The virus strains in LAIV are cold-adapted and temperature sensitive, so they replicate in the nasal mucosa rather than the lower respiratory tract, and they are attenuated so they do not produce classic influenza-like illness

Vaccines currently available for use

- Flumist® Quadrivalent (AstraZeneca) live attenuated vaccine

Note: Although 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 quadrivalent LAIV formulation. Comparative vaccine efficacy and effectiveness data of the quadrivalent formulation of LAIV and TIV or QIV, 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 compared the efficacy of LAIV to TIV in asthmatic children 6 to 17 years of age⁽¹⁷¹⁻¹⁷³⁾. 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⁽¹⁷⁴⁾. Further details regarding the recommendation rationale for LAIV are found in section V.

The USA experienced reduced effectiveness of LAIV (quadrivalent formulation) in children during the 2013-14 influenza season which the manufacturer determined was attributable to reduced stability in the A/California H1N1 vaccine strain when exposed to temperature fluctuations and has subsequently modified its formulation to correct this issue. This reduced effectiveness was not observed in Canada. This observation emphasizes the need for ongoing monitoring of vaccine effectiveness. In accordance with usual practice, NACI continues to monitor the efficacy, effectiveness and immunogenicity of influenza vaccines and reviews additional information as it becomes available.

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⁽¹⁷⁴⁾. 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 regarding immunogenicity of LAIV, consult the [NACI supplemental statement for FluMist®](#).

The quadrivalent formulation of LAIV has shown non-inferiority based on immunogenicity 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⁽¹⁷⁵⁻¹⁷⁷⁾.

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⁽¹⁷⁴⁾. 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 immunization (i.e., “shedding”). The frequency of shedding decreases with increasing age and time since vaccination. Shedding is generally below the levels needed to transmit infection, although in rare instances, shed vaccine viruses can be transmitted from vaccine recipients to unvaccinated 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⁽¹⁷⁸⁾. 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⁽¹⁷⁹⁻¹⁸²⁾.

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⁽⁵⁻⁷⁾. 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 T-cell response and viral replication (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)⁽¹⁸³⁾ and Greenhawt et al. (2012)⁽¹⁸⁴⁾. 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 egg allergic 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%⁽¹⁸³⁾. 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 giving 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⁽¹⁸⁴⁾.

Data are not currently available to support the safe administration of LAIV to egg allergic individuals, therefore this practice is not currently recommended.

Guillain-Barré syndrome (GBS)

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⁽¹⁸⁵⁾.

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 vaccinations^(186, 187), which is consistent with a 2013 study by Kwong et al⁽¹⁸⁸⁾. 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 decreased thereafter, but remained significantly elevated 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⁽¹⁸⁹⁻¹⁹²⁾.

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

V. 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 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 Fluvad® can be found in supplementary NACI statements for each product^(147, 174). 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](#).

PEDIATRIC CONSIDERATIONS

The first time that children <9 years of age receive seasonal influenza immunization, a two-dose schedule is required to achieve protection⁽¹⁹³⁻¹⁹⁵⁾. Several studies have looked at whether these two initial doses need to be given in the same season^(70, 71, 196). 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^(70, 71). 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^(69, 71). Issues related to effective prime-boost when there is a major change in influenza B lineage across sequential seasons requires further evaluation⁽¹⁹⁷⁾. Because children 6-23 months of age are less likely to have had prior priming exposure to an influenza virus, special effort is warranted to ensure that a two-dose schedule is followed for previously unvaccinated children in this age group.

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^(117, 198). 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 pediatric age group, it is important to consider the following:

- the burden of influenza B disease in the pediatric 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 2001-2002 to 2012-2013 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⁽¹⁹⁹⁾. 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 pediatric influenza-associated hospitalizations (children ≤16 years of age) reported by IMPACT between 2004-2005 and 2012-2013 (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 relative to all influenza infections in the general population during the same time period. Additional information can be found in the [Statement on Seasonal Influenza Vaccine for 2014-2015](#).

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

seasons ($\geq 70\%$ 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

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. It is important to note that QIV provides protection against two, rather than only one, of the strains of influenza B that may circulate. Either unadjuvanted or adjuvanted TIV also may be used, but provide protection against only one strain of influenza B.

NACI has reviewed the available evidence on Flud Pediatric™ and has concluded that Flud Pediatric™ may be used in children 6 to 23 months of age (NACI Recommendation Grade B). There is currently insufficient efficacy data on ATIV compared to unadjuvanted TIV or QIV to determine the relative clinical benefit of ATIV.

See Section IV. Vaccine preparations available for use in Canada for more information on ATIV.

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).

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. It is important to note that QIV provides protection against two, rather than only one, of the strains of influenza B that may circulate. 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. 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.

Additional detail regarding these recommendations can be found in Appendix B of this statement and in [Recommendations on the use of live, attenuated influenza vaccine \(FluMist®\): Supplementation Statement on Seasonal Influenza Vaccine for 2011-2012.](#)

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 on LAIV in adults 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

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

Choice of vaccine product for adults ≥65 years of age

In choosing a vaccine product, it is important to consider the relative burden of influenza disease caused by the various influenza subtypes (i.e., influenza A(H1N1), influenza A(H3N2) and influenza B) in this age group, as well as the efficacy, immunogenicity and safety profile of the available vaccines.

A study focusing on estimates of deaths associated with influenza in the USA has established that the average annual rate of influenza-associated deaths for adults aged ≥65 years was 17.0 deaths per 100,000 (range: 2.4–36.7)⁽²⁰⁰⁾. The study also states that deaths among persons aged ≥65 years accounted for 87.9% of the overall estimated average annual influenza-associated deaths with underlying pneumonia and influenza causes. When influenza-related deaths were estimated using underlying respiratory and circulatory causes, these estimates increased to 66.1 deaths per 100,000 (range: 8.0–121.1) and 89.4%, respectively. This study described a wide variation in the estimated number of deaths from season to season, which was closely related to the particular influenza virus types and subtypes in circulation. Estimates presented in the study of yearly influenza-associated deaths with underlying pneumonia and influenza causes (1976 to 2007) reveal a large difference between influenza type A and B with a calculated median of >6,000 deaths associated with

influenza type A and half that for influenza type B ($\approx 3,360$) for persons aged ≥ 65 years. During the 22 seasons in which influenza A(H3N2) was the prominent strain, the average mortality rates were 2.7 times higher than for the nine seasons that it was not (all age groups combined) and on average, there were about 37% more annual influenza-associated deaths, regardless of the underlying medical cause. A higher risk was also reported by Cromer et al (2014) in their assessment of the burden of influenza in England by age and clinical risk group⁽²⁰¹⁾.

Canadian surveillance data shows that hospitalization rates among individuals ≥ 65 years of age were higher during the 2014-15 season, a season in which H3N2 circulation predominated and there was a vaccine mismatch with the circulating H3N2 strain, compared to the previous five influenza seasons and also compared to the 2012-13 season when H3N2 also predominated. Similar to the hospitalization rates, death rates among seniors were highest in the 2014-15 season compared to the previous five seasons and compared to the previous H3N2 season in 2012-13. Deaths rates among other age groups were similar to or lower than the previous five influenza seasons. Laboratory detections over this same time period showed that influenza seasons predominated by Influenza subtype A(H3N2) disproportionately affected adults ≥ 65 years of age while seasons with greater A(H1N1) detections resulted in a higher prevalence of positive cases in younger age groups.

