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

Statement on Seasonal Influenza Vaccine for 2014-2015
PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (hereafter referred to as the Agency) with ongoing and timely medical, scientific, and public health advice relating to immunization. The Agency acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) of the Canadian manufacturer(s) of the vaccine(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of the Agency’s Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.
# TABLE OF CONTENT

Summary of information contained in this NACI Statement .......................................................... 3
I. Introduction ........................................................................................................................................... 6
II. Methods ................................................................................................................................................ 7
III. Epidemiology ........................................................................................................................................ 8
IV. Seasonal Influenza Vaccines ........................................................................................................... 15
V. Recommendations ............................................................................................................................ 33
VI. Immunization of Health Care Workers .......................................................................................... 51
List of Abbreviations ............................................................................................................................. 52
Acknowledgments .................................................................................................................................... 55
References .................................................................................................................................................. 56
SUMMARY OF INFORMATION CONTAINED IN THIS NACI STATEMENT

The following table highlights key information for immunization providers. Please refer to the remainder of the Statement for details.

<table>
<thead>
<tr>
<th>1. What</th>
<th>Influenza is a respiratory infection caused by influenza A or B viruses. In Canada it generally occurs each year in the late fall and winter months. Symptoms typically include the sudden onset of headache, chills, cough, fever, loss of appetite, myalgia, fatigue, coryza, sneezing, watery eyes and throat irritation. Nausea, vomiting and diarrhoea may also occur, especially in children. Most people will recover from influenza within a week to ten days, but some - including those 65 years of age and older, and adults and children with chronic conditions - are at greater risk of more severe complications, such as pneumonia. Additional information about groups that are at increased risk of influenza complications is available below in Table 5 and in Section V of this document.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>What influenza vaccines are authorized for use in Canada? There are currently eight trivalent influenza vaccines and two quadrivalent influenza vaccines authorized for use in Canada. Each province or territory will advise which vaccines will be made available for the publicly-funded program in that jurisdiction. Seven of the seasonal influenza vaccines are trivalent inactivated vaccines (TIV), either split virus or subunit. Five of these (Agriflu®, Fluviral®, Fluzone®, Influvac®, and Vaxigrip®) are traditional intramuscular (IM) products that do not contain an adjuvant. The sixth (Fluad®) is an MF59-adjuvanted vaccine for persons ≥65 years of age that is also given IM. The seventh TIV product (Intanza®) is authorized for persons ≥18 years of age and is given by the intradermal route. Intanza is available in two formulations: 9 µg/strain for persons 18-59 years of age and 15 µg/strain for persons 60 years of age and older. The eighth trivalent influenza vaccine (FluMist®) is a live attenuated influenza vaccine (LAIV) that is authorized for use in those 2-59 years of age. The virus strains in FluMist® 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. The two quadrivalent inactivated influenza vaccine products that are authorized for use in Canada (Flulaval™ Tetra and Fluzone® Quadrivalent) are split-virion, inactivated vaccines that do not contain an adjuvant and</td>
</tr>
</tbody>
</table>
are administered via the IM route. Specific information as to what quadrivalent products will be available to Canada in 2014-2015 is not yet known.

Influenza vaccine is safe and well-tolerated and may be given to persons starting from six months of age (noting product-specific age indications and contraindications).

2. Who

Recent literature reviews conducted by NACI have shown that healthy individuals aged 5 to 64 years benefit from influenza vaccination, in addition to the people for whom the vaccine has been indicated in the past. With evidence showing that influenza vaccine benefits people of all ages, NACI now recommends influenza vaccination for all individuals 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 5 (see section V.2 for details).

3. How

Vaccine administration

*Dose and schedule*

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 <9 years of age receiving seasonal influenza vaccine for the first time should be given two doses, with a minimum interval of four weeks between doses. The route of administration and dosage varies by product (see section IV.3 of this statement for details). For intramuscular TIV, the dose is 0.5 ml for all age groups.

*Contraindications and precautions*

Persons who 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 developed Guillain-Barré Syndrome (GBS) within six weeks of influenza vaccination, should not receive a further dose.

NACI has concluded that egg allergic individuals may be vaccinated against influenza using TIV and QIV without a prior influenza vaccine skin test and with the full dose. The vaccine may be given in any settings where vaccines are routinely administered (see section IV.3.1 for details). However, immunizers administering vaccine should be prepared for and have the necessary equipment to respond to a vaccine emergency at all times. LAIV should not be given to egg-allergic individuals as it has not yet been studied in this group. There are additional contraindications for LAIV (see section IV.7 for details).

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 could be deferred until resolution of the illness.

**Co-administration with other vaccines**

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 section IV.5 for details). For concomitant parenteral injections, different injection sites and separate needles and syringes should be used.

**Adverse events**

Soreness at the injection site may occur after administration of inactivated vaccines and is more common with adjuvanted or intradermal vaccines. Fever and other systemic reactions are infrequent. The most common adverse events after LAIV administration are nasal congestion and coryza.

**Vaccine storage**

Influenza vaccine should be stored at 2 to 8°C and should never be frozen.

4. **Why**

**Key counselling points when discussing these recommendations**

- Vaccination is the safest, longest-lasting and most effective way to prevent influenza.
- Each year there is a new vaccine to protect against the expected influenza virus strains of the coming influenza season. Even if the strains have not changed, getting the influenza vaccine every year is necessary to maximize protection as its duration may not span two influenza seasons.
- Influenza vaccine is safe and well-tolerated.
I. INTRODUCTION

I.1 Overview and summary of changes

The purpose of this statement is to provide the NACI recommendations for immunization with the seasonal influenza vaccine for the 2014-2015 season.

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 and can be found at www.who.int/influenza/vaccines/virus/recommendations/en/.

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.

The 2014-2015 statement has been updated from the 2013-2014 influenza season and includes product information for the eight trivalent influenza vaccines currently authorized for use in Canada; Influvac®, Fluviral®, Vaxigrip®, Intanza®, FluMist®, Agriflu®, Flud®; and Fluzone® (see Table 3 for product characteristics) as well as two new quadrivalent vaccines, Flulaval™ Tetra and Fluzone® Quadrivalent. There have been several changes in the recommendations regarding influenza vaccines since the Statement on Seasonal Influenza Vaccine for 2013-14 as outlined below.

Recent literature reviews conducted by NACI have shown that healthy individuals aged 5-64 years benefit from influenza vaccination. With evidence showing that influenza vaccine benefits people of all ages, NACI now recommends influenza vaccination for all individuals 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 5 (see section V.2 for details).

Given the burden of disease, the immunogenicity and the safety data available for the quadrivalent vaccine, NACI recommends that inactivated quadrivalent influenza vaccines and, when available, live quadrivalent influenza vaccines can be used as per their product monograph. Additionally, the preferential recommendation for LAIV in children and adolescents has been clarified to reflect the available evidence for the preferential use in younger children (younger than 6 years of age). Finally, after careful review, NACI has concluded that egg allergic individuals may be vaccinated against influenza using TIV without a prior influenza vaccine skin test and with the full dose and in any settings where vaccines are routinely administered. Similar recommendations have been made for QIV. However, as with all vaccine administration, immunizers should have the necessary equipment to be prepared to respond to a vaccine emergency at all times (see section IV.3.1 for details).
I.2 Background

Influenza A viruses are classified into subtypes on the basis of two surface proteins: haemagglutinin (HA) and neuraminidase (NA). Three subtypes of haemagglutinin (H1, H2 and H3) and two subtypes of neuraminidase (N1 and N2) are recognized among influenza A viruses as having caused widespread human disease. Immunity to the HA and NA proteins reduces the likelihood of infection and 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, generally requires seasonal influenza vaccines to be reformulated annually. Trivalent 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 one of the two influenza B lineages (Yamagata or Victoria). Quadrivalent seasonal influenza vaccines contain standardized amounts of the HA protein from the representative seed strains of the two human influenza A subtypes (H3N2 and H1N1) and from the two influenza B lineages (Yamagata and Victoria). 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 age, prior antigenic experience with the two B lineages, or both\(^{(1)-(6)}\).

II. METHODS

Details regarding NACI’s evidence-based process for developing a statement are outlined in Evidence-Based Recommendations for Immunization: Methods of the NACI (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-1/), January 2009, CCDR.

Annual influenza vaccine recommendations are developed by the Influenza Working Group (IWG) for consideration by NACI. Recommendation development includes review of a variety of issues including the burden of influenza illness and the target populations for vaccination; safety, immunogenicity, efficacy, and effectiveness of influenza vaccines; vaccine schedules; and other aspects of influenza immunization.

To develop the 2014-2015 statement, the IWG and NACI identified key questions which guided specific literature reviews and data syntheses, including an evidence review on the immunization of healthy people 5-18 years of age, healthy people 19-64 years of age and the use of the quadrivalent influenza vaccine. The IWG also reassessed the evidence used to support a preferential recommendation of LAIV in children and adolescents 2-17 years of age and the evidence regarding influenza vaccine use in egg allergic individuals. Following
critical appraisal of individual studies and the development of summary tables with ratings of the quality of the evidence, proposed recommendations regarding influenza vaccine use were developed.

The results of the above mentioned evidence reviews were presented to NACI on September 9th, 2013. The evidence regarding quadrivalent influenza vaccine was presented to NACI on November 6, 2013. Following the thorough review of the evidence, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and identified knowledge gaps are described in this statement. The Agency maintains documentation of these processes throughout knowledge synthesis and recommendation development.

III. EPIDEMIOLOGY

III.1 Disease description

It is estimated that between 10-20% of the population becomes infected with influenza each year\(^7\). Rates of influenza infection are highest in children aged 5–9 years, but rates of serious illness and death are highest in children aged <2 years, older persons (>65 years), and persons with underlying medical conditions\(^8\). Influenza infection not only causes primary illness but can also lead to severe secondary medical complications, including viral pneumonia, secondary bacterial pneumonia and worsening of underlying medical conditions. It is estimated that in a given year, an average of 12,200 hospitalizations related to influenza\(^9\);\(^11\), and that approximately 3,500 deaths attributable to influenza occur annually\(^12\). However, it should be noted that influenza testing is often not conducted to confirm an influenza diagnosis, and that patients may present to hospital with complications of influenza after viral shedding has been stopped. For this reason, the overall incidence of influenza is best determined by periodic cohort studies. The rate of hospitalization and death due to influenza is best estimated by modeling of excess deaths and hospitalizations due to cardiorespiratory conditions during influenza season\(^13\).

III.2 Influenza surveillance

National influenza surveillance is coordinated through the Centre for Immunization and Respiratory Infectious Diseases (CIRID) in partnership the National Microbiology Laboratory (NML) at the Public Health Agency of Canada. The FluWatch program consists of a collaborative network of laboratories, hospitals, doctors’ offices, and provincial and territorial public health authorities. FluWatch collects data and information from various sources to provide a national picture of influenza activity which is published weekly in FluWatch (http://www.phac-aspc.gc.ca/fluwatch) weekly reports. Each of the different data sources contribute to a fuller understanding of the epidemiology of the influenza season. However, the data sources capture a very small proportion of the influenza infections that take place in Canada each year, and each has a bias towards certain ages, severity, people with comorbidities, et cetera.
There are eight major components to FluWatch: (1) Respiratory Virus Detection Surveillance System (RVDSS); (2) Influenza strain characterization and antiviral resistance for circulating influenza viruses; (3) Influenza-like illness (ILI) consultation rates; (4) Regional influenza activity levels; (5) Pharmacy Surveillance; (6) Severe Outcomes Surveillance; (7) Emerging Respiratory Pathogens; and (8) International influenza updates. Each component is described briefly below. Detailed methodology for FluWatch has been described previously (14).

1. **RVDSS:** Participating sentinel laboratories report the total number of influenza tests performed and the total number of tests positive for influenza by virus type and where available, by hemagglutinin subtype.

2. **Strain Characterization and Antiviral Resistance:** The National Microbiology Laboratory (NML) conducts national surveillance on human influenza virus strains in collaboration with provincial laboratories and other Canadian hospital- and university-based laboratories. A proportion (approximately 10%) of the weekly influenza detections across Canada are referred to the NML for strain characterization. Each week NML sends the results of strain characterization and antiviral sensitivity testing for inclusion in the FluWatch report.