Vaccine efficacy, immunogenicity and safety are discussed in section IV.

Based on the available evidence, NACI concludes that there is evidence that high dose TIV should provide superior protection compared with standard dose TIV for adults ≥ 65 years of age. This superior relative protection compared to standard dose TIV appears to increase with increasing age over 65 years. A similar conclusion has not been reached for adjuvanted TIV. Although a few observational studies suggest that Fludax[®] may be effective at reducing the risk of hospitalization for influenza and influenza complications in the elderly, compared to unvaccinated individuals and those who received unadjuvanted trivalent inactivated subunit vaccine, these studies have significant methodological limitations that make their interpretation difficult⁽¹⁴⁷⁻¹⁵²⁾. As noted in Section IV (immunogenicity of Fludax[®]), adjuvanted TIV has been shown in clinical trials to induce higher immunogenicity and broader cross-reactivity compared to unadjuvanted, standard dose TIV. However, it is not yet known how immunogenicity and vaccine effectiveness compare between adjuvanted TIV and high dose TIV. There are currently no data on the comparative efficacy or effectiveness of QIV and high dose TIV.

Considering the burden of disease associated with influenza A(H3N2) and the evidence of superior efficacy of high dose TIV compared to standard dose TIV, it appears that high dose TIV would provide the greatest benefit to the ≥ 65 years age group.

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.

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 influenza vaccine
BMI	Body mass index
CAEFISS	Canadian Adverse Events Following Immunization Surveillance System
CBER	Centre for Biologics Evaluation and Research
CCDR	Canada Communicable Disease Report
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
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

USA	United States of America
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, 2016-2017*

Manufacturer and Product name	BGP Pharma ULC (Abbott) Influvac®	GSK Fluviral®	Novartis Agriflu®	Novartis Fluad Pediatric™ and Fluad®	Sanofi Pasteur Vaxigrip®	Sanofi Pasteur Fluzone®	Sanofi Pasteur Fluzone® High-Dose	AstraZeneca FluMist® Quadrivalent	GSK Flulaval® Tetra	Sanofi Pasteur Fluzone® Quadrivalent
Vaccine preparations	TIV	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	Inactivated - split virus	Live attenuated	Inactivated - split virus	Inactivated - split virus
Route of administration	IM**	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	≥65 years	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	60 µg HA /0.5 mL dose	10 ^{6.5-7.5} 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	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	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

| I STATEMENT ON SEASONAL INFLUENZA VACCINE FOR 2016-2017

Manufacturer and Product name	BGP Pharma ULC (Abbott) Influvac®	GSK Fluviral®	Novartis Agriflu®	Novartis Fluad Pediatric™ and Fluad®	Sanofi Pasteur Vaxigrip®	Sanofi Pasteur Fluzone®	Sanofi Pasteur Fluzone® High-Dose	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	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	No	Yes	Yes - multi-dose vials only
Antibiotics (traces)	Gentamicin	None	Kanamycin Neomycin	Kanamycin Neomycin	Neomycin	None	No	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	Formaldehyde Egg protein Triton X-100	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.

**Refer to product monograph for alternate route(s) of administration

Appendix B: Additional information on the use of LAIV

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.

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. It is important to note that QIV provides protection against two, rather than only one, of the strains of influenza B that may circulate.

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⁽¹⁷¹⁻¹⁷³⁾. 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⁽¹⁷¹⁾. 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. It is important to note that QIV provides protection against two, rather than only one, of the strains of influenza B that may circulate.

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⁽²⁰²⁾. 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⁽¹⁷¹⁾. 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 or current wheezing. In such situations, given the burden of influenza B disease in children, QIV should be used. If QIV is not available, TIV should be used. It is important to note that QIV provides protection against two, rather than only one, of the strains of influenza B that may circulate.

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. It is important to note that QIV provides protection against two, rather than only one, of the strains of influenza B that may circulate.

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⁽²⁰³⁾. 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 a 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.

REFERENCES

1. World Health Organization. Influenza (Seasonal) Fact sheet No211. 2014.
2. Statistics Canada. The 10 leading causes of death, 2011 Ottawa, Canada2014 [Accessed 2015 July]. Available from: <http://www.statcan.gc.ca/pub/82-625-x/2014001/article/11896-eng.htm>.
3. Schanzer DL, McGeer A and Morris K. Statistical estimates of respiratory admissions attributable to seasonal and pandemic influenza for Canada. *Influenza Other Respir Viruses*. 2013;7(5):799-808.
4. Schanzer DL, Sevenhuysen C, Winchester B and Mersereau T. Estimating influenza deaths in Canada, 1992-2009. *PLoS One*. 2013;8(11).
5. Breiman RF, Brooks WA, Goswami D, Lagos R, Borja-Tabora C, Lanata CF, et al. A multinational, randomized, placebo-controlled trial to assess the immunogenicity, safety, and tolerability of live attenuated influenza vaccine coadministered with oral poliovirus vaccine in healthy young children. *Vaccine*. 2009;27(40):5472-79.
6. Lum LC, Borja-Tabora CF, Breiman RF, Vesikari T, Sablan BP, Chay OM, et al. Influenza vaccine concurrently administered with a combination measles, mumps, and rubella vaccine to young children. *Vaccine*. 2010;28(6):1566-74.
7. Nolan T, Bernstein DI, Block SL, Hilty M, Keyserling HL, Marchant C, et al. Safety and immunogenicity of concurrent administration of live attenuated influenza vaccine with measles-mumps-rubella and varicella vaccines to infants 12 to 15 months of age. *Pediatrics*. 2008;121(3):508-16.
8. National Advisory Committee on Immunization. Statement on thimerosal. *CCDR*. 2003;29(ACS-1):1-12.
9. National Advisory Committee on Immunization. Thimerosal: updated statement. An Advisory Committee Statement (ACS). *CCDR*. 2007;33(ACS-6):1-13.
10. Gerber JS and Offit PA. Vaccines and autism: a tale of shifting hypotheses. *Clin Infect Dis*. 2009;48(4):456-61.
11. Gilca R, De Serres G, Boulianne N, Ouhoumane N, Papenburg J, Douville-Fradet M, et al. Risk factors for hospitalization and severe outcomes of 2009 pandemic H1N1 influenza in Quebec, Canada. *Influenza Other Respir Viruses*. 2011;5(4):247-55.
12. Mertz D, Kim TH, Johnstone J, Lam PP, Science M, Kuster SP, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. *BMJ (Clinical research ed)*. 2013;347:f5061.
13. Poepl W, Hell M, Herkner H, Stoiser B, Fritsche G, Schurz-Bamieh N, et al. Clinical aspects of 2009 pandemic influenza A (H1N1) virus infection in Austria. *Infection*. 2011;39(4):341-52.