3. **Influenza-Like Illness (ILI) Consultations:** Sentinel physicians report the total number of patients seen for any reason and the total number of patients meeting a standard national case definition for ILI for one clinic day each week.

4. **Outbreaks and Activity Levels:** Provincial and territorial representatives provide weekly assessments of influenza activity for each region in their jurisdiction and the number of outbreaks of influenza or ILI in schools, hospitals and residential institutions and other settings. Influenza activity levels are reported as meeting one of four standard categories: no activity, sporadic activity, localized activity or widespread activity.

5. **Pharmacy Surveillance:** Pharmacy sales data are provided by Rx Canada Inc. and sourced from major retail drug chains representing over 3,000 stores nationwide.

6. **Severe Outcomes Surveillance:** Hospitalizations and deaths in Canada are monitored two ways: hospital-based surveillance and provincial/territorial reporting directly to the Agency. The FluWatch program uses two sources of information for hospital-based surveillance: the Immunization Monitoring Program Active (IMPACT) network for paediatric hospitalizations, and, new in 2012-13, the PHAC/CIHR Influenza Research Network (PCIRN) Serious Outcomes Surveillance (SOS) network for adult hospitalizations and deaths. The number of hospitalizations and deaths reported through hospital-based surveillance represent a subset of all influenza-associated hospitalizations and deaths in Canada since not all of the hospitals in Canada are included in these networks. Data received from the provinces and territories includes community deaths based on laboratory-confirmed cases and may also include cases reported by the IMPACT and PCIRN networks. These duplicate cases cannot be removed because of insufficient identifiers. Provincial and territorial data may miss deaths depending on the timing of the death...
relative to when the laboratory-confirmed case was reported. Both surveillance systems miss deaths among those with suspected influenza that are not laboratory confirmed.

7. **Emerging Respiratory Pathogens:** Humans can become ill when infected with viruses from animal sources, such as influenza viruses of avian or swine origin and other respiratory viruses. The Agency monitors reports of human illness associated with emerging respiratory pathogens including novel influenza viruses.

8. **International Influenza Updates:** The Agency monitors international influenza activity and links to major international influenza reports are included in the FluWatch (http://www.phac-aspc.gc.ca/fluwatch/) weekly report.

### III.2.1 Influenza B in Canada

Surveillance data from the 2001/02 to 2012/13 seasons show that influenza B has accounted for 17% of all positive laboratory-confirmed tests for influenza, with the percentage of total laboratory-confirmed cases attributed to influenza B ranging from 0.1% to 53.1% (Table 1). The circulation of influenza B predominantly follows influenza A and typically peaks in the spring (Figure 1). However, the behaviour of influenza B is less predictable as there have been seasons with minimal circulation and seasons with high circulation (Figure 2). Isolate testing by the National Microbiology Laboratory (NML) has also demonstrated that the predominantly circulating B lineage has differed from the WHO recommended B lineage for the Northern hemisphere influenza vaccine in seven out of the last 12 seasons (Table 1, Figure 3).

Individuals who have influenza B are more likely to be younger than 20 years of age (Figure 2). Using case-based laboratory data, children 0-4 years of age accounted for, on average, 19.5% of reported influenza B cases (range 5.1% - 27.3%), and children and young adults 5 to 19 years of age accounted for 31.4% of influenza B cases (range 5.1% - 66.8%) during the 2001/02 to 2012/13 seasons (Table 2). When excluding the two seasons with minimal influenza B circulation (2003/04 and 2009/10), the average proportion increases slightly to 20.9% and 36.1% for those 0-4 and 5-19 years of age respectively.

Data on severe outcomes (e.g., hospitalization, ICU admission and death) is collected from hospital surveillance networks and from participating provincial and territorial epidemiologists. Influenza B was confirmed in 15.1% to 58.2% of paediatric influenza-associated hospitalizations (children ≤16 years of age) reported by IMPACT between 2004/05 and 2012/13 (excluding the 2009-2010 pandemic season). The proportion of children hospitalized with influenza B was generally similar to the proportion of influenza B detections in the general population (Table 1).

Data are available on adult hospitalizations for the 2010/11, 2011/12 and 2012/13 seasons. Adult hospital surveillance networks (Canadian Nosocomial Infection Surveillance Program [CNISP] from 2010-2012 and PCIRN-SOS in 2012/13) reported 9.3%, 54.1% and 7.7% of influenza-associated hospitalizations attributed to influenza B respectively. Over the same period, provincial and territorial aggregate reporting of all age groups identified 16.6%,
57.1%, and 13.7% of hospitalizations, and approximately 20-30% of ICU admissions associated with influenza B. In 2012/13, for which data on both age and influenza type were available, approximately 40% of hospitalizations associated with influenza B were in individuals <20 years of age, and 35% were in individuals ≥65 years of age. ICU admissions due to influenza B were highest in individuals ≥65 years of age (39%), followed by those 45 to 64 years of age (27%), with approximately 25% in individuals <20 years of age. Of the 317 influenza-associated deaths reported by participating provinces and territories from the 2010/11 to 2012/13 seasons, 6.3% were due to influenza B, and the majority (70%) were in individuals ≥65 years of age.

Table 1: Influenza B in Canada: Summary of Laboratory Testing and Hospitalizations

<table>
<thead>
<tr>
<th>Season</th>
<th>% of influenza B of total laboratory confirmed influenza cases</th>
<th>% of influenza B of total paediatric influenza hospitalizations</th>
<th>% of influenza B of total adult influenza hospitalizations</th>
<th>No. of B isolates tested by NML (%) of total influenza isolates</th>
<th>Predominant B lineage identified by NML</th>
<th>WHO recommended B lineage in vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVDSS</td>
<td>IMPACT</td>
<td>CNISP/PCIRN-SOS</td>
<td>WHO and NML</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001/02</td>
<td>12.9</td>
<td>-</td>
<td>-</td>
<td>152 (26.4)</td>
<td>Victoria</td>
<td>Yamagata</td>
</tr>
<tr>
<td>2002/03</td>
<td>40.2</td>
<td>-</td>
<td>-</td>
<td>128 (22.7)</td>
<td>Victoria</td>
<td>Victoria</td>
</tr>
<tr>
<td>2003/04</td>
<td>1.4</td>
<td>-</td>
<td>-</td>
<td>40 (4.7)</td>
<td>Yamagata</td>
<td>Victoria</td>
</tr>
<tr>
<td>2004/05</td>
<td>16.6</td>
<td>30.7</td>
<td>-</td>
<td>214 (19.0)</td>
<td>Yamagata</td>
<td>Yamagata</td>
</tr>
<tr>
<td>2005/06</td>
<td>39.4</td>
<td>38.1</td>
<td>-</td>
<td>472 (45.8)</td>
<td>Victoria</td>
<td>Yamagata</td>
</tr>
<tr>
<td>2006/07</td>
<td>12.8</td>
<td>15.3</td>
<td>-</td>
<td>119 (11.6)</td>
<td>Yamagata</td>
<td>Victoria</td>
</tr>
<tr>
<td>2007/08</td>
<td>42.5</td>
<td>36.9</td>
<td>-</td>
<td>673 (46.4)</td>
<td>Yamagata</td>
<td>Victoria</td>
</tr>
<tr>
<td>2008/09a</td>
<td>39.7</td>
<td>46.9</td>
<td>-</td>
<td>570 (42.5)</td>
<td>Victoria</td>
<td>Yamagata</td>
</tr>
<tr>
<td>2008/09b</td>
<td>0.3</td>
<td>1.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2009/10b</td>
<td>0.1</td>
<td>0</td>
<td>-</td>
<td>7 (0.8)</td>
<td>Victoria</td>
<td>Victoria</td>
</tr>
</tbody>
</table>
### Table 2: Proportion of influenza B laboratory detections of the total reported laboratory confirmed influenza cases by age group, RVDSS

<table>
<thead>
<tr>
<th>Season</th>
<th>0-4 yrs</th>
<th>5-19 yrs</th>
<th>20-44 yrs</th>
<th>45-64 yrs</th>
<th>65+ yrs</th>
<th>Age not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001-02</td>
<td>23.0%</td>
<td>54.5%</td>
<td>9.5%</td>
<td>4.0%</td>
<td>8.9%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2002-03</td>
<td>19.6%</td>
<td>66.8%</td>
<td>8.0%</td>
<td>4.0%</td>
<td>1.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2003-04</td>
<td>20.0%</td>
<td>10.0%</td>
<td>12.5%</td>
<td>17.5%</td>
<td>40.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2004-05</td>
<td>18.4%</td>
<td>21.9%</td>
<td>21.6%</td>
<td>12.7%</td>
<td>21.5%</td>
<td>3.8%</td>
</tr>
<tr>
<td>2005-06</td>
<td>21.5%</td>
<td>51.7%</td>
<td>16.2%</td>
<td>6.2%</td>
<td>4.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2006-07</td>
<td>18.8%</td>
<td>13.0%</td>
<td>24.1%</td>
<td>20.8%</td>
<td>23.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2007-08</td>
<td>16.6%</td>
<td>22.9%</td>
<td>17.2%</td>
<td>16.6%</td>
<td>26.3%</td>
<td>0.4%</td>
</tr>
<tr>
<td>2008-09</td>
<td>22.4%</td>
<td>44.0%</td>
<td>22.2%</td>
<td>5.7%</td>
<td>5.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>2009-10</td>
<td>5.1%</td>
<td>5.1%</td>
<td>2.6%</td>
<td>2.6%</td>
<td>33.3%</td>
<td>51.3%</td>
</tr>
<tr>
<td>2010-11</td>
<td>27.3%</td>
<td>35.7%</td>
<td>20.1%</td>
<td>7.1%</td>
<td>9.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2011-12</td>
<td>30.7%</td>
<td>20.9%</td>
<td>19.1%</td>
<td>10.5%</td>
<td>18.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>2012-13</td>
<td>20.2%</td>
<td>25.6%</td>
<td>17.4%</td>
<td>16.7%</td>
<td>20.0%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

aPrior to A/H1N1 pandemic (data up to April 11, 2009); b A/H1N1 pandemic; c Data obtained from CNISP; d Data obtained from PCIRN-SOS
Figure 1: Reported number of laboratory-confirmed influenza cases in Canada by season, RVDSS, 2001/02-2012/13, with pandemic data suppressed for influenza A (2009/10)
Figure 2: Number of laboratory-confirmed cases of influenza B, by age group and season, Canada, 2001/02-2012/13

Figure 3: Percentage of influenza B isolates tested by NML by lineage and season, NML, Canada, 2001/02 to 2012/13
IV. SEASONAL INFLUENZA VACCINES

IV.1 Preparations authorized for use in Canada

This section describes trivalent influenza vaccine preparations authorized for use in Canada as of the release date of this statement.

*Readers are referred to section V.3 Choice of Product / Quadrivalent Influenza Vaccine for all information related to quadrivalent influenza vaccine.*

Should additional vaccine preparations become available for use in Canada subsequent to the release of this statement and prior to the 2014-15 influenza vaccine season, NACI will communicate relevant information regarding the new vaccine preparations if required.

IV.1.1 Overview

There are eight seasonal trivalent influenza vaccines currently authorized for use in Canada, of which seven are inactivated and one is a live attenuated vaccine. In addition, there are two quadrivalent vaccines that are reviewed in Section V.3. The eight seasonal trivalent influenza vaccines are:

- Agriflu® (Novartis)
- Fluad® (Novartis)
- FluMist® (AstraZeneca) live attenuated vaccine
- Fluviral® (GlaxoSmithKline)
- Fluzone® (Sanofi Pasteur)
- Influvac® (Abbott)
- Intanza® (Sanofi Pasteur) 9 µg and 15 µg formulations
- Vaxigrip® (Sanofi Pasteur)

This statement describes the use of all eight trivalent vaccines. Further detail for Intanza®, FluMist®, and Fluad® may be found in supplementary NACI statements for each product. The antigenic characteristics of current and emerging influenza virus strains provide the basis for selecting the strains included in each year’s vaccine. All manufacturers that distribute influenza vaccine products in Canada confirm to the Biologics and Genetic Therapies Directorate of 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.

All products are manufactured by a process involving chicken eggs, which may result in the vaccine containing trace amounts of residual egg protein. Information on the management of egg allergic patients is provided in Section IV.3.1 of this statement. All influenza vaccines currently available in Canada are considered safe for use in persons with latex allergies.
The decision to include specific influenza vaccines as part of publicly-funded provincial and territorial programs depends on multiple factors such as cost-benefit evaluation and other programmatic and operational factors, for example shelf-life and implementation strategies. Not all products will be made available in all jurisdictions and availability of some products may be limited; therefore individual provinces and territories must be consulted regarding products available in that jurisdiction.

IV.1.2 Inactivated influenza vaccine

There are two main types of inactivated influenza vaccine; split virus vaccines 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.

The inactivated influenza vaccine products currently authorized for use in Canada are a mix of split virus and subunit vaccines, which are standardized to contain the same HA content. The amount of neuraminidase in the vaccines is not standardized.

One of the trivalent inactivated influenza vaccine products, Fluad®, contains 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. None of the other inactivated products contain an adjuvant.

One of the TIV products (Intanza®) is administered intra-dermally; the other inactivated products are administered intramuscularly.

IV.1.3 Live attenuated influenza vaccine (LAIV)

FluMist® is a live attenuated influenza vaccine for administration by intranasal spray and authorized for use in persons 2-59 years of age. Each 0.2 mL dose of FluMist®, (given as 0.1 mL in each nostril) contains $10^{6.5-7.5}$ fluorescent focus units (FFU) of live attenuated virus reassortants of each of three strains propagated in pathogen-free eggs. The influenza strains in FluMist® 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.

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. However, key relevant details and differences between products are highlighted in Table 3.
### Table 3: Characteristics of influenza vaccines authorized for use in Canada, 2014-2015

<table>
<thead>
<tr>
<th>Manufacturer and Product name</th>
<th>Abbott Influvac®</th>
<th>GSK Fluviral®</th>
<th>Novartis Agriflu®</th>
<th>Novartis Fluad®</th>
<th>Sanofi Pasteur Vaxigrip®</th>
<th>Sanofi Pasteur Fluzone®</th>
<th>Sanofi Pasteur Intanza®</th>
<th>AstraZeneca FluMist®</th>
<th>GSK Flulaval™ Tetra</th>
<th>Sanofi Pasteur Fluzone® Quadrivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine preparations</td>
<td>TIV</td>
<td>TIV</td>
<td>TIV</td>
<td>TIV</td>
<td>TIV</td>
<td>TIV</td>
<td>TIV</td>
<td>LAIV</td>
<td>QIV</td>
<td>QIV</td>
</tr>
<tr>
<td>Vaccine type</td>
<td>Inactivated - subunit</td>
<td>Inactivated - split virus</td>
<td>Inactivated - subunit</td>
<td>Inactivated - split virus</td>
<td>Inactivated - split virus</td>
<td>Inactivated - split virus</td>
<td>Live attenuated</td>
<td>Inactivated - split virus</td>
<td>Inactivated - split virus</td>
<td></td>
</tr>
<tr>
<td>Route of administration</td>
<td>IM</td>
<td>IM</td>
<td>IM</td>
<td>IM</td>
<td>IM</td>
<td>ID</td>
<td>Intranasal spray</td>
<td>IM</td>
<td>IM</td>
<td></td>
</tr>
<tr>
<td>Authorized ages for use</td>
<td>≥ 18 years</td>
<td>≥ 6 months</td>
<td>≥ 65 years</td>
<td>≥ 6 months</td>
<td>≥ 6 months</td>
<td>≥ 6 months</td>
<td>≥ 18 years</td>
<td>2-59 years</td>
<td>≥ 6 months</td>
<td>≥ 6 months</td>
</tr>
<tr>
<td>Antigen content (each of strains)</td>
<td>15 µg HA /0.5 mL dose</td>
<td>15 µg HA /0.5 mL dose</td>
<td>15 µg HA /0.5 mL dose</td>
<td>15 µg HA /0.5 mL dose</td>
<td>9 µg HA /0.1 mL (18-59 years)</td>
<td>15 µg HA /0.1 mL (60+ years)</td>
<td>10^6.5-7.5 FFU of live attenuated reassortants /0.2 mL dose given as 0.1 mL in each nostril</td>
<td>15 µg HA /0.5 mL dose</td>
<td>15 µg HA /0.5 mL dose</td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>MF59 (oil-in-water emulsion)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Formats available</td>
<td>Single dose pre-filled syringes with or without a needle</td>
<td>5 mL multidose vial</td>
<td>Single dose pre-filled syringes without a needle</td>
<td>Single dose pre-filled syringes without a needle</td>
<td>5 mL multidose vial, single dose ampoule, single-dose pre-filled</td>
<td>5 mL multidose vial, single dose ampoule, single-dose pre-filled</td>
<td>Single dose pre-filled syringes with micro-injection system</td>
<td>Prefilled single use glass sprayer</td>
<td>5 mL multidose vial</td>
<td>Single dose vials, single-dose pre-filled syringes without attached</td>
</tr>
<tr>
<td>Manufacturer and Product name</td>
<td>Abbott Influvac®</td>
<td>GSK Fluvar®</td>
<td>Novartis Agriflu®</td>
<td>Novartis Fluarad®</td>
<td>Sanofi Pasteur Vaxigrip®</td>
<td>Sanofi Pasteur Fluzone®</td>
<td>Sanofi Pasteur Intanza®</td>
<td>AstraZeneca FluMist®</td>
<td>GSK Fluvaval™ Tetra</td>
<td>Sanofi Pasteur Fluzone® Quadrivalent</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------</td>
<td>-------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>--------------------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Syringes with or without a needle</td>
<td>Syringes without a needle</td>
<td>Two formulations (as above)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post puncture shelf life for multi-dose vials</td>
<td>n/a</td>
<td>28 days</td>
<td>n/a</td>
<td>n/a</td>
<td>7 days</td>
<td>28 days</td>
<td>n/a</td>
<td>n/a</td>
<td>28 days</td>
<td>n/a</td>
</tr>
<tr>
<td>Thimerosal</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes - multi-dose vials only</td>
<td>Yes - multi-dose vials only</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Antibiotics (traces)</td>
<td>Gentamicin</td>
<td>None</td>
<td>Kanamycin</td>
<td>Neomycin</td>
<td>Kanamycin</td>
<td>Neomycin</td>
<td>Neomycin</td>
<td>Gentamicin</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Other clinically relevant non-medicinal ingredients*</td>
<td>Egg protein</td>
<td>Chicken protein</td>
<td>Formaldehyde</td>
<td>Sodium deoxycholate</td>
<td>Sucrose</td>
<td>Egg protein</td>
<td>Formaldehyde</td>
<td>Polysorbate 80</td>
<td>CTAB</td>
<td>Egg protein</td>
</tr>
<tr>
<td>* consult product monograph for complete listing of non-medicinal ingredients and excipients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CTAB (Cetyltrimethyl-ammonium bromide), FFU (fluorescent focus units), GSK (GlaxoSmithKline), HA (haemagglutinin), ID (intradermal), IM (intramuscular), LAIV (live attenuated influenza vaccine), TIV (Trivalent inactivated vaccine)
IV.2 Efficacy, effectiveness and immunogenicity

Vaccine efficacy (estimates of how well the vaccine works at preventing infection under ideal circumstances, as exist in a clinical trial) varies with the capability of the individual’s immune system (often affected by age, chronic diseases, medications, etc.), the match between the vaccine and circulating strains of virus, how efficacy and effectiveness is measured (laboratory-confirmed versus influenza-like illness), the laboratory test used (polymerase chain reaction, serology, culture), the case definition of illness, and the vaccine itself (inactivated versus live attenuated). Immunogenicity can be used in studies when a correlate of protection exists, such as serum hemagglutinin antibodies in the case of influenza. Immunogenicity against the strains included in the influenza vaccine is typically measured by comparing the pre-vaccination and post-vaccination hemagglutinin inhibition (HI) antibody titres, usually 21-28 days after vaccination.

IV.2.1 Efficacy and effectiveness

Multiple studies have shown that influenza vaccine is efficacious with higher efficacy demonstrated against laboratory-confirmed influenza than clinically defined outcomes\(^{(18)}\). 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% \(^{(19)}\)-(\(^{(37)}\)). Efficacy against serologically-confirmed influenza ranged from 54% to 63% and efficacy against clinical illness ranged between 33% to 36% \(^{(38)}\)-(\(^{(40)}\)). Vaccine efficacy against influenza-like illness was generally not well demonstrated in the studies included in the 2013 literature review in healthy children, although one of the six studies assessing this suggested vaccine efficacy of 68-85% against this outcome\(^{(19)}\)-(\(^{(21)}\)-(\(^{(23)}\)-(\(^{(27)}\)-(\(^{(31)}\)-(\(^{(41)}\)). Other studies have shown that LAIV is more efficacious than TIV in children. NACI has reassessed the data comparing efficacy of LAIV versus TIV in children and concludes that there is strong evidence in young children (up to six years of age) that LAIV protects better than TIV, with less evidence in older children\(^{(42)}\)-(\(^{(43)}\). Further details are available in the recommendation rationale for FluMist® in section V.3, the FluMist® Statement (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-7/index-eng.php) and Appendix 1 of the 2012-2013 Seasonal Influenza Vaccine Statement (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-2/appendix1-annexe1-eng.php).

In a systematic review of healthy adults, inactivated influenza vaccine efficacy against laboratory-confirmed influenza was estimated to be 80% (95% CI [56%,91%]) and vaccine effectiveness against influenza-like illness was estimated at 30% (95% CI [17%, 41%]) when the vaccine strain matched the circulating strains and circulation was high\(^{(44)}\). Two other studies found somewhat lower vaccine efficacy at 55% (95% CI [41%, 65%]) in the 2006-07 season\(^{(45)}\) and 68% (95% CI [46%, 81%]) in the 2007-08 season\(^{(46)}\). 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\(^{(47)}\)-(\(^{(49)}\).
In the elderly, vaccine effectiveness is about half of that in healthy adults and varies depending on the outcome measures and the study population\(^{(50)(51)}\). Systematic reviews have demonstrated that the influenza vaccine decreases the incidence of pneumonia, hospital admissions and deaths in the elderly \(^{(50)}\) and reduces exacerbations in persons with chronic obstructive pulmonary disease\(^{(52)}\).

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 \(^{(53)}\), hospitalizations for cardiac disease and stroke in the elderly \(^{(54)}\), and hospitalization and deaths in persons with diabetes mellitus 18 years of age and older\(^{(55)}\). 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\(^{(56)-(60)}\).

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. The included studies in 18-64 year olds covered nine influenza seasons and had a random-effects pooled vaccine efficacy of 59% (95% CI [51, 67]). The authors found no papers that met their inclusion criteria for TIV efficacy in children or in older adults. These authors found vaccine effectiveness was variable for seasonal influenza with six of 17 analyses in nine studies showing significant protection against medically attended influenza in the outpatient or inpatient setting. The pooled efficacy for LAIV in children was similar to other published data\(^{(61)}\). The author’s conclusions in this review may be subject to interpretation because of the restrictive inclusion criteria that were used to select evidence for this review. The NACI methodology uses broader inclusion criteria for available evidence, and thus, interpretation of evidence may vary from other reviews.

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

With the exception of LAIV, there is limited efficacy information for the newer vaccine products. While brief summaries are provided below, the individual NACI supplemental statements for Intanza®\(^{(15)}\) (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-4/index-eng.php), FluMist®\(^{(16)}\) (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-7/index-eng.php), and Fluad®\(^{(17)}\) (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-6/index-eng.php) should be consulted for details.

**TIV for intradermal use (TIV-ID) (Intanza®)**

The efficacy of Intanza® against laboratory-confirmed influenza and its serious complications has not been directly studied\(^{(15)}\).
LAIV (FluMist®)

A number of studies (LAIV versus placebo and LAIV versus TIV) have been conducted in children and adults. Two studies have directly compared the efficacy of LAIV and TIV in younger children (up to age 5 and 6) and one study has compared the efficacy of LAIV in asthmatic children 6 to 17 years of age. 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.