14. Centers for Disease Control and Prevention. People at high risk of development flu-related complications 2015 [Accessed 2015 March 1]. Available from: http://www.cdc.gov/flu/about/disease/high_risk.htm.
15. Public Health England. Green Book Chapter 19: Influenza 2014 [Accessed 2015 March 1]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/456568/2904394_Green_Book_Chapter_19_v10_0.pdf.
16. NHMRC Australian Technical Advisory Group on Immunisation. Part 4: Vaccine-preventable diseases - 4.7 Influenza. The Australian Immunisation Handbook 10th ed. 2015. Canberra: Australian Government Department of Health; 2015.
17. Burton C, Vaudry W, Moore D, Bettinger JA, Tran D, Halperin SA, et al. Burden of seasonal influenza in children with neurodevelopmental conditions. *Ped Infect Dis J*. 2014;33(7):710-14.
18. Simonsen L, Fukuda K, Schonberger LB and Cox NJ. The Impact of Influenza Epidemics on Hospitalizations. *J Infect Dis*. 2000;181(3):831-37.
19. Schanzer DL, Tam TW, Langley JM and Winchester BT. Influenza-attributable deaths, Canada 1990-1999. *Epidemiol Infect*. 2007;135(7):1109-16.
20. Louie JK, Acosta M, Jamieson DJ, Honein MA and California P. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N Engl J Med*. 2010;362(1):27-35.
21. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA*. 2010;303(15):1517-25.
22. Mak TK, Mangtani P, Leese J, Watson JM and Pfeifer D. Influenza vaccination in pregnancy: current evidence and selected national policies. *Lancet Infect Dis*. 2008;8(1):44-52.
23. McNeil S, Halperin B and MacDonald N. Influenza in pregnancy: the case for prevention. *Adv Exp Med Biol*. 2009;634:161-83.
24. Rasmussen SA, Jamieson DJ and Bresee JS. Pandemic influenza and pregnant women. *Emerg Infect Dis*. 2008;14(1):95-100.
25. Centers for Disease Control and Prevention. Maternal and infant outcomes among severely ill pregnant and postpartum women with 2009 pandemic influenza A (H1N1)--United States, April 2009-August 2010. *MMWR Morb Mortal Wkly Rep*. 2011;60(35):1193-96.
26. Pierce M, Kurinczuk J, Spark P, Brocklehurst P and Knight M. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. *BMJ*. 2011;342:d3214-d14.
27. Goldenberg R, Culhane J, Iams J and Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606):75-84.

28. McNeil SA, Dodds LA, Fell DB, Allen VM, Halperin BA, Steinhoff MC, et al. Effect of respiratory hospitalization during pregnancy on infant outcomes. *Am J Obstet Gynecol*. 2011;204(6 Suppl 1):S54-S57.
29. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med*. 2008;359(15):1555-64.
30. Poehling K, Szilagyi P, Staat M, Snively B, Payne D, Bridges C, et al. Impact of maternal immunization on influenza hospitalizations in infants. *Am J Obstet Gynecol*. 2011;204(6 Suppl 1):S141-S48.
31. Eick AA, Uyeki TM, Klimov A, Hall H, Reid R, Santosham M, et al. Maternal influenza vaccination and effect on influenza virus infection in young infants. *Arch Pediatr Adolesc Med*. 2011;165(2):104-11.
32. France EK, McClure D, Hambidge S, Xu S, Yamasaki K, Shay D, et al. Impact of maternal influenza vaccination during pregnancy on the incidence of acute respiratory illness visits among infants. *Arch Pediatr Adolesc Med*. 2006;160(12):1277-83.
33. Steinhoff M, Omer S, Roy E, El Arifeen S, Raqib R, Dodd C, et al. Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial. *CMAJ*. 2012;184(6):645-53.
34. Fell DB, Sprague AE, Liu N, Yasseen AS, III, Wen SW, Smith G, et al. H1N1 influenza vaccination during pregnancy and fetal and neonatal outcomes. *Am J Public Health*. 2012;102(6):e33-e40.
35. Omer S, Goodman D, Steinhoff M, Rochat R, Klugman K, Stoll B, et al. Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study. *PLoS Med*. 2011;8(5):e1000441-e41.
36. Dodds L, MacDonald N, Scott J, Spencer A, Allen VM and McNeil SA. The association between influenza vaccine in pregnancy and adverse neonatal outcomes. *J Obstet Gynecol Can*. 2012;34(8):714-20.
37. Tamma PD, Ault KA, del Rio C, Steinhoff MC, Halsey N and Omer S. Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol*. 2009;201(6):547-52.
38. MacDonald NE, Riley LE and Steinhoff MC. Influenza immunization in pregnancy. *Obstet Gynecol*. 2009;114(2 Pt 1):365-68.
39. Moro PL, Broder K, Zheteyeva Y, Walton K, Rohan P, Sutherland A, et al. Adverse events in pregnant women following administration of trivalent inactivated influenza vaccine and live attenuated influenza vaccine in the Vaccine Adverse Event Reporting System, 1990-2009. *Am J Obstet Gynecol*. 2011;204(2):146e1-46e7.
40. Public Health Agency of Canada. Vaccine surveillance report: adverse events following immunization 2015 [Accessed 2015 December 15]. Available from: <http://www.phac-aspc.gc.ca/im/vs-sv/index-eng.php>.

41. European Medicines Agency. Fifteenth Pandemic Pharmacovigilance update. 8 April 2010. Immunization 2010 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/04/WC500089253.pdf].
42. Centers for Disease Control and Prevention. Deaths related to 2009 pandemic influenza A (H1N1) among American Indian/Alaska Natives - 12 states, 2009. MMWR Morb Mortal Wkly Rep. 2009;58(48):1341-44.
43. National Center for Education Statistics. Individuals, families and children in poverty. In: Status and trends in the education of American Indians and Alaska Natives 2008 [Available from: http://nces.ed.gov/pubs2008/nativetrends/ind_1_6.asp].
44. Indigenous and Northern Affairs Canada. Royal Commission on Aboriginal peoples: People to people, nation to nation. Highlights from the report of the Royal Commission on Aboriginal peoples 1996 [Web Page]. Available from: <http://www.aadnc-aandc.gc.ca/eng/1100100014597/1100100014637>.
45. Clark M, Riben P and Nowgesic E. The association of housing density, isolation and tuberculosis in Canadian First Nations communities. Int J Epidemiol. 2002;31(5):940-45.
46. Carman WF, Elder AG, Wallace LA, McAulay K, Walker A, Murray GD, et al. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. Lancet. 2000;355(9198):93-97.
47. Hayward AC, Harling R, Wetten S, Johnson AM, Munro S, Smedley J, et al. Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. BMJ. 2006;333(7581):1241.
48. Pearson ML, Bridges CB and Harper SA. Healthcare Infection Control Practices Advisory Committee (HICPAC). Advisory Committee on Immunization Practices (ACIP). Influenza vaccination of health-care personnel: recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55(RR-2):1-16.
49. Potter J, Stott DJ, Roberts MA, Elder AG, O'Donnell B, Knight PV, et al. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. J Infect Dis. 1997;175(1):1-6.
50. Lemaitre M, Meret T, Rothan-Tondeur M, Belmin J, Lejonc JL, Luquel L, et al. Effect of influenza vaccination of nursing home staff on mortality of residents: a cluster-randomized trial. J Am Geriatr Soc. 2009;57(9):1580-86.
51. Saxen H and Virtanen M. Randomized, placebo-controlled double blind study on the efficacy of influenza immunization on absenteeism of health care workers. Ped Infect Dis J. 1999;18(9):779-83.
52. Wilde JA, McMillan JA, Serwint J, Butta J, O'Riordan MA and Steinhoff MC. Effectiveness of influenza vaccine in health care professionals: a randomized trial. JAMA. 1999;281(10):908-13.