MF59-adjuvanted TIV (Fluad®)

The efficacy of Fluad® has not been directly studied, although a few observational studies suggest that it may be effective at reducing the risk of hospitalization for influenza and its complications in the elderly compared to unvaccinated individuals and those who received unadjuvanted subunit vaccine. However these studies have significant methodological limitations that make their interpretation difficult.

A Canadian observational study performed in British Columbia by Van Buynder et al. evaluated the comparative effectiveness of Fluad® to TIV in reducing laboratory confirmed influenza in the elderly. In the first year of the study (2011-2012 season), elderly people in 3 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, Fluad® effectiveness was 58% (95% CI: 5-82) and TIV effectiveness was 24% (95% CI: -129% to 75 %) (personal communication, P Van Buynder, December 2013). The study did not evaluate protection against hospitalization. As this study continued for a second year, further results will be discussed once published. The methodological limitations of this study should be taken into consideration when interpreting the results. NACI concludes there is insufficient evidence to make a recommendation for the preferential use of Fluad® over the other TIV products currently authorized for use in Canada.

IV.2.2 Immunogenicity

Intramuscular administration of TIV results in the production of circulating IgG antibodies to the viral haemagglutinin and neuraminidase proteins, as well as a more limited cytotoxic T lymphocyte response. Both humoral and cell-mediated responses are thought to play a role in immunity to influenza.

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.

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). As influenza viruses change over time, immunity conferred in one season will not reliably prevent infection by an antigenically drifted strain. For this reason, the antigenic components of the vaccine are reviewed and often change each year, and annual immunization is recommended. Even if the vaccine strains have not changed, immunity generally wanes within a year of receiving the vaccine and re-immunization reinforces optimal protection for the coming influenza season. Repeated annual administration of influenza vaccine has not been demonstrated to impair the immune response of the recipient to influenza virus.

Although the initial antibody response in elderly recipients may be lower to some influenza vaccine components, a literature review identified no evidence for a subsequent antibody decline that was any more rapid in the elderly than in younger age groups. 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. 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.

**MF59-adjuvanted TIV (Fluad®)**

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. 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. MF59 further facilitates the internalization of antigen by these dendritic cells. 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.

There is evidence from randomized controlled trials that Fluad® induces higher immunogenicity and broader cross-reactivity in adults 65 years of age and older as compared to the non-adjuvanted subunit vaccines. Furthermore, 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 Fluad® to split-virus vaccine generally compared it to a vaccine called Mutagrip®, which is not available in Canada. The one study that compared Fluad® to Vaxigrip® found similar seroprotection and seroconversion rates for H3N2 and a higher immune response for H1N1 and B for Fluad® recipients <75 years of age. For those 75 years of age and older, higher seroprotection and seroconversion rates were noted for all three strains in those receiving Fluad®. In a randomized
A clinical trial comparing Intanza® (intradermal TIV) to Fluar® in participants aged 65 years and older, non-inferiority of the intradermal vaccine compared with the adjuvanted vaccine was demonstrated for the A/H1N1 and B strains with the HI method and for all three strains with the single radial haemolysis (SRH) method (85).

A Canadian study conducted by PCIRN looked at the immunogenicity of Fluar® (Adjuvanted Trivalent Inactivated Vaccine: ATIV), Intanza 15® (TIV-ID) and Agriflu® (sub-unit TIV) in ambulatory seniors (≥65 years) living in the community (86). This randomized controlled study comprised 911 participants. For the B strain (Brisbane), the baseline antibody titers 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 haemagglutination inhibition assay (HAI), but not by SRH. For H3N2, seroprotection rates were significantly higher after ATIV than after other vaccines by both HAI and SRH, while rates did not differ significantly between TIV-ID and the sub-unit TIV. In the microneutralization (MN) assay, titers ≥40 to H3N2 were achieved more frequently after ATIV than after the other vaccines. GMTs were highest after ATIV for both A viruses. When immune responses were compared using criteria for licensing influenza vaccines in seniors, all 3 vaccines met the seroprotection criterion for each virus (both HAI and SRH assays). By HAI, ATIV and TIV-ID met the seroconversion and GM fold increase criteria for the A viruses. TIV did not meet the seroconversion criterion for H3N2. By SRH assay, the GM fold increase criterion was not met for any virus after TIV-ID or TIV but it was met for the A viruses after ATIV. While statistically significant, the differences in seroprotection rates and GMT ratios after ATIV or TIV were of modest magnitude. Whether this would result in greater protection against infection is not yet certain.

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

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

**TIV-ID (Intanza®)**

The skin is a potent immune organ and contains a larger number of antigen-presenting dendritic cells than muscle. Influenza antigen administered by the intradermal route has a high likelihood of being processed by local dendritic cells. Thus, the vaccine is thought to stimulate both cell-mediated immunity and antibody production. The intradermal product Intanza® has been shown to elicit an immune response that is comparable to TIV with or without adjuvant, administered by the intramuscular route, with some variation in results according to the serological method used (15). For further details, consult the Addendum to the 2010-2011 Seasonal Trivalent Inactivated Influenza Vaccine: Recommendations on the use of intradermal trivalent inactivated influenza vaccine (TIV-ID) (15) (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-4/index-eng.php).
LAIV (FluMist®)

LAIV (FluMist®), 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 LAIV is predictive of protection. However, efficacy studies have shown protection in the absence of a significant antibody response (16). 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 (16). For further details consult the rationale below and NACI supplemental statement for FluMist® (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-7/index-eng.php).

Paediatric considerations

The first time that children <9 years of age receive seasonal influenza immunization; a two-dose schedule is required to achieve protection (87)-(89). Several studies have looked at whether these two initial doses need to be given in the same season (3)(6)(90). 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 (3)(6). 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 (2)(6). Issues related to effective prime-boost when there is a major change in influenza B lineage across sequential seasons requires further evaluation (91). 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 (92)(93). This moderate improvement in antibody response without an increase in reactogenicity is the basis for the full dose recommendation for TIV for all ages. For more information, refer to Statement on Seasonal Influenza Vaccine for 2011-2012 (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-5/index-eng.php).

LAIV has generally been shown to be equally, if not more, immunogenic than TIV for all three strains in young children ≤ 6 years of age, whereas TIV was typically more immunogenic in adults than LAIV. There is less available evidence of LAIV superiority in children > 6 years of age.

Immunization with currently available influenza vaccines is not recommended for infants <6 months of age because of a lack of efficacy in this age group.
IV.3 Administration of influenza vaccine: dosage and schedule

With the variety of influenza vaccines that are now available, it is important for practitioners to understand and respect the specific differences in age indications, route of administration, dosage and schedule for the product(s) that they will be using. The recommended dosage schedule for the authorized products is presented in Table 4.

NACI recommends that children 6 to 35 months of age should be given a full dose (0.5 mL) of TIV or QIV as is recommended for older children and adults. The first time children 6 months to <9 years of age receive seasonal influenza vaccine, a two-dose schedule is required with a minimum interval of four weeks between doses. Eligible children <9 years of age who have previously received one or more doses of seasonal influenza vaccine should receive one dose per influenza vaccination season thereafter.

Vaccine administration practices are discussed in the Canadian Immunization Guide (http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php). 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. The recommended injection site for Intanza®, which is given intradermally using the supplied micro-injection device, is the deltoid region.

LAIV (FluMist®) is intended for intranasal administration only and should not be administered by the intramuscular or intradermal route. It is supplied in a pre-filled single use sprayer containing 0.2 mL of vaccine. Approximately 0.1 mL (half) is sprayed into the first nostril with the recipient upright, then the dose divider clip is removed and the remainder of the vaccine (0.1 mL) is sprayed into the other nostril.

Table 4: Influenza vaccine: Recommended dosage and route, by age, for the 2014-2015 Season

<table>
<thead>
<tr>
<th>Age group</th>
<th>TIV without adjuvant† or QIV IM</th>
<th>MF59-adjuvanted TIV (Fluad®) IM</th>
<th>TIV for intradermal use (Intanza®) ID</th>
<th>LAIV (FluMist®)* IN</th>
<th>Number of doses required</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–23 months</td>
<td>0.5 mLii</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 or 2**</td>
</tr>
<tr>
<td>2–8 years</td>
<td>0.5 mL</td>
<td>-</td>
<td>-</td>
<td>0.2 mL (0.1 mL per nostril)</td>
<td>1 or 2**</td>
</tr>
<tr>
<td>9-17 years</td>
<td>0.5 mL</td>
<td>-</td>
<td>-</td>
<td>0.2 mL (0.1 mL per nostril)</td>
<td>1</td>
</tr>
<tr>
<td>18-59 years</td>
<td>0.5 mL</td>
<td>-</td>
<td>0.1 mL (9 µg/strain)‡</td>
<td>0.2 mL (0.1 mL per nostril)</td>
<td>1</td>
</tr>
<tr>
<td>60-64</td>
<td>0.5 mL</td>
<td>-</td>
<td>0.1 mL (15 µg/strain)</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

---

† 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.

‡ 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.
STATEMENT ON SEASONAL INFLUENZA VACCINE FOR 2014-2015

<table>
<thead>
<tr>
<th>years</th>
<th>TIV=Trivalent inactivated vaccine</th>
<th>QIV=Quadrivalent inactivated vaccine</th>
<th>LAIV = Live attenuated influenza vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥65 years</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.1 mL (15 µg/strain)</td>
</tr>
</tbody>
</table>

TIV=Trivalent inactivated vaccine QIV=Quadrivalent inactivated vaccine LAIV = Live attenuated influenza vaccine

IM=Intramuscular ID=Intradermal IN = intranasal

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

*With respect to the live attenuated influenza vaccine, NACI recommends its use for healthy children and adolescents 2 to 17 years of age without contraindications. There is evidence for the preferential use of LAIV in young children (younger than 6 years of age) based on superior efficacy of LAIV compared to TIV (Grade A), with weaker evidence of superior efficacy in older children (Grade I). It is anticipated that the superior efficacy for LAIV over TIV extends beyond age 6 years, but the evidence does not indicate at which specific age the efficacies of LAIV and TIV become equivalent. If LAIV is not available for those for whom it is considered superior, TIV should be used.

**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.

‡ For adults with immune compromising conditions, the 15µg formulation should be considered to improve response.
IV.3.1 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 per usual – please see the Canadian Immunization Guide (http://www.phac-aspc.gc.ca/publicat/cig-gci/p01-09-eng.php). However, as with all vaccine administration, immunizers should have the necessary equipment to be prepared to respond to a vaccine emergency at all times.

Supporting this change in recommendation is work done by DesRoches et al. (2012)\(^{(94)}\) and Greenhawt et al. (2012)\(^{(95)}\). DesRoches et al. conducted two studies, a prospective cohort study (2010/2011 and 2011/2012 flu seasons), in 5 Canadian hospitals and a retrospective cohort study (2007/2008, 2008/2009 and 2009/2010 flu seasons) based out of one Canadian hospital. Recruitment included patients with egg-allergy, including severe allergy defined as the occurrence of anaphylaxis or cardiorespiratory symptoms upon egg ingestion. For both studies, patients were examined immediately before vaccination with Fluviral® and remained under observation for 60 minutes post-vaccination before being re-examined. Over the 5 influenza seasons, 457 doses of the seasonal TIV were administered to 367 patients, among whom 132 (153 doses) had a history of severe egg-allergy. Four patients reported mild allergic-like symptoms after previous influenza vaccination (1 urticaria, 2 vomiting, and 1 eczema), but none experienced an adverse event when given the current vaccine. While 13 patients developed mild allergic-like symptoms in the 24 hours following vaccination, none of the 367 patients developed anaphylaxis.

DesRoches et al. also conducted a literature review on egg-allergic patients who had been vaccinated. A total of 26 studies were found, representing 4729 doses of influenza vaccine administered to 4172 patients with egg allergy, of which 513 patients had been identified as having severe egg allergy. None of the 4172 patients experienced anaphylaxis post influenza immunization. For the 597 doses administered to the 513 patients with a history of severe allergic reaction to egg, the 95% CI of the risk of anaphylaxis was 0% to 0.62% \(^{(94)}\). Greenhawt et al. (2012), using inclusion criteria of a history of a severe reaction, including anaphylaxis, to the ingestion of egg and a positive skin test result or evidence of serum specific IgE antibody to egg, conducted a 2-phase multi-centre study in which phase 1 consisted of a randomized, prospective, double-blind, placebo control trial of TIV to egg-allergic children, using a 2-step approach in which group A received 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 \(^{(95)}\).

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

\(^{iii}\)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.
IV.4 Storage requirements

Influenza vaccine should be stored at +2°C to +8°C and should not be frozen. Refer to the individual product monographs for further details.

IV.5 Simultaneous administration with other vaccines

Studies have been done showing no interference when administering LAIV concomitantly with MMR, MMRV or oral polio vaccines (96)-(98). No studies have been done to assess the possibility of interference between LAIV and other live vaccines administered sequentially within a period shorter than 28 days. Based on expert opinion, NACI recommends that intranasal LAIV can be administered with or at any time before or after live attenuated or inactivated vaccines. No interference is expected with the administration of intranasal LAIV and parenteral live vaccines because the mucosa associated lymphoid tissue (MALT) is populated by B cells, T cells and accessory cells that are phenotypically and functionally distinct compared to the systemic lymphoid tissue that responds to parenteral vaccines. Interference is also not expected with the administration of intranasal LAIV and live oral vaccines, as mucosal immune responses also demonstrate a high level of compartmentalization between separate mucosal sites (nasal versus oral) as a result of strong restrictions on lymphoid cell recirculation (99).

The administration of LAIV with or at any time before or after live attenuated or inactivated vaccines is a change from the 2012-2013 influenza statement, in which specific timing rules applied to LAIV and other live vaccines. Note that the timing rules related to two parenteral live vaccines still apply. For more information regarding vaccination administration timing rules, please refer to the Canadian Immunization Guide (http://www.phac-aspc.gc.ca/publicat/cig-gci/p01-09-eng.php).

When multiple injections are given at one clinic visit, it is preferable to administer them in different limbs. If this is not possible, 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, according to the Canadian Immunization Guide (100).

IV.6 Adverse events

Inactivated Influenza Vaccines

Inactivated influenza vaccination cannot cause influenza because the vaccine does not contain live virus. With IM products, soreness at the injection site lasting up to two days is common in adults but rarely interferes with normal activities. 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 local reactions, primarily soreness at the vaccination site, occur in ≤7% of healthy children who are <3 years of age. Post-vaccination fever may be observed in ≤12% of immunized children 1 to 5 years of age.
The multidose formulations of inactivated influenza vaccine that are authorized for use in Canada contain minute quantities of thimerosal, which is used as a preservative\(^{(101)}\).\(^{(102)}\). 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\(^{(103)}\). 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 TIV (and LAIV) are thimerosal-free.

Oculorespiratory syndrome (ORS), defined as the onset of bilateral red eyes, and/or respiratory symptoms (cough, wheeze, chest tightness, dyspnea, dysphagia, hoarseness or sore throat), and/or facial swelling occurring within 24 hours of influenza immunization was reported following receipt of TIV during the 2000–2001 influenza season\(^{(104)}\). Since that time, fewer cases have been reported. Although the pathophysiologic mechanism underlying ORS remains unknown, it is considered distinct from an IgE-mediated 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. For further details on ORS, consult CCDR 2005 Volume 31 (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/05vol31/dr3121a-eng.php).

**MF59-adjuvanted TIV (Fluad®)**

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

In subsequent influenza seasons, rates of local and systemic reactions are similar for Fluad® following re-immunization. The proportion of serious adverse events is comparable between Fluad® and comparator vaccines\(^{(17)}\).

**TIV-ID (Intanza®)**

TIV-ID (Intanza®) produces more frequent and more extensive erythema, swelling, induration and pruritus than vaccine given by the IM route. These reactions are generally mild and resolve spontaneously within a few days. Systemic reactions following Intanza® are comparable to IM vaccine, except for myalgia which is less common with Intanza®. For further details, consult the NACI Intanza® addendum\(^{(15)}\).

**LAIV (FluMist®)**

LAIV (FluMist®) is made from attenuated viruses that are able to replicate efficiently only at temperatures in the nasal mucosa. The most common adverse events experienced by LAIV recipients are nasal congestion and coryza. In a large efficacy trial, wheezing occurred in LAIV recipients at rates above those in TIV recipients only in children <24 months of age\(^{(16)}\).
Studies on FluMist® have shown that vaccine virus can be recovered by nasal swab in children and adults following vaccination (i.e. “shedding”). The frequency of shedding decreases with increasing age and time since vaccination. Shedding is generally below the levels needed to transmit infection, although in rare instances, shed vaccine viruses can be transmitted from vaccine recipients to unvaccinated persons. For more detailed information on LAIV and viral shedding, consult the NACI FluMist supplemental statement (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-7/index-eng.php)\(^{(16)}\).

Other vaccine safety considerations

Allergic responses to influenza vaccine are a rare consequence of hypersensitivity to some vaccine components. Please refer to the Canadian Immunization Guide\(^{(100)}\) for further details about administration of vaccine and management of adverse events, including anaphylaxis.

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 Guillain-Barré Syndrome (GBS). However, evidence was inadequate to accept or reject a causal relation between GBS in adults and seasonal influenza vaccination\(^{(105)}\). More recent studies suggest that the absolute risk of GBS in the period following seasonal and A(H1N1)pdm09 influenza vaccination is about one excess case per 1 million vaccines\(^{(106)-(107)}\), which is consistent with a 2013 study by Kwong et al.\(^{(108)}\). This self-controlled study, which explored the risk of GBS after seasonal influenza vaccination and influenza health-care encounters (a proxy for influenza illness), found the attributable risks were 1.03 GBS admissions per million vaccinations, compared with 17.2 GBS admissions per million influenza-coded health-care encounters. These observations demonstrate that both influenza vaccines and influenza illness are associated with small attributable risks of GBS, although the risk associated with influenza infection is larger than that associated with vaccination. Kwong found that the risk of GBS after vaccination was highest during weeks 2-4, whereas for influenza illness, the risk was greatest within the first week after a health-care encounter and remained high for up to 4 weeks. The risk of GBS associated with influenza vaccination must be balanced against the risk of GBS associated with influenza infection itself and all the other benefits of influenza vaccination\(^{(109)-(113)}\).

IV.7 Contraindications and Precautions

IV.7.1 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 (See Section IV.3.1).

For more information on vaccine safety and anaphylaxis, please see the Canadian Immunization Guide (http://www.phac-aspc.gc.ca/publicat/cig-gci/p02-eng.php).

Additional LAIV (FluMist®) - specific contraindications

FluMist® should not be administered to:
- Children <24 months of age due to increased risk of wheezing.
- Individuals with severe asthma (as defined as currently on oral or high dose inhaled glucocorticosteroids or active wheezing) or those with medically attended wheezing in the 7 days prior to vaccination.
- Children and adolescents (2-17 years of age) currently receiving acetylsalicylic acid or acetylsalicylic acid-containing therapy because of the association of Reye's syndrome with acetylsalicylic acid and wild-type influenza infection. It is recommended that acetylsalicylic acid-containing products in children <18 years of age be delayed for four weeks after receipt of FluMist®.
- 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 nursing mothers.
- Persons with immune compromising conditions, due to underlying disease, therapy or both, as the vaccine contains live attenuated virus.

### IV.7.2 Precautions

Prior to the administration of influenza vaccine, it is important to consider the following precautions including allergic reactions to previous vaccine doses, oculorespiratory syndrome (ORS), and severe acute illness with or without fever.

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, dyspnea) within 24 hours of influenza vaccination, an apparent significant allergic reaction to the vaccine or any other symptoms (e.g., throat constriction, dysphagia) that raise concern regarding the safety of re-immunization. This advice may be obtained from local medical officers of health or other experts in infectious disease, allergy, immunology, public health or any combination of these specialties.

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.

Individuals who have experienced ORS - including those with a severe presentation (bilateral red eyes, cough, sore throat, hoarseness, facial swelling) but without lower respiratory tract symptoms - may be safely re-immunized with influenza vaccine. Advice of an expert should be sought before vaccinating persons who experienced ORS with lower respiratory tract symptoms. For more information on ORS see Oculo-respiratory syndrome following influenza vaccination: Review of post-marketing surveillance through four influenza seasons in Canada (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/05vol31/dr3121a-eng.php). Health care providers who are unsure whether an individual previously has experienced ORS versus an IgE-mediated hypersensitivity immune response should seek advice.

Although, as noted in section IV.6 of this statement, the evidence considering influenza vaccination and GBS was 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.

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 could be deferred until resolution of the illness.

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.

**Additional LAIV (FluMist®) - specific precautions**

FluMist® vaccine recipients should avoid close association with persons with severe immune compromising conditions (e.g., bone marrow transplant recipients requiring protective isolation) for at least two weeks following vaccination, because of the theoretical risk for transmission of the vaccine virus to the immunocompromised person.

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

**IV.8 Surveillance of adverse events following immunization**

Post marketing surveillance of adverse events following immunization (AEFIs) can provide important safety data on vaccines authorized for use, including the identification of previously unknown AEFIs, an increase in the frequency or severity of previously identified vaccine-related reactions or both. In Canada, post market safety data are collected through passive surveillance systems, with data reported on a voluntary basis. AEFI reports are captured in the Canadian Adverse Event Following Immunization Surveillance System (CAEFISS).

CAEFISS also has an active surveillance component conducted by a paediatric hospital-based surveillance program known as IMPACT (Immunization Program Monitoring Program ACTive). It is important to understand that, although such systems provide important information for safety signals, the reporting of an AEFI does not imply causality and in the majority of cases causality cannot be established. In addition, since the size of the population at risk cannot be determined and not all AEFIs are reported, it is not possible to use passive surveillance data to estimate the incidence of AEFIs.

Data from CAEFISS have shown seasonal influenza vaccines to have a safe and stable AEFI profile with no unexpected events. One exception was a notable signal in 2000/2001 related to ORS as noted in IV.6 above. The number and type of AEFI reports received for influenza vaccines administered in 2012/2013 season was similar to that of previous seasons. Early in the 2012/2013 season, distribution of Agriflu® and Fluad® in Canada was temporarily suspended
as a precautionary measure following reports of clumping of particles in the vaccine in Europe. A review by Health Canada found no safety issues and the products were released for use across Canada. No signal in CAEFISS has been detected for these or other influenza vaccines and the safety profile is consistent with that of past seasons.

V. RECOMMENDATIONS

V.1 General considerations

Health care providers 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 resources.

Although vaccination before the onset of the influenza season is preferred, vaccine may still be administered up until the end of the season. 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.

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

V.2 Recommended recipients

Current influenza vaccines authorized for use in Canada are immunogenic, safe and associated with minimal side effects. Influenza vaccine may be administered to anyone ≥6 months of age who does not have any contraindications.

Recent literature reviews conducted by NACI have shown that healthy individuals aged 5-64 years benefit from influenza vaccination. With evidence showing that influenza vaccine benefits people of all ages, NACI now recommends influenza vaccination for all individuals 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 5.

With respect to indirect protection, meaning protection of other groups or individuals in contact with the vaccinated individuals, NACI has reviewed evidence in school aged children. While some studies showed indirect protection, others did not. The decision to include specific groups as part of publicly-funded provincial/territorial programs depends on multiple factors such as cost-benefit evaluation and other programmatic and operational factors, such as shelf-life and implementation strategies.

NACI has not reviewed evidence for the benefit of immunizing healthy 5 to 64 years old at the population level (for example publicly-funding influenza vaccine for these groups or for universal programs). Additional evidence such as more extensive data on burden of illness, cost-effectiveness, programmatic aspects and program objectives should be reviewed to better
inform decisions at the provincial or local level with respect to publicly funding influenza vaccine for healthy 5 to 64 year olds or implementing universal influenza immunization programs.

To reduce the morbidity and mortality associated with influenza, immunization programs should focus on those at high risk of influenza-related complications, those capable of transmitting influenza to individuals at high risk of complications (see Table 5) and those who provide essential community services. These groups remain the priority for influenza vaccination programs in Canada.