53. Shugarman LR, Hales C, Setodji CM, Bardenheier B and Lynn J. The influence of staff and resident immunization rates on influenza-like illness outbreaks in nursing homes. *J Am Med Dir Assoc.* 2006;7(9):562-67.
54. Amodio E, Restivo V, Firenze A, Mammina C, Tramuto F and Vitale F. Can influenza vaccination coverage among healthcare workers influence the risk of nosocomial influenza-like illness in hospitalized patients? *J Hosp Infect.* 2014;86(3):182-87.
55. Ambrose CS, Levin MJ and Belshe RB. The relative efficacy of trivalent live attenuated and inactivated influenza vaccines in children and adults. *Influenza Other Respir Viruses.* 2011;5(2):67-75.
56. Public Health Agency of Canada. *Guidance: Infection Prevention and Control Measures for Healthcare Workers in Acute Care and Long-term Care Settings - Seasonal influenza.* Ottawa: Government of Canada; 2010.
57. Accreditation Canada. *Infection prevention and control standards.* 9th ed. Ottawa: Accreditation Canada; 2013.
58. Aoki FY, Allen UD, Stiver HG, Laverdiere M and Evans GA. AMMI Canada Guideline: The use of antiviral drugs for influenza: A foundation document for practitioners. *Can J Infect Dis Med Microbiol.* 2013;24(Suppl C):1C.
59. Grotto I, Mandel Y, Green MS, Varsano N, Gdalevich M, Ashkenazi I, et al. Influenza vaccine efficacy in young, healthy adults. *Clin Infect Dis.* 1998;26(4):913-17.
60. Leighton L, Williams M, Aubery D and Parker SH. Sickness absence following a campaign of vaccination against influenza in the workplace. *Occup Med (Lond).* 1996;46(2):146-50.
61. Nichol KL, Lind A, Margolis KL, Murdoch M, McFadden R, Hauge M, et al. The effectiveness of vaccination against influenza in healthy, working adults. *N Engl J Med.* 1995;333(14):889-93.
62. Bridges CB, Lim W, Hu-Primmer J, Sims L, Fukuda K, Mak KH, et al. Risk of influenza A (H5N1) infection among poultry workers, Hong Kong, 1997-1998. *J Infect Dis.* 2002;185(8):1005-10.
63. Puzelli S, Di Trani L, Fabiani C, Campitelli L, De Marco MA, Capua I, et al. Serological analysis of serum samples from humans exposed to avian H7 influenza viruses in Italy between 1999 and 2003. *J Infect Dis.* 2005;192(8):1318-22.
64. Tweed SA, Skowronski DM, David ST, Larder A, Petric M, Lees W, et al. Human illness from avian influenza H7N3, British Columbia. *Emerg Infect Dis.* 2004;10(12):2196-99.
65. Skowronski DM, Li Y, Tweed SA, Tam TW, Petric M, David ST, et al. Protective measures and human antibody response during an avian influenza H7N3 outbreak in poultry in British Columbia, Canada. *CMAJ.* 2007;176(1):47-53.

66. Department of Health U. K. Flu vaccination for poultry workers 2007 [Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_063041].
67. Gray GC, Trampel DW and Roth JA. Pandemic influenza planning: shouldn't swine and poultry workers be included? *Vaccine*. 2007;25(22):4376-81.
68. Heckler R, Baillot A, Engelmann H, Neumeier E and Windorfer A. Cross-protection against homologous drift variants of influenza A and B after vaccination with split vaccine. *Intervirology*. 2007;50(1):58-62.
69. Walter EB, Neuzil KM, Zhu Y, Fairchok MP, Gagliano ME, Monto AS, et al. Influenza vaccine immunogenicity in 6- to 23-month-old children: Are identical antigens necessary for priming? *Pediatrics*. 2006;118(3):e570-e78.
70. Englund JA, Walter EB, Fairchok MP, Monto AS and Neuzil KM. A comparison of 2 influenza vaccine schedules in 6- to 23-month-old children. *Pediatrics*. 2005;115(4):1039-47.
71. Englund JA, Walter EB, Gbadebo A, Monto AS, Zhu Y and Neuzil KM. Immunization with trivalent inactivated influenza vaccine in partially immunized toddlers. *Pediatrics*. 2006;118(3):e579-e85.
72. Levandowski RA, Gross PA, Weksler M, Staton E, Williams MS and Bonelli J. Cross-reactive antibodies induced by a monovalent influenza B virus vaccine. *J Clin Microbiol*. 1991;29(7):1530-32.
73. Levandowski RA, Regnery HL, Staton E, Burgess BG, Williams MS and Groothuis JR. Antibody responses to influenza B viruses in immunologically unprimed children. *Pediatrics*. 1991;88(5):1031-36.
74. Langley JM and Faughnan ME. Prevention of influenza in the general population. *CMAJ*. 2004;171(10):1213-22.
75. Cowling BJ, Fang VJ, Nishiura H, Chan KH, Ng S, Ip DKM, et al. Increased risk of noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine. *Clin Infect Dis*. 2012;54(12):1778-83.
76. Cowling BJ, Ng S, Ma ES, Fang VJ, So HC, Wai W, et al. Protective efficacy against pandemic influenza of seasonal influenza vaccination in children in Hong Kong: a randomized controlled trial. *Clin Infect Dis*. 2012;55(5):695-702.
77. Fujieda M, Maeda A, Kondo K, Kaji M and Hirota Y. Inactivated influenza vaccine effectiveness in children under 6 years of age during the 2002-2003 season. *Vaccine*. 2006;24(7):957-63.
78. Katayose M, Hosoya M, Haneda T, Yamaguchi H, Kawasaki Y, Sato M, et al. The effectiveness of trivalent inactivated influenza vaccine in children over six consecutive influenza seasons. *Vaccine*. 2011;29(9):1844-49.