NACI also recommends immunization against seasonal influenza for people in direct contact with poultry infected with an avian influenza during culling operations; 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 (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/13vol39/acs-dcc-4/index-eng.php).
Table 5: Influenza vaccination is particularly recommended for the following groups:

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

- Adults (including pregnant women) and children with the following chronic health conditions:
  - cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma);
  - diabetes mellitus and other metabolic diseases;
  - cancer, immune compromising conditions (due to underlying disease and/or therapy);
  - renal disease;
  - anemia or hemoglobinopathy;
  - conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration;
  - morbid obesity (BMI ≥40); and
  - children and adolescents (age 6 months to 18 years) with conditions treated 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.

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

- Aboriginal Peoples.

### People capable of transmitting influenza to those at high risk

- Health care and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk of influenza complications.

- Household contacts (adults and children) of individuals at high risk of influenza-related complications (whether or not the individual at high risk has been immunized):
  - household contacts of individuals at high risk, as listed in the section above;
  - household contacts of infants <6 months of age as these infants are at high risk of complications from influenza but cannot receive influenza vaccine; and
  - 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.

V. 2.1 People at high risk of influenza-related complications or hospitalization

Adults (including pregnant women) and children with chronic health conditions as noted in Table 5.

A number of chronic health conditions, as noted in Table 5, are associated with increased risk of influenza-related complications and influenza can lead to exacerbation of the chronic disease.

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 (115), and mortality rates increase with increased age (13).

All children 6 to 59 months of age.


Pregnant women

NACI recommends the inclusion of all pregnant women, at any stage of pregnancy, among high priority recipients of influenza vaccine due to the risk of influenza-associated morbidity in pregnant women (116)-(120), evidence of adverse neonatal outcomes associated with maternal respiratory hospitalization or influenza during pregnancy (121)-(124), evidence that vaccination of pregnant women protects their newborns from influenza and influenza-related hospitalization (125)-(128), 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 (129)-(132).
The safety of influenza vaccine during pregnancy has been reviewed (133). Active studies of influenza vaccination during pregnancy have not shown evidence of harm to the mother or fetus associated with influenza immunization (134). 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 influenza vaccine in pregnancy over several decades (116)(117)(133)(135). 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 (136)(137).


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 high-priority 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) (138) obesity, delayed access to health care and increased susceptibility to disease because of poor housing and overcrowding (139)(141). For further details on the evidence reviewed to inform this recommendation see the Statement on Seasonal Influenza Vaccine for 2011-2012 (http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-5/index-eng.php).

V.2.2 People Capable of Transmitting Influenza to Those at High Risk of Influenza-Related Complications or Hospitalization

People who are potentially capable of transmitting influenza to those at high risk should receive annual vaccination, regardless of whether the high-risk 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 (142)-(148). Immunization of care providers and residents is associated with decreased risk of ILI outbreaks (149). 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 care providers in facilities and community settings

This group includes health care workers, regular visitors, emergency response workers, those who have contact with residents of continuing 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, health care workers include any person, paid or unpaid, who provides services, works, volunteers or trains in a health care setting. For more information regarding immunization of health care workers, please refer to section VI of this document.

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

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

**Those providing regular child care to children ≤59 months of age whether in or out of the home**

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

**V.2.3 Others**

**People who provide essential community services**

Vaccination for these individuals should be encouraged in order to minimize the disruption of services and routine activities during annual epidemics. Employers and their employees, including healthy working adults, should consider yearly influenza immunization, as this intervention has been shown to decrease work absenteeism due to respiratory and related illnesses.

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

These individuals may be at increased risk of avian influenza infection because of exposure during the culling operation \(^{150}-^{153}\). Although seasonal influenza immunization will not prevent avian influenza infection, some countries \(^{154}\) and provinces, have recommended influenza immunization on a yearly basis for these workers based on the rationale that preventing infection with human influenza strains may reduce the theoretical potential for human-avian reassortment of genes should such workers become co-infected with human and avian influenza viruses \(^{155}\). It should be noted that vaccination with seasonal influenza vaccine will not produce protective antibodies against the human vaccine strains for approximately 14 days.

Direct involvement may be defined as sufficient contact with infected poultry to allow transmission of an avian virus to the exposed person. The relevant individuals include those performing the cull, as well as others who may be directly exposed to the avian virus, such as supervising veterinarians and inspectors. It is essential that biosecurity measures such as personal protective equipment and antivirals be used. For further information regarding recommendations during a domestic avian influenza outbreak, see the Agency guidance at http://www.phac-aspc.gc.ca/publicat/daio-enia/pdf/nat-ai-guide-2006_e.pdf.
Recent literature reviews conducted by NACI have shown that healthy individuals aged 5 to 18 years benefit from influenza vaccination. The review examined the burden of disease, efficacy, effectiveness, safety and immunogenicity of influenza vaccine in healthy 5-18 year olds and found that the burden of influenza infection, illness and complications in children is significant. Although children <5 years of age experience higher rates of morbidity and mortality compared to healthy children aged 5-18 years, IMPACT surveillance data from the 2004-05 through to the 2011-12 influenza seasons show that the proportion of children aged 5-16 years hospitalized for influenza infections, out of all children (0 to 16 years of age) hospitalized for influenza infections, ranged between 24% to 51%, depending on the season. One study in this literature review found that hospitalization rates per 10,000 children declined with age, with the highest rates in children less than 1 year of age at 8 per 10,000 children, followed by 1-4 years of age at 1.8 per 10,000, 5-8 years of age at 1.6 per 10,000, 10-14 years of age at 1 per 10,000, and 15-19 years of age at 0.2 per 10,000. Using IMPACT data from the 2003-04 season, one study found that 84% of children admitted with laboratory confirmed influenza were under five years of age but that the percentage requiring ICU admission was higher in children ≥5 years old than in younger children (21.9% versus 9.9%; OR: 2.55 95% CI [1.32, 4.90]), as was the percentage requiring mechanical ventilation (12.2% versus 5.0%; OR: 2.66; 95% CI [1.11, 6.24]). The percentage of children with influenza with underlying illness was higher in children ≥5 years old than in younger children (80.5% versus 34.5%; OR: 7.83 95% CI [4.24-14.63]) but percentages of ICU admissions and mechanical ventilation did not differ significantly between previously healthy children and those with an underlying condition or illness. In logistic regression, age >5 years remained an independent risk factor for ICU admission after adjustment for underlying illness (OR: 2.347; 95% CI: 1.21-4.57).

One study in this review found that the rate of outpatient visits for acute respiratory diseases during periods in which influenza predominated over other respiratory diseases among healthy children 5-17 years of age was 6.7 (95% CI [6.6, 6.9]) per 100 person-months compared to 3.6 (95% CI [3.4, 3.7]) per 100 person-months during the summer baseline period. Another study that looked at age-related trends in influenza medical visits found that older school-aged children (10 to 19 years of age) had the lowest peak rates of influenza-related medical visits at 0.3 per 1000 people) compared to younger age groups. Studies that looked at influenza-associated deaths found that death due to influenza is not a common occurrence in the 5-18 year old age group.

The literature review of persons 5-18 years of age found that overall efficacy/effectiveness of TIV against laboratory-confirmed influenza in children within this age group was frequently in the range of approximately 65-85%, although not all studies presented vaccine efficacy results against “any influenza” as opposed to against one or more individual components.

Efficacy/effectiveness of LAIV vaccination against laboratory-confirmed influenza was less strongly demonstrated in the studies meeting the review’s inclusion criteria of healthy children, and was <40% in all but one study included. Vaccine efficacy (VE) of TIV against influenza-like illness was generally low in the studies included in this review, although one of the 6 studies assessing this suggested high VE (68-85%) against this outcome. This study, however, may have suffered from selection bias, as 64% of non-vaccinees were categorized as “healthy”, compared to 78% or 77% in the vaccine recipients of 1- or 2-dose, respectively. In the literature review, there were few LAIV studies with a high-clinical value (RCT being the
highest) and high quality rating specific to the 5-18 year-old age group that provided efficacy and effectiveness data of LAIV against lab-confirmed influenza (29)(162)-(170).

In a single RCT with subjects predominantly from this age group, a VE of <70% was estimated over two seasons with circulating H3N2 and a VE of >90% was estimated over two seasons with circulating H1N1; however the vaccine used was a 1980’s pre-licensure research lab-produced LAIV, which differed from the current, commercially available LAIV (29). A non-randomized community-based controlled trial specific to 5-18 year olds suggested a much lower vaccine effectiveness (~37%) (162), as did a retrospective study comparing an intervention and control community both before and after the introduction of a school-based vaccination program. The crude seasonal vaccine estimates from this study ranged from non-significant in some years to 56% in others (163). Regarding vaccine effectiveness against medically attended acute respiratory illness (MAARI) as an outcome, different analytic approaches and seasons of the multi-year Central Texas Trial did not always report on or demonstrate direct vaccine effectiveness of LAIV; when a significant vaccine effectiveness was reported it did not exceed 31% in 5-9 year olds or 24% in 10-18 year olds (162)(166)-(168)(171)(172). In one of the study years, authors noted these levels of protection, despite a strain mismatch in the vaccine, relative to the circulating H3N2 virus, and an unexpectedly early influenza season arrival that coincided with the vaccination campaign. Effectiveness of LAIV against school absenteeism was shown in a number of studies.

The literature review of persons 5-18 years of age considered studies of the indirect efficacy and effectiveness of TIV on other community or family members and found that they included positive and negative findings. The studies that looked at indirect effectiveness of LAIV were unable to demonstrate any reductions in lab-confirmed influenza and no or low (6-15%) reductions in MAARI rates of communities or of specific age groups within them; however it was not clear that the small reductions in MAARI rates were attributable to herd effects from school children vaccination (162)(164)(166)(167)(171)(173).

Three randomized, controlled trials, one nonrandomized trial and one post-marketing open-label clinical trial related to immunogenicity of TIV and for LAIV were included in the literature review of persons 5-18 years of age (68)(174)-(179). Together they confirmed that seasonal influenza vaccine is immunogenic in children 5-18 years of age.

Nine studies considering reactogenicity and adverse events to TIV and seven to LAIV were included in the literature review of persons 5-18 years of age (29)(88)(173)(174)(176)-(178)(180)-(187). No new or unexpected adverse events of concern were identified and both TIV and LAIV were considered safe and well tolerated in this age group.

**Healthy persons 19 to 64 years of age**

Recent literature reviews conducted by NACI have shown that healthy individuals aged 19 to 64 years benefit from influenza vaccination.

Influenza is ranked among the top 10 infectious diseases affecting the Canadian population (188). A meta-analysis, using data from observational studies and randomized trials, estimated that the incidence of influenza in working-aged adults ranges from 1.2% (95% CI [0.9%, 1.7%]) for those who were vaccinated to 9% (95% CI [6%, 14%]) for those who were unvaccinated (189). The highest incidence was reported for unvaccinated adults exposed to children at 24% (95% CI [15%, 39%]). Only a fraction of people with influenza seek medical attention for their illness.
with the propensity to seek care dependent upon the severity and duration of symptoms, underlying health conditions, and other factors. Administrative data from Canadian sources indicated that an average of 3.0% of adults 20-49 years old and 4.0% of adults 50-64 years old visited a physician’s office or emergency room annually for pneumonia- or influenza-related illnesses between 1997 and 2004 (190).

The number of Canadian adults hospitalized for influenza-related illness also varies considerably, depending on the source of data. A review of hospital discharge data for Canada showed that an average of 93 and 313 hospital stays annually per 100,000 Canadians aged 20-49 and 50-64 years, respectively, were attributable to influenza or pneumonia for 1997-98 through 2003-04 (190). The mortality rate due to influenza is much lower for adults 19-64 years of age than it is for very young children or people 65 years and older. It has been estimated that an average of 3500 deaths per year were attributable to influenza. Of these, about 150-160 deaths due to influenza occur every year in adults 50 to 64 years of age (about 1.8 per 100,000), with significantly fewer deaths in younger adults (13).

The literature review of persons 19-64 years of age found vaccine efficacy of TIV against laboratory confirmed influenza varied somewhat by year and study, with lower efficacy estimates in seasons of low attack rates and a mismatch between the vaccine and circulating virus strains. Vaccine efficacy estimates of 55% (95% CI [41, 65]) were noted in the 2006-07 season and 68% (95% CI [46, 81]) in the 2007-08 season (45). Vaccine efficacy estimates for LAIV in this age group ranged from 7.5% (95% CI [-194, 67]) in the 2005-06 season with low attack rates and low efficacy estimates for TIV, to 48% (95% CI [-7, 74]) in the 2004-05 influenza season and 36% during the 2007-08 season in healthy adults in the USA. The comparative studies examined in this review that looked at TIV versus LAIV found an estimated reduction in laboratory-confirmed influenza for people receiving TIV over those receiving LAIV (53% in the 2003-04 season, 9% in the 2005-06 and 50% in 2006-07). Vaccine effectiveness estimates of TIV using ILI as the outcome in studies identified for this review ranged from 14% (95% [7, 20]) in 1996-97 to 34% in the 1998-99 influenza season. One study estimated the effectiveness of LAIV in healthy adults over three seasons using ILI as their outcome and found the estimates to be lower than the estimates for TIV effectiveness from the same study. In studies that looked at the relative effectiveness of TIV and LAIV using healthcare encounters for ILI as the outcome, no differences were found when the ILI definition was broad; however a 20% reduction in ILI for TIV compared to LAIV was noted when the ILI definition was restricted to physician diagnosis of influenza.

The rate of seroprotection of TIV in healthy adults 19-64 years of age varied somewhat by vaccine component with an estimate range from 82% (95% CI [60,95]) (191) to 100% (95% CI [95, 100]) (192) for the A/H1N1 component, 63% (95% CI [51, 75]) (191) to 100% (95% CI [95, 100]) (192,193) for the A/H3N2 component and 56% (95% CI [51, 61]) (193) to 100% (95% CI [95, 100]) (192) for the B component. Participants 19-49 years of age in the studies reviewed tended to have a somewhat higher rate of seroprotection than people 50-64 years old. Two studies compared seroprotective rates in these age groups. No differences in rates of seroprotection against the A/H1N1 or A/H3N2 components were noted in either study. However, seroprotection against the B components were higher for younger people in both studies (194,195). The studies that looked at rates of seroprotection for adults 19-64 years of age using intradermal TIV found 90-100% of the participants were seroprotected to all three components following vaccination (196,197). In a study comparing seroprotective rates by age group, younger adults had higher rates of seroprotection than participants 50-64 years of age (195). Rates of seroconversion for TIV were found to be high for vaccine naïve participants. Lower rates of seroconversion were
noted for people with recent influenza vaccinations but they had correspondingly high rates of seroprotection. LAIV does not induce the same rates of seroprotection, as measured by HI antibody titres, as the inactivated vaccines and rates of HI antibody seroconversion are not reliable estimates of protection against infection for people receiving LAIV.

The literature review of persons 19-64 years of age considered several studies regarding vaccine safety and reactogenicity and noted no unexpected reactions to TIV, TIV-ID and LAIV.

**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 5.

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 have already been vaccinated in the preceding fall or winter with the Northern Hemisphere vaccine depends on individual risk assessment, the similarity or differences between the Northern and Southern hemisphere vaccines, and the availability of a reliable and safe vaccine at the traveller's destination.

**V.3 Choice of product**

With the recent authorization 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 6 summarizes NACI’s current recommendations for the choice(s) of currently available influenza vaccines in specific age and risk groups. More details along with brief supporting rationale are outlined in the following text.
Table 6: Choice of influenza vaccine for selected age and risk groups *(for persons without a contraindication to the vaccine)*

<table>
<thead>
<tr>
<th>Recipient by age group</th>
<th>Vaccine types available for use</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 6-23 months of age</td>
<td>TIV</td>
<td>Only TIV and QIV are available for this age group.</td>
</tr>
<tr>
<td></td>
<td>QIV*</td>
<td><strong>For recommendations regarding use of LAIV in healthy children and adolescents 2 to 17 years of age without contraindications, see note below the table.</strong></td>
</tr>
<tr>
<td></td>
<td>TIV</td>
<td>LAIV is not recommended for children with immune compromising conditions, see below.</td>
</tr>
<tr>
<td></td>
<td>QIV*</td>
<td>LAIV or TIV can be used in children with chronic health conditions, including non-severe asthma.</td>
</tr>
<tr>
<td>Children 2-17 years of age</td>
<td>TIV</td>
<td>TIV, QIV and TIV-ID are the preferred products for adults with chronic health conditions.</td>
</tr>
<tr>
<td></td>
<td>QIV*</td>
<td>For adults with immune compromising conditions:</td>
</tr>
<tr>
<td></td>
<td>TIV-ID (9 µg)</td>
<td>• LAIV is not recommended.</td>
</tr>
<tr>
<td></td>
<td>LAIV</td>
<td>• TIV-ID 15 µg formulation can be considered.</td>
</tr>
<tr>
<td>Adults 18-59 years of age</td>
<td>TIV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QIV*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TIV-ID (15 µg)</td>
<td></td>
</tr>
<tr>
<td>Adults 60-64 years of age</td>
<td>TIV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QIV*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TIV-ID (15 µg)</td>
<td></td>
</tr>
<tr>
<td>Adults 65+ years of age</td>
<td>TIV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QIV*</td>
<td></td>
</tr>
</tbody>
</table>
STATEMENT ON SEASONAL INFLUENZA VACCINE FOR 2014-2015

<table>
<thead>
<tr>
<th>Pregnant women</th>
<th>TIV-ID (15 µg)</th>
<th>MF59-adjuvanted TIV</th>
<th>QIV*</th>
<th>TIV-ID (9 µg)</th>
</tr>
</thead>
</table>

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

*For QIV use, see section on Quadrivalent Influenza Vaccine below,

**LAIV: With respect to the live attenuated influenza vaccine, NACI recommends its use for healthy children and adolescents 2 to 17 years of age without contraindications. There is evidence for the preferential use of LAIV in young children (younger than 6 years of age) based on superior efficacy of LAIV compared to TIV (Grade A), with weaker evidence of superior efficacy in older children (Grade I). It is anticipated that the superior efficacy for LAIV over TIV extends beyond age 6 years, but the evidence does not indicate at which specific age the efficacies of LAIV and TIV become equivalent. If LAIV is not available for those for whom it is considered superior, TIV should be used.

Quadrivalent Influenza Vaccine

NACI recommends that, once available in Canada, quadrivalent vaccines, either inactivated or live attenuated vaccines, can be used (NACI recommendation grade A). The decision to include specific influenza vaccines as part of publicly-funded provincial and territorial programs depends on multiple factors such as cost-benefit evaluation and other programmatic and operational factors, for example shelf-life and implementation strategies. Not all products will be made available in all jurisdictions and availability of some products may be limited; therefore individual provinces and territories must be consulted regarding products available in that jurisdiction.

Two quadrivalent influenza vaccine products (Flulaval™ Tetra and Fluzone® Quadrivalent) are now authorized for use in Canada. These products are split-virion, inactivated vaccines that do not contain an adjuvant and are administered via the IM route. Neither product contains latex in its vial stopper/container closure system. Additional details regarding these vaccines can be found in the product monographs.

Relevant key points for use of these vaccines are noted here.

**Age authorized for use:** Six months and older

**Dose:** 0.5 ml for all ages (six months and older)

**Schedule:** As per other influenza vaccines: 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 <9 years of age receiving seasonal influenza vaccine for the first time should be given two doses, with a minimum interval of four weeks between doses.
**Use in children:** QIV can be used in children from 6 months of age and over. For children 2 years of age and older, NACI is assessing whether a trivalent LAIV, Quadrivalent LAIV or an inactivated QIV is likely to provide greater protection.

**Co-administration with other vaccines:** Based on expert opinion, NACI recommends that, as with all influenza vaccines, QIV may be given at the same time as or at any time before or after administration of other live attenuated or inactivated vaccines. For concomitant parenteral injections, different injection sites and separate needles and syringes should be used.

**Use in egg allergic individuals:** 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, NACI recommends that egg-allergic individuals may be vaccinated against influenza using QIV in the same manner as with TIV, i.e., 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. Waiting period post immunization would be as per usual – please see the Canadian Immunization Guide (http://www.phac-aspc.gc.ca/publicat/cig-gci/p01-09-eng.php). However, as with all vaccine administration, immunizers should have the necessary equipment to be prepared to respond to a vaccine emergency at all times.

**Use in pregnant women:** NACI recommends the inclusion of all pregnant women, at any stage of pregnancy, among high priority recipients of influenza vaccine due to the risk of influenza-associated morbidity in pregnant women. Based on the experience with TIV in pregnant women, it is NACI’s expert opinion that, as an inactivated vaccine, QIV can be used in pregnant women.

As influenza B occurs more frequently in children and adolescents, should both quadrivalent and trivalent influenza vaccines be available and the quadrivalent products be in a limited supply, consideration should be given to offer the quadrivalent products to this group. As studies with trivalent formulations have shown that in children up to 6 years old, the live attenuated vaccine has superior efficacy compared to the inactivated products, with less evidence in older children up to 17 years of age, consideration could be given to the quadrivalent live attenuated vaccine in this age group. There are no comparative efficacy studies available comparing Q-LAIV and QIV in children or other age groups at this time.

NACI has conducted a literature review of available information on quadrivalent influenza vaccines, which is available in a separate document. The following is a summary of some key points from that literature review. NACI has reviewed the immunogenicity and safety data for the quadrivalent vaccines that are currently produced by manufacturers who supply influenza vaccine in Canada: GlaxoSmithKline (GSK), 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 formulation. As expected, these studies showed that the immune response to the B strain found only in the quadrivalent formulation was better in subjects who received the quadrivalent vaccine. These findings were consistent across age groups and different types of vaccines (inactivated and LAIV).

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

In the Phase III trials, recipients of the trivalent formulations showed, although 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 CHMP and CBER guidelines and criteria including 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 (198).

The 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.

The burden of influenza B disease in Canada warrants further research. NACI reviewed the available sources of epidemiologic data regarding influenza B. Characterization of laboratory confirmed influenza has shown that the percentage of B strains out of the total cases is quite variable from one season to the next (average 17% range 0.1% to 53%). As indicated in section III.2.1 (Figure 3), in about half of the influenza seasons that occurred over the past 10 years, there has been a mismatch between the predominant circulating strain of influenza B and the vaccine strain. Individuals who have influenza B are more likely to be younger than 20 years of age.

The proportion of hospitalizations due to influenza B has been generally similar to the proportion of influenza B detections in the general population over the past ten years. For the 2010/2011 to 2012/13 seasons for which there are data from the paediatric and adult surveillance networks, 30-58% of paediatric influenza-related hospitalizations were attributable to influenza B, whereas 8%-54% of adult influenza-related hospitalizations were attributable to influenza B infection.

There is insufficient data on the absolute number and rate of influenza B related hospitalizations by age group in Canada. However, data on the absolute number and rate of overall influenza-related hospitalizations has demonstrated that there is a greater burden of influenza illness requiring hospitalization in adults than in children. Aggregate reporting from participating provinces and territories identified 7,152 influenza-related hospitalizations (for influenza A and B) in adults (≥20 years of age) and 2,625 hospitalizations (for influenza A and B) in children (<20 years) between the 2010/11 and 2012/13 seasons. The Canadian studies by Schanzer et al (2006, 2008) estimated that from 1994/95 through 1999/2000, there were 12-24 per 100,000 paediatric influenza-attributable hospital admissions per year, and 60-80 per 100,000 adult
admissions per year. This suggests that while the proportion of influenza B-related hospitalizations is higher in children, there is also a significant burden of influenza B illness in adults.

Mortality attributable to influenza follows a similar trend in both paediatric and adult populations with more influenza deaths in adults, but a higher proportion of influenza-related deaths in children being attributable to influenza B.

Between the 2004/05 and 2012/13 seasons, including the 2009/10 pandemic season, 5,309 children ≤16 years of age with available information on influenza type and underlying medical conditions were hospitalized at participating IMPACT sites. Influenza B was identified in 28% of total influenza-related hospitalizations and 50% of influenza-related deaths (n=18). Healthy children (without any underlying medical condition) with influenza B were identified in an average of 12.5% (range 8.2%-26.5%) of the total influenza-related hospitalizations. Approximately 60% of healthy children hospitalized with influenza B were <5 years of age. On average, healthy children accounted for one third of influenza-related ICU admissions, of which one third of the influenza-related ICU admissions involving healthy children were due to influenza B.