79. Kawai N, Ikematsu H, Iwaki N, Satoh I, Kawashima T, Tsuchimoto T, et al. A prospective, Internet-based study of the effectiveness and safety of influenza vaccination in the 2001-2002 influenza season. *Vaccine*. 2003;21(31):4507-13.
80. Kawai S, Nanri S, Ban E, Inokuchi M, Tanaka T, Tokumura M, et al. Influenza Vaccination of Schoolchildren and Influenza Outbreaks in a School. *Clin Infect Dis*. 2011;53(2):130-36.
81. Kwong JC, Ge H, Rosella LC, Guan J, Maaten S, Moran K, et al. School-based influenza vaccine delivery, vaccination rates, and healthcare use in the context of a universal influenza immunization program: an ecological study. *Vaccine*. 2010;28(15):2722-29.
82. Kwong JC, Maaten S, Upshur RE, Patrick DM and Marra F. The effect of universal influenza immunization on antibiotic prescriptions: an ecological study. *Clin Infect Dis*. 2009;49(5):750-56.
83. Loeb M, Russell ML, Moss L, Fonseca K, Fox J, Earn DJ, et al. Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial. *JAMA*. 2010;303(10):943-50.
84. Maeda T, Shintani Y, Miyamoto H, Kawagoe H, Nakano K, Nishiyama A, et al. Prophylactic effect of inactivated influenza vaccine on young children. *Pediatr Int*. 2002;44(1):43-46.
85. Neuzil KM, Dupont WD, Wright PF and Edwards KM. Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985 to 1990: the pediatric experience. *Ped Infect Dis J*. 2001;20(8):733-40.
86. Nicholls S, Carroll K, Crofts J, Ben-Eliezer E, Paul J, Zambon M, et al. Outbreak of influenza A (H3N2) in a highly-vaccinated religious community: a retrospective cohort study. *Comm Dis Public Health*. 2004;7(4):272-77.
87. Ochiai H, Fujieda M, Ohfuji S, Fukushima W, Kondo K, Maeda A, et al. Inactivated influenza vaccine effectiveness against influenza-like illness among young children in Japan--with special reference to minimizing outcome misclassification. *Vaccine*. 2009;27(50):7031-35.
88. Pebody RG, Andrews N, Fleming DM, McMenamin J, Cottrell S, Smyth B, et al. Age-specific vaccine effectiveness of seasonal 2010/2011 and pandemic influenza A(H1N1) 2009 vaccines in preventing influenza in the United Kingdom. *Epidemiol Infect*. 2012:1-11.
89. Reichert TA, Sugaya N, Fedson DS, Glezen WP, Simonsen L and Tashiro M. The Japanese experience with vaccinating schoolchildren against influenza. *N Engl J Med*. 2001;344(12):889-96.
90. Treanor JJ, Talbot HK, Ohmit SE, Coleman LA, Thompson MG, Cheng PY, et al. Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. *Clin Infect Dis*. 2012;55(7):951-59.
91. Yamaguchi S, Ohfuji S and Hirota Y. Influenza vaccine effectiveness in primary school children in Japan: a prospective cohort study using rapid diagnostic test results. *J Infect Chemother*. 2010;16(6):407-13.

92. Belongia EA, Kieke BA, Donahue JG, Coleman LA, Irving SA, Meece JK, et al. Influenza vaccine effectiveness in Wisconsin during the 2007-08 season: comparison of interim and final results. *Vaccine*. 2011;29(38):6558-63.
93. Charu V, Viboud C, Simonsen L, Sturm-Ramirez K, Shinjoh M, Chowell G, et al. Influenza-related mortality trends in Japanese and American seniors: Evidence for the indirect mortality benefits of vaccinating schoolchildren. *PLoS One*. 2011;6(11):e26282-e82.
94. Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thorning S and Thomas RE. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev*. 2010;(2)(2):CD004876.
95. Negri E, Colombo C, Giordano L, Groth N, Apolone G and La Vecchia C. Influenza vaccine in healthy children: a meta-analysis. *Vaccine*. 2005;23(22):2851-61.
96. Manzoli L, Schioppa F, Boccia A and Villari P. The efficacy of influenza vaccine for healthy children: a meta-analysis evaluating potential sources of variation in efficacy estimates including study quality. *Ped Infect Dis J*. 2007;26(2):97-106.
97. Cowling BJ, Ng S, Ma ESK, Cheng CKY, Wai W, Fang VJ, et al. Protective efficacy of seasonal influenza vaccination against seasonal and pandemic influenza virus infection during 2009 in Hong Kong. *Clin Infect Dis*. 2010;51(12):1370-79.
98. Jefferson TO, Rivetti D, Di Pietrantonj C, Rivetti A and Demicheli V. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev*. 2007(2).
99. Vesikari T, Beran J, Durviaux S, Stainier I, Idrissi ME, Walravens K, et al. Use of real-time polymerase chain reaction (rtPCR) as a diagnostic tool for influenza infection in a vaccine efficacy trial. *J Clin Virol*. 2012;53(1):22-28.
100. Monto AS. Implications of antiviral resistance of influenza viruses. *Clin Infect Dis*. 2009;48(4):397-99.
101. Ohmit SE, Victor JC, Rotthoff JR, Teich ER, Truscon RK, Baum LL, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. *N Engl J Med*. 2006;355(24):2513-22.
102. Herrera GA, Iwane MK, Cortese M, Brown C, Gershman K, Shupe A, et al. Influenza vaccine effectiveness among 50-64-year-old persons during a season of poor antigenic match between vaccine and circulating influenza virus strains: Colorado, United States, 2003-2004. *Vaccine*. 2007;25(1):154-60.
103. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ and Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. *JAMA*. 1994;272(21):1661-65.
104. Poole PJ, Chacko E, Wood-Baker RW and Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2006(1):002733.

105. Hak E, Buskens E, van Essen GA, de Bakker DH, Grobbee DE, Tacken MA, et al. Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions: the PRISMA study. *Arch Intern Med.* 2005;165(3):274-80.
106. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K and Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *N Engl J Med.* 2003;348(14):1322-32.
107. Looijmans-Van den Akker I, Verheij TJ, Buskens E, Nichol KL, Rutten GE and Hak E. Clinical effectiveness of first and repeat influenza vaccination in adult and elderly diabetic patients. *Diabetes Care.* 2006;29(8):1771-76.
108. Jackson LA, Jackson ML, Nelson JC, Neuzil KM and Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. *Int J Epidemiol.* 2006;35(2):337-44.
109. Jackson LA, Nelson JC, Benson P, Neuzil KM, Reid RJ, Psaty BM, et al. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. *Int J Epidemiol.* 2006;35(2):345-52.
110. Simonsen L. Commentary: Observational studies and the art of accurately measuring influenza vaccine benefits. *Int J Epidemiol.* 2007;36(3):631-32.
111. Simonsen L, Viboud C and Taylor RJ. Effectiveness of influenza vaccination. *N Engl J Med.* 2007;357(26):2729-30.
112. Orenstein EW, De Serres G, Haber MJ, Shay DK, Bridges CB, Gargiullo P, et al. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. *Int J Epidemiol.* 2007;36(3):623-31.
113. Osterholm MT, Kelley NS, Sommer A and Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. *Lancet Infect Dis.* 2012;12(1):36-44.
114. McLean HQ, Thompson MG, Sundaram ME, Kieke BA, Gaglani M, Murthy K, et al. Influenza vaccine effectiveness in the United States during 2012-2013: variable protection by age and virus type. *J Infect Dis.* 2015;211(10):1529-40.
115. McLean HQ, Thompson MG, Sundaram ME, Meece JK, McClure DL, Friedrich TC, et al. Impact of repeated vaccination on vaccine effectiveness against influenza A(H3N2) and B during 8 seasons. *Clin Infect Dis.* 2014;59(10):1375-85.
116. Thomas PG, Keating R, Hulse-Post DJ and Doherty PC. Cell-mediated protection in influenza infection. *Emerg Infect Dis.* 2006;12(1):48-54.
117. Langley JM, Vanderkooi OG, Garfield HA, Herbert J, Chandrasekaran V, Jain VK, et al. Immunogenicity and safety of 2 dose levels of a thimerosal-free trivalent seasonal influenza vaccine in children aged 6-35 months: A randomized, controlled trial. *J Ped Infect Dis.* 2012;1(1):55-58.
118. Kanra G, Marchisio P, Feiterna-Sperling C, Gaedicke G, Lazar H, Durrer P, et al. Comparison of immunogenicity and tolerability of a virosome-adjuvanted and a split influenza vaccine in children. *Ped Infect Dis J.* 2004;23(4):300-06.