Information on underlying medical conditions collected by IMPACT is separated into two categories: conditions for which influenza immunization has been recommended by NACI (i.e. NACI risk factors for influenza), and other underlying medical conditions (i.e. non-risk factors for influenza).

The proportion of hospitalizations and ICU admissions for children with NACI risk factors for influenza is reported below. Excluding the 2009/10 pandemic season for which underlying medical conditions were not classified into the two categories, an average of 14% (range 5-26%) of the total influenza hospitalizations were children with influenza B and at least one underlying NACI risk factor for influenza. Half of the children with influenza B and an underlying NACI risk factor for influenza were <5 years of age. Approximately 16% of all hospitalized children with influenza and an underlying NACI risk factor for influenza were admitted into the ICU, and one third of these were due to influenza B.

Considering the burden of disease associated with influenza B, it appears that the quadrivalent formulations would provide greatest benefit to paediatric populations. In a study by Skowronska et al., children primed with influenza vaccine containing B/Yamagata-lineage antigen who later received annual TIV doses containing B/Victoria-lineage antigen strongly recalled antibodies to the B/Yamagata antigen of first exposure, but elicited lower B/Victoria responses. Extrapolating from this study, this result furthers the consideration that should be given to offering QIV to children, should this product be in limited supply.

Quadrivalent vaccines would also be of benefit when there is a mismatch between the B strain in the trivalent vaccine formulation and the dominant circulating B strain. To quantify the added benefits of using QIV over TIV with more precision, economic analyses that factor in different scenarios would be needed. It has been hypothesized that the potential net impact of QIV on influenza-associated outcomes would fluctuate from season to season, with the incidence of influenza caused by the two B strains, and with QIV vaccine coverage, and its effectiveness. The addition of the second B strain could result in modest reductions in influenza-associated outcomes.
The literature review that was conducted by NACI did not find any data on QIV administration in pregnant women, in persons allergic to eggs, or concerning co-administration of other vaccines with QIV. Given the burden of disease, the immunogenicity and the safety data available for quadrivalent vaccines, NACI recommends that, when available, live and inactivated quadrivalent influenza vaccines can be used as per their product monograph.

**Children 6 to 23 months of age**

At this time, only TIV or QIV is available for use in this age group.

**Children 2 to 17 years of age**

**Healthy Children and Adolescents 2 to 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 without contraindications.

There is evidence for the preferential use of LAIV in young children (younger than 6 years of age) based on superior efficacy of LAIV compared to TIV (Grade A), with weaker evidence of superior efficacy in older children (Grade I). There may be some benefit in using QIV in this age group, but the relative benefit in relation to trivalent or quadrivalent LAIV is under consideration by NACI.

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. If LAIV is not available for those for whom it is considered superior, TIV should be used.

Two studies have directly compared the efficacy of LAIV and TIV in younger children (up to age 5 and 6) and one study has compared the efficacy of LAIV in asthmatic children 6 to 17 years of age. 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. 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. 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, 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 administrated 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). Either inactivated TIV or QIV can be used.*

Live vaccines are generally contraindicated in people with immune compromising conditions, with some exceptions. NACI concludes that there is insufficient evidence supporting the use of LAIV in those with immune compromising conditions, in terms of both safety and effectiveness. 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 LAIV found increased rates of wheezing in children 6-23 months of age when compared to TIV. 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 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. 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. Inactivated influenza vaccines can be used.

**Children with other Chronic Health Conditions**

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

A limited number of immunogenicity and efficacy studies have been conducted in this population as a result of these conditions, being fairly limited in this age group. 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 TIV in children with chronic health conditions. Inactivated influenza vaccines can be used.

**Adults 18 to 59 years of age**

There are four types of vaccine available for use in adults 18-59 years of age: TIV, TIV-ID, QIV and LAIV. For healthy adults in this age group, NACI considers all four types of vaccine to be acceptable choices (unless contraindicated) and does not have a preference for use.

For adults in this age group with chronic health conditions, either TIV, QIV or TIV-ID (9 µg/strain) may be used. If TIV-ID is being used for adults with immune compromising conditions, the 15 µg formulation should be considered to improve response.

At this time NACI concludes that there is insufficient evidence to recommend use of LAIV in adults with chronic health conditions, particularly given the evidence suggesting better immune response to TIV in this age group (16).


For information related to health care workers see section VI, below.

**Adults 60 to 64 years of age**

The vaccines available for use in adults 60-64 years of age, with or without chronic health conditions, are TIV, QIV and TIV-ID (15µg/strain). NACI concludes that there is insufficient evidence to make a recommendation for the preferential use for either TIV, QIV or TIV-ID in this age group (15).

**Adults ≥65 years of age**

Four types of vaccine are available for use in adults ≥65 years of age: TIV, QIV, TIV-ID (15µg/strain) and MF59-adjuvanted TIV. NACI concludes that there is insufficient evidence to make a recommendation for the preferential use of either TIV, QIV, TIV-ID (15µg/strain) or MF59-adjuvanted TIV in adults ≥65 years of age (17)(63)-(66).

**Pregnant women**

TIV, QIV and TIV-ID (9 µg) are available for use in pregnant women. NACI has no preference for the use of available products. 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.
VI. IMMUNIZATION OF HEALTH CARE WORKERS

Influenza vaccination provides benefits to health care workers (HCWs) and to the patients they care for. NACI considers the provision of influenza vaccination to be an essential component of the standard of care for all HCWs for the protection of their patients. This includes any person, paid or unpaid, who provides services, works, volunteers or trains in a health care setting.

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

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

To protect vulnerable patients during influenza outbreaks, HCWs with confirmed or presumed influenza and unvaccinated HCWs who are not receiving antiviral prophylaxis should be excluded from direct patient contact. Health care organizations should have policies in place to deal with this issue.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices (US)</td>
</tr>
<tr>
<td>AEFI</td>
<td>Adverse event following immunization</td>
</tr>
<tr>
<td>AMMI</td>
<td>Association of Medical Microbiology and Infectious Disease</td>
</tr>
<tr>
<td>ATIV</td>
<td>Adjuvanted trivalent inactivated vaccine</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CAEFISS</td>
<td>Canadian Adverse Events Following Immunization Surveillance System</td>
</tr>
<tr>
<td>CBER</td>
<td>Centre for Biologics Evaluation Research</td>
</tr>
<tr>
<td>CCDR</td>
<td>Canada Communicable Disease Report</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Harmonization of Medicinal Products</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CIHR</td>
<td>Canadian Institutes of Health Research</td>
</tr>
<tr>
<td>CIRID</td>
<td>Centre for Immunization and Respiratory Infectious Diseases</td>
</tr>
<tr>
<td>FFU</td>
<td>Fluorescent focus units</td>
</tr>
<tr>
<td>GBS</td>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>GM</td>
<td>Geometric mean</td>
</tr>
<tr>
<td>GMT</td>
<td>Geometric mean titre</td>
</tr>
<tr>
<td>HA</td>
<td>Haemagglutinin</td>
</tr>
<tr>
<td>HAI</td>
<td>Hemagglutination inhibition assay</td>
</tr>
<tr>
<td>HCW</td>
<td>Health care worker</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>ID</td>
<td>Intradermal</td>
</tr>
<tr>
<td>IgE</td>
<td>Immune globulin E</td>
</tr>
<tr>
<td>IgG</td>
<td>Immune globulin G</td>
</tr>
<tr>
<td>ILI</td>
<td>Influenza-like illness</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>IMPACT</td>
<td>Immunization Monitoring Program, ACTive</td>
</tr>
<tr>
<td>IWG</td>
<td>Influenza Working Group</td>
</tr>
<tr>
<td>LAIV</td>
<td>Live attenuated influenza vaccine</td>
</tr>
<tr>
<td>MAARI</td>
<td>Medically attended acute respiratory illness</td>
</tr>
<tr>
<td>mL</td>
<td>Millilitre</td>
</tr>
<tr>
<td>MN</td>
<td>Microneutralization</td>
</tr>
<tr>
<td>NA</td>
<td>Neuraminidase</td>
</tr>
<tr>
<td>NACI</td>
<td>National Advisory Committee on Immunization</td>
</tr>
<tr>
<td>NML</td>
<td>National Microbiology Laboratory</td>
</tr>
<tr>
<td>ORS</td>
<td>Oculorespiratory syndrome</td>
</tr>
<tr>
<td>PCIRN</td>
<td>PHAC/CIHR Influenza Research Network</td>
</tr>
<tr>
<td>pH1N1</td>
<td>Pandemic H1N1 2009</td>
</tr>
<tr>
<td>PHAC</td>
<td>Public Health Agency of Canada</td>
</tr>
<tr>
<td>QIV</td>
<td>Quadrivalent inactivated influenza vaccine</td>
</tr>
<tr>
<td>Q-LAIV</td>
<td>Quadrivalent live attenuated influenza vaccine</td>
</tr>
<tr>
<td>TIV</td>
<td>Trivalent inactivated influenza vaccine</td>
</tr>
<tr>
<td>TIV-ID</td>
<td>Trivalent inactivated influenza vaccine administered intradermally</td>
</tr>
<tr>
<td>μg</td>
<td>Microgram</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>VAERS</td>
<td>Vaccine Adverse Event Reporting System (US)</td>
</tr>
<tr>
<td>VE</td>
<td>Vaccine efficacy</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
ACKNOWLEDGMENTS

†NACI Members: Dr. I. Gemmill (Chair), Dr. S. Deeks, Dr. B. Henry, Dr. D. Kumar, Dr. C. Quach-Thanh, Dr. M. Salvadori, Dr. B. Seifert, Dr. N. Sicard, Dr. W. Vaudry, Dr. R. Warrington.

Former NACI Members: Dr. N. Crowcroft, Dr. B. Warshawsky (Chair).

Liaison Representatives: Dr. J. Blake (Society of Obstetricians and Gynaecologists of Canada), Dr. J. Brophy (Canadian Association for Immunization Research and Evaluation), Dr. J. Emili (College of Family Physicians of Canada), Dr. M. Lavoie (Council of Chief Medical Officers of Health), Dr. A. Mawle (Centres for Disease Control and Prevention, U.S.), Dr. D. Moore (Canadian Paediatric Society), Dr. A. Pham-Huy (Association of Medical Microbiology and Infectious Disease Canada), Ms. E. Sartison (Canadian Immunization Committee).

Former Liaison Representatives: Dr. A. Corriveau (Council of Chief Medical Officers of Health), Dr. A. Opavsky (Association of Medical Microbiology and Infectious Disease Canada) Dr. S. Rechner (College of Family Physicians of Canada).

Ex-Officio Representatives: Dr. G. Coleman (Biologics and Genetic Therapies Directorate, Health Canada), Dr. (LCol) P. Eagan (Department of National Defence and the Canadian Armed Forced), Dr. Diego Garcia (First Nations and Inuit Health Branch, Health Canada), Dr. B. Law, (Centre for Immunization and Respiratory Infectious Diseases [CIRID], Public Health Agency of Canada [PHAC]), Dr. E. Taylor (Marketed Health Products Directorate, Health Canada), Dr. T. Wong (CIRID, PHAC), Ms. M. St-Laurent (CIRID, PHAC), Ms. G. Charos (CIRID, PHAC).

Former Ex-Officio Representatives: Dr. M. Carew (First Nations and Inuit Health Branch, Health Canada), Dr. A. Klein (Biologics and Genetic Therapies Directorate, Health Canada), Dr. B. Raymond (Centre for Immunization and Respiratory Infectious Diseases, PHAC/Canadian Immunization Committee).

†This statement was prepared by: Ms. L. Cochrane, Ms. L. Colas, and approved by NACI.

NACI gratefully acknowledges the contribution of Dr. O. Baclic, Dr. B. Cholin, Dr. S. Desai, Dr. S. Halperin, Dr. J. Langley, Dr. A. McGeer, and Dr. P. Van Buynder.
REFERENCES


49. Herrera GA, Iwane MK, Cortese M, et al. Influenza vaccine effectiveness among 50-64-year-old persons during a season of poor antigenic match between vaccine and


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