119. Baxter R, Jeanfreau R, Block SL, Blatter M, Pichichero M, Jain VK, et al. A Phase III evaluation of immunogenicity and safety of two trivalent inactivated seasonal influenza vaccines in US children. *Ped Infect Dis J.* 2010;29(10):924-30.
120. Pavia-Ruz N, Weber MAR, Lau YL, Nelson EAS, Kerdpanich A, Huang LM, et al. A randomized controlled study to evaluate the immunogenicity of a trivalent inactivated seasonal influenza vaccine at two dosages in children 6 to 35 month of age. *Hum Vaccin Immunother.* 2013;9(9):1978-88.
121. Skowronski DM, Tweed SA and De Serres G. Rapid decline of influenza vaccine-induced antibody in the elderly: is it real, or is it relevant? *J Infect Dis.* 2008;197(4):490-502.
122. Anema A, Mills E, Montaner J, Brownstein JS and Cooper C. Efficacy of influenza vaccination in HIV-positive patients: a systematic review and meta-analysis. *HIV Med.* 2008;9(1):57-61.
123. Cooper C, Hutton B, Fergusson D, Mills E, Klein MB, Boivin G, et al. A review of influenza vaccine immunogenicity and efficacy in HIV-infected adults. *Can J Infect Dis Med Microbiol.* 2008;19(6):419-23.
124. Scharpe J, Evenepoel P, Maes B, Bammens B, Claes K, Osterhaus AD, et al. Influenza vaccination is efficacious and safe in renal transplant recipients. *Am J Transplant.* 2008;8(2):332-37.
125. Manuel O, Humar A, Chen MH, Chernenko S, Singer LG, Cobos I, et al. Immunogenicity and safety of an intradermal boosting strategy for vaccination against influenza in lung transplant recipients. *Am J Transplant.* 2007;7(11):2567-72.
126. Buxton JA, Skowronski DM, Ng H, Marion SA, Li Y, King A, et al. Influenza revaccination of elderly travelers: antibody response to single influenza vaccination and revaccination at 12 weeks. *J Infect Dis.* 2001;184(2):188-91.
127. Ljungman P, Nahi H and Linde A. Vaccination of patients with haematological malignancies with one or two doses of influenza vaccine: a randomised study. *Br J Haematol.* 2005;130(1):96-98.
128. McElhaney JE, Hooton JW, Hooton N and Bleackley RC. Comparison of single versus booster dose of influenza vaccination on humoral and cellular immune responses in older adults. *Vaccine.* 2005;23(25):3294-300.
129. Gross PA, Weksler ME, Quinnan GV, Jr., Douglas RG, Jr., Gaerlan PF and Denning CR. Immunization of elderly people with two doses of influenza vaccine. *J Clin Microbiol.* 1987;25(9):1763-65.
130. Edwards KM, Dupont WD, Westrich MK, Plummer WD, Jr., Palmer PS and Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. *J Infect Dis.* 1994;169(1):68-76.

131. Gonzalez M, Pirez MC, Ward E, Dibarboure H, Garcia A and Picolet H. Safety and immunogenicity of a paediatric presentation of an influenza vaccine. *Arch Dis Child*. 2000;83(6):488-91.
132. Piedra PA, Glezen WP, Mbawuike I, Gruber WC, Baxter BD, Boland FJ, et al. Studies on reactivity and immunogenicity of attenuated bivalent cold recombinant influenza type A (CRA) and inactivated trivalent influenza virus (TI) vaccines in infants and young children. *Vaccine*. 1993;11(7):718-24.
133. DiazGranados CA, Dunning AJ, Jordanov E, Landolfi V, Denis M and Talbot HK. High-dose trivalent influenza vaccine compared to standard dose vaccine in elderly adults: safety, immunogenicity and relative efficacy during the 2009-2010 season. *Vaccine*. 2013;31(6):861-66.
134. Diaz Granados CA, Dunning AJ, Robertson CA, Talbot HK, Landolfi V and Greenberg DP. Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty. *J Am Geriatr Soc*. 2014;62:S37-S38.
135. DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med*. 2014;371(7):635-45.
136. DiazGranados CA, Dunning AJ, Robertson CA, Talbot HK, Landolfi V and Greenberg DP. Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty. *Vaccine*. 2015;33(36):4565-71.
137. Izurieta HS, Thadani N, Shay DK, Lu Y, Maurer A, Foppa IM, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. *Lancet Infect Dis*. 2015;15(3):293-300.
138. Falsey AR, Treanor JJ, Tornieporth N, Capellan J and Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *J Infect Dis*. 2009;200(2):172-80.
139. Couch RB, Winokur P, Brady R, Belshe R, Chen WH, Cate TR, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. *Vaccine*. 2007;25(44):7656-63.
140. Keitel WA, Atmar RL, Cate TR, Petersen NJ, Greenberg SB, Ruben F, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. *Arch Intern Med*. 2006;166(10):1121-27.
141. U. S. National Institutes of Health. Study of Fluzone® influenza virus vaccine 2011-2012 formulation (intramuscular route) among adults 2013 [Accessed 2014 August 2]. Available from: <https://www.clinicaltrials.gov/ct2/show/study/NCT01430819>.
142. Tsang P, Gorse GJ, Strout CB, Sperling M, Greenberg DP, Ozol-Godfrey A, et al. Immunogenicity and safety of Fluzone intradermal and high-dose influenza vaccines in older adults >65 years of age: A randomized, controlled, phase II trial. *Vaccine*. 2014;32(21):2507-17.

143. Nace DA, Lin CJ, Ross TM, Saracco S, Churilla RM and Zimmerman RK. Randomized, controlled trial of high-dose influenza vaccine among frail residents of long-term care facilities. *J Infect Dis.* 2015;211(12):1915-24.
144. Jain VK, Rivera L, Zaman K, Espos, Jr., Sirivichayakul C, Quiambao BP, et al. Vaccine for prevention of mild and moderate-to-severe influenza in children. *N Engl J Med.* 2013;369(26):2481-91.
145. Belshe RB. The need for quadrivalent vaccine against seasonal influenza. *Vaccine.* 2010;28(SUPPL. 4):D45-D53.
146. Frey SE, Reyes MR, Reynales H, Bermal NN, Nicolay U, Narasimhan V, et al. Comparison of the safety and immunogenicity of an MF59-adjuvanted with a non-adjuvanted seasonal influenza vaccine in elderly subjects. *Vaccine.* 2014;32(39):5027-34.
147. National Advisory Committee on Immunization. Recommendations on the use of MF59-adjuvanted trivalent seasonal influenza vaccine (Fluad®): Supplemental statement on seasonal influenza vaccine for 2011-2012. *CCDR.* 2011;37(ACS-6):March.
148. Puig-Barbera J, Diez-Domingo J, Perez Hoyos S, Belenguer Varea A and Gonzalez Vidal D. Effectiveness of the MF59-adjuvanted influenza vaccine in preventing emergency admissions for pneumonia in the elderly over 64 years of age. *Vaccine.* 2004;23(3):283-89.
149. Puig-Barbera J, Diez-Domingo J, Varea AB, Chavarri GS, Rodrigo JA, Hoyos SP, et al. Effectiveness of MF59-adjuvanted subunit influenza vaccine in preventing hospitalisations for cardiovascular disease, cerebrovascular disease and pneumonia in the elderly. *Vaccine.* 2007;25(42):7313-21.
150. Iob A, Brianti G, Zamparo E and Gallo T. Evidence of increased clinical protection of an MF59-adjuvant influenza vaccine compared to a non-adjuvant vaccine among elderly residents of long-term care facilities in Italy. *Epidemiol Infect.* 2005;133(4):687-93.
151. Mannino S, Villa M, Apolone G, Weiss NS, Groth N, Aquino I, et al. Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy. *Am J Epidemiol.* 2012;176(6):527-33.
152. Skowronski DM, De Serres G, Janjua NZ and Hottes TS. Re: "Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy". *Am J Epidemiol.* 2013;177(6):593-94.
153. Van Buynder PG, Konrad S, Van Buynder JL, Brodtkin E, Krajden M, Ramler G, et al. The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly. *Vaccine.* 2013;31(51):6122-28.
154. Mosca F, Tritto E, Muzzi A, Monaci E, Bagnoli F, Iavarone C, et al. Molecular and cellular signatures of human vaccine adjuvants. *Proc Natl Acad Sci USA.* 2008;105(30):10501-06.
155. Calabro S, Tortoli M, Baudner B, Pacitto A, Cortese M, O'Hagan D, et al. Vaccine adjuvants alum and MF59 induce rapid recruitment of neutrophils and monocytes that participate in antigen transport to draining lymph nodes. *Vaccine.* 2011;29(9):1812-23.

156. Seubert A, Monaci E, Pizza M, O'Hagan D and Wack A. The adjuvants aluminum hydroxide and MF59 induce monocyte and granulocyte chemoattractants and enhance monocyte differentiation toward dendritic cells. *J Immunol.* 2008;180(8):5402-12.
157. O'Hagan DT, Rappuoli R, De Gregorio E, Tsai T and Del Giudice G. MF59 adjuvant: the best insurance against influenza strain diversity. *Expert Rev Vaccines.* 2011;10(4):447-62.
158. Squarcione S, Sgricia S, Biasio LR and Perinetti E. Comparison of the reactogenicity and immunogenicity of a split and a subunit-adjuvanted influenza vaccine in elderly subjects. *Vaccine.* 2003;21(11-12):1268-74.
159. Van Damme P, Arnou R, Kafeja F, Fiquet A, Richard P, Thomas S, et al. Evaluation of non-inferiority of intradermal versus adjuvanted seasonal influenza vaccine using two serological techniques: a randomised comparative study. *BMC Infect Dis.* 2010;10:134.
160. Vesikari T, Knuf M, Wutzler P, Karvonen A, Kieninger-Baum D, Schmitt HJ, et al. Oil-in-water emulsion adjuvant with influenza vaccine in young children. *N Engl J Med.* 2011;365:1406-16.
161. European Medicines Agency. Withdrawal Assessment Report: FLUAD PAEDIATRIC Influenza Vaccine, Surface Antigen, Inactivated, Adjuvanted with MF59C.1 2012 [Accessed 2015 June 15]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2012/04/WC500126030.pdf.
162. Sancho A, Melchiorri D, Abadie E and Committee for Medicinal Products for Human Use EMA. More on influenza vaccine in young children. *N Engl J Med.* 2012;366(26):2528-29.
163. Ambrose CS and Belshe RB. Influenza vaccine in young children. *N Engl J Med.* 2012;366(4):383-84.
164. Vesikari T, Groth N, Karvonen A, Borkowski A and Pellegrini M. MF59[®]-adjuvanted influenza vaccine (FLUAD[®]) in children: Safety and immunogenicity following a second year seasonal vaccination. *Vaccine.* 2009;27:6291-95.
165. Vesikari T, Pellegrini M, Karvonen A, Groth N, Borkowski A, Hagan DT, et al. Enhanced immunogenicity of seasonal influenza vaccines in young children using MF59 adjuvant. *Ped Infect Dis J.* 2009;28:563-71.
166. Della Cioppa G, Vesikari T, Sokal E, Lindert K and Nicolay U. Trivalent and quadrivalent MF59 (R)-adjuvanted influenza vaccine in young children: A dose- and schedule-finding study. *Vaccine.* 2011;29(47):8696-704.
167. Zedda L, Forleo-Neto E, Vertruyen A, Raes M, Marchant A, Jansen W, et al. Dissecting the immune response to MF59-adjuvanted and nonadjuvanted seasonal influenza vaccines in children less than three years of age. *Ped Infect Dis J.* 2015;34(1):73-78.
168. Nolan T, Bravo L, Ceballos A, Mitha E, Gray G, Quiambao B, et al. Enhanced and persistent antibody response against homologous and heterologous strains elicited by a MF59-adjuvanted influenza vaccine in infants and young children. *Vaccine.* 2014;32(46):6146-56.

169. Black S, Della Cioppa G, Malfroot A, Nacci P, Nicolay U, Pellegrini M, et al. Safety of MF59-adjuvanted versus non-adjuvanted influenza vaccines in children and adolescents: an integrated analysis. *Vaccine*. 2010;28:7331-36.
170. Vaarala O, Vuorela A, Partinen M, Baumann M, Freitag TL, Meri S, et al. Antigenic differences between AS03 adjuvanted influenza A (H1N1) pandemic vaccines: implications for pandemrix-associated narcolepsy risk. *PLoS ONE*. 2014;9(12):e114361.
171. Fleming DM, Crovari P, Wahn U, Klemola T, Schlesinger Y, Langussis A, et al. Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. *Ped Infect Dis J*. 2006;25(10):860-69.
172. Ashkenazi S, Vertruyen A, Aristegui J, Esposito S, McKeith DD, Klemola T, et al. Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infections. *Ped Infect Dis J*. 2006;25(10):870-79.
173. Belshe RB, Coelingh K, Ambrose CS, Woo JC and Wu X. Efficacy of live attenuated influenza vaccine in children against influenza B viruses by lineage and antigenic similarity. *Vaccine*. 2010;28(9):2149-56.
174. National Advisory Committee on Immunization. Recommendations on the use of live, attenuated influenza vaccine (FluMist®): Supplemental statement on seasonal influenza vaccine 2011-2012. *CCDR*. 2011;37(ACS-7):March.
175. Block SL, Falloon J, Hirschfield JA, Krilov LR, Dubovsky F, Yi T, et al. Immunogenicity and safety of a quadrivalent live attenuated influenza vaccine in children. *Ped Infect Dis J*. 2012;31(7):745-51.
176. Block SL, Yi T, Sheldon E, Dubovsky F and Falloon J. A randomized, double-blind noninferiority study of quadrivalent live attenuated influenza vaccine in adults. *Vaccine*. 2011;29(50):9391-97.
177. MedImmune. A study to evaluate the immunogenicity of quadrivalent LAIV (MEDI8662) in adults 18-49 years of age 2011 [Accessed 2015 June 15]. Available from: <https://clinicaltrials.gov/ct2/show/results/NCT00952705?term=MEDI8662&rank=1>.
178. Public Health Agency of Canada. Canadian Immunization Guide: Part 1 - Key immunization information 2013: Timing of vaccine administration 2013 [Accessed 2015 June 1]. Available from: <http://www.phac-aspc.gc.ca/publicat/cig-gci/p01-09-eng.php>.
179. Nascimento Silva JR, Camacho LA, Siqueira MM, Freire Mde S, Castro YP, Maia Mde L, et al. Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps and rubella. *Vaccine*. 2011;29(37):6327-34.
180. Stefano I, Sato HK, Pannuti CS, Omoto TM, Mann G, Freire MS, et al. Recent immunization against measles does not interfere with the sero-response to yellow fever vaccine. *Vaccine*. 1999;17(9-10):1042-46.

181. Tauraso NM, Myers MG, Nau EV, O'Brien TC, Spindel SS and Trimmer RW. Effect of interval between inoculation of live smallpox and yellow-fever vaccines on antigenicity in man. *J Infect Dis.* 1972;126(4):362-71.
182. Verstraeten T, Jumaan AO, Mullooly JP, Seward JF, Izurieta HS, DeStefano F, et al. A retrospective cohort study of the association of varicella vaccine failure with asthma, steroid use, age at vaccination, and measles-mumps-rubella vaccination. *Pediatrics.* 2003;112(2):e98-103.
183. Des Roches A, Paradis L, Gagnon R, Lemire C, Bérubé P, Carr S, et al. Egg-allergic patients can be safely vaccinated against influenza. *J Allergy Clin Immunol.* 2012;130(5):1213-16.
184. Greenhawt MJ, Spergel JM, Rank MA, Green TD, Masnoor D, Sharma H, et al. Safe administration of the seasonal trivalent influenza vaccine to children with severe egg allergy. *Ann Allergy Asthma Immunol.* 2012;109(6):426-30.
185. Institute of Medicine. Immunization safety review: Influenza vaccines and neurological complications. Washington, D.C.: Institute of Medicine of the National Academies; 2008.
186. Juurlink DN, Stukel TA, Kwong J, Kopp A, McGeer A, Upshur RE, et al. Guillain-Barre syndrome after influenza vaccination in adults: a population-based study. *Arch Intern Med.* 2006;166(20):2217-21.
187. Centers for Disease Control and Prevention. Preliminary results: surveillance for Guillain-Barre syndrome after receipt of influenza A (H1N1) 2009 monovalent vaccine - United States, 2009-2010. *MMWR.* 2010;59:657-61.
188. Kwong JC, Vasa PP, Campitelli MA, Hawken S, Wilson K, Rosella LC, et al. Risk of Guillain-Barre syndrome after seasonal influenza vaccination and influenza health-care encounters: A self-controlled study. *Lancet Infect Dis.* 2013;13(9):769-76.
189. Sivadon-Tardy V, Orlikowski D, Porcher R, Sharshar T, Durand MC, Enouf V, et al. Guillain-Barre syndrome and influenza virus infection. *Clin Infect Dis.* 2009;48(1):48-56.
190. Stowe J, Andrews N, Wise L and Miller E. Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenza like illness using the United Kingdom General Practice Research Database. *Am J Epidemiol.* 2009;169(3):382-88.
191. Tam CC, O'Brien SJ, Petersen I, Islam A, Hayward A and Rodrigues LC. Guillain-Barre syndrome and preceding infection with campylobacter, influenza and Epstein-Barr virus in the general practice research database. *PLoS ONE.* 2007;2(4):e344.
192. Andrews N, Stowe J, Al-Shahi Salman R and Miller E. Guillain-Barre syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: self-controlled case series. *Vaccine.* 2011;29(45):7878-82.
193. Ritzwoller DP, Bridges CB, Shetterly S, Yamasaki K, Kolczak M and France EK. Effectiveness of the 2003-2004 influenza vaccine among children 6 months to 8 years of age, with 1 vs 2 doses. *Pediatrics.* 2005;116(1):153-59.

194. Neuzil KM, Jackson LA, Nelson J, Klimov A, Cox N, Bridges CB, et al. Immunogenicity and reactogenicity of 1 versus 2 doses of trivalent inactivated influenza vaccine in vaccine-naïve 5-8-year-old children. *J Infect Dis*. 2006;194(8):1032-39.
195. Shuler CM, Iwamoto M, Bridges CB, Marin M, Neeman R, Gargiullo P, et al. Vaccine effectiveness against medically attended, laboratory-confirmed influenza among children aged 6 to 59 months, 2003-2004. *Pediatrics*. 2007;119(3):e587-e95.
196. Allison MA, Daley MF, Crane LA, Barrow J, Beaty BL, Allred N, et al. Influenza vaccine effectiveness in healthy 6- to 21-month-old children during the 2003-2004 season. *J Pediatr*. 2006;149(6):755-62.
197. Skowronski DM, Hottes TS, De Serres G, Ward BJ, Janjua NZ, Sabaiduc S, et al. Influenza B/Victoria antigen induces strong recall of B/Yamagata but lower B/Victoria response in children primed with two doses of B/Yamagata. *Ped Infect Dis J*. 2011;30(10):833-39.
198. Skowronski DM, Hottes TS, Chong M, De Serres G, Scheifele DW, Ward BJ, et al. Randomized controlled trial of dose response to influenza vaccine in children aged 6 to 23 months. *Pediatrics*. 2011;128(2):e276-e89.
199. Statistics Canada. Table 051-0001 - Estimates of population, by age group and sex for July 1, Canada, provinces and territories, annual (persons unless otherwise noted), CANSIM (database) 2014 [Accessed 2015 June]. Available from: <http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo10a-eng.htm>.
200. Centers for Disease Control and Prevention. Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. *MMWR Morb Mortal Wkly Rep*. 2010;59(33):1057-62.
201. Cromer D, van Hoek AJ, Jit M, Edmunds WJ, Fleming D and Miller E. The burden of influenza in England by age and clinical risk group: a statistical analysis to inform vaccine policy. *J Infect*. 2014;68(4):363-71.
202. Belshe RB, Edwards KM, Vesikari T, Black SV, Walker RE, Hultquist M, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. *N Engl J Med*. 2007;356(7):685-96.
203. Boikos C, De Serres G, Lands LC, Boucher FD, Tapiero B, Daigneault P, et al. Safety of live-attenuated influenza vaccination in cystic fibrosis. *Pediatrics*. 2014;134(4):e983-e91.