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

STATEMENT ON SEASONAL INFLUENZA VACCINE FOR 2013–2014

Please note: The provision of recommendations regarding immunization of swine workers as a means to protect swine herds is not within the scope of NACI. For animal health concerns, the reader should refer to appropriate animal health resources.

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 currently 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). NACI recommendations for use and other information set out herein may differ from that set out in the product monograph(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 Public Health Agency of Canada’s Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

IMPORTANT note regarding antiviral guidelines: Antiviral recommendations are no longer under the purview of NACI. Guidance for the practitioner on the use of antiviral medication (www.ammi.ca/guidelines) has been developed by the Association of Medical Microbiology and Infectious Disease Canada (AMMI Canada).

NACI Members: Dr. B. Warshawsky (Chairperson), Dr. N. Crowcroft, Dr. I. Gemmill, Dr. B. Henny, Dr. D. Kumar, Dr. S. McNeil, Dr. C. Quach-Thanh, Dr. M. Salvadori, Dr. B. Seifert, Dr. N. Sicard, Dr. W. Vaudry, Dr. R. Warington.

Liaison Representatives: Dr. S. Deeks (Canadian Public Health Association), Dr. A. Mawle (Centres for Disease Control and Prevention, U.S.), Dr. D. Moore (Canadian Paediatric Society), Dr. H. Morrison (Council of Chief Medical Officers of Health), Dr. A. Opavsky (Association of Medical Microbiology and Infectious Disease Canada), Dr. A. Pham-Huy (Canadian Association for Immunization Research and Evaluation), Dr. S. Rechner (College of Family Physicians of Canada), Dr. V. Senikas (Society of Obstetricians and Gynaecologists of Canada).

Ex-Officio Representatives: Dr. M. Carew (First Nations and Inuit Health Branch, Health Canada), Dr. (LCol) P. Egan (Department of National Defence), Dr. A. Klein (Biologics and Genetic Therapies Directorate, Health Canada), Dr. B. Law (Centre for Immunization and Respiratory Infectious Diseases, PHAC), Dr. C. Légaré (Marketed Biologicals, Biotechnology and Natural Health Products Bureau, Health Canada), Dr. B. Raymond (Centre for Immunization and Respiratory Infectious Diseases, PHAC/Canadian Immunization Committee), Ms. M. St-Laurent (Surveillance and Outbreak Response Division, PHAC).

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

Preamble ........................................................................................................... 1

Summary of Information ..................................................................................... 4

I. Introduction ...................................................................................................... 6
   I.1 Overview and Summary of Changes .......................................................... 6
   I.2 Background ............................................................................................... 6

II. Methods ............................................................................................................ 7

III. Epidemiology .................................................................................................. 7
   III.1 Disease Description .................................................................................. 7
   III.2 National Influenza Surveillance during the 2012–2013 Season .................. 7
      III.2.1 Disease Distribution ........................................................................ 7
      III.2.2 Severe Illness Surveillance ............................................................... 9
   III.3 International Influenza Surveillance ...................................................... 10
      III.3.1 Novel Human Influenza Viruses (Avian or Swine origin) .................. 11
   III.4 Antiviral Resistance .............................................................................. 11

IV. Seasonal Influenza Vaccine ............................................................................ 12
   IV.1 Preparations Authorized for Use in Canada ............................................. 12
      IV.1.1 Overview .......................................................................................... 12
      IV.1.2 Trivalent Inactivated Influenza Vaccine (TIV) .................................... 12
      IV.1.3 Live Attenuated Influenza Vaccine (LAIV) ........................................ 12
   IV.2 Efficacy, Effectiveness and Immunogenicity ............................................ 14
      IV.2.1 Efficacy and Effectiveness ............................................................... 14
      IV.2.2 Immunogenicity .............................................................................. 15
   IV.3 Administration of Influenza Vaccine: Dosage and Schedule .................... 17
      IV.3.1 Administration of influenza vaccine to egg allergic persons ............... 18
   IV.4 Storage Requirements ............................................................................ 18
   IV.5 Simultaneous Administration with Other Vaccines ............................... 18
   IV.6 Adverse Events ....................................................................................... 18
   IV.7 Contraindications and Precautions ....................................................... 20
      IV.7.1 Contraindications ............................................................................ 20
      IV.7.2 Precautions ..................................................................................... 20
   IV.8 Surveillance of Adverse Events Following Immunization ....................... 21
V. Recommendations for the 2013–2014 Seasonal Influenza Vaccine ........................................... 21
   V.1 General Considerations ........................................................................................................... 21
   V.2 Recommended Recipients ....................................................................................................... 22
       V.2.1 People at High Risk of Influenza-Related Complications or Hospitalization ..................... 23
       V.2.2 People Capable of Transmitting Influenza to Those at High Risk of Influenza-Related
            Complications or Hospitalization ....................................................................................... 24
       V.2.3 Others .............................................................................................................................. 25
       V.2.4 Further Comments Regarding Influenza Immunization .................................................... 25
   V.3 Choice of Product ................................................................................................................... 26

VI. Immunization of Health Care Workers ..................................................................................... 28
    List of Abbreviations ................................................................................................................... 29
    References ................................................................................................................................... 32

Appendix 1: Evidence Review on Occupational Exposure of Swine and Poultry Workers
(Note: This appendix is available as a separate document.)
Summary of Information

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

**TABLE 1: Summary of information contained in this NACI Statement**

<table>
<thead>
<tr>
<th>What is influenza?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza is a respiratory infection caused by influenza A and 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, muscle aches and fatigue, runny nose, sneezing, watery eyes and throat irritation. Nausea, vomiting and diarrhea may also occur, especially in children. Most people will recover within a week or ten days, but some—including those 65 years of age and older 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 later in this table and in section V of this document.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What influenza vaccines are authorized for use in Canada?</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are currently eight seasonal trivalent 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 product (Flumist®) is a live attenuated influenza vaccine (LAIV) that is authorized for use from 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. 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).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Who to immunize?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunization programs should focus on:</td>
</tr>
<tr>
<td>• those at high risk of influenza-related complications—adults and children with underlying health conditions, including morbid obesity, residents of nursing homes and other chronic care facilities; people ≥ 65 years of age; children 6 to 59 months of age; pregnant women; and Aboriginal peoples;</td>
</tr>
<tr>
<td>• those capable of spreading influenza to individuals at high risk of complications—health care providers in facilities and community settings; household contacts of high-risk persons including those ≤59 months of age; those providing care to children ≤59 months of age; and those providing services in closed settings to those at high risk (e.g. crew on a ship); and</td>
</tr>
<tr>
<td>• those who provide essential community services. NACI also encourages influenza vaccine for all Canadians aged 6 months and older, because they can also benefit from influenza protection.</td>
</tr>
</tbody>
</table>
Dose, schedule, contraindications and precautions, and co-administration.

Children who have been previously immunized with seasonal influenza vaccine and adults are to 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 (Refer to section IV.3 of this statement for details). For intramuscular TIV, the dose is 0.5 ml for all age groups.

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 developed Guillain-Barré Syndrome (GBS) within six weeks of influenza vaccination should not receive a further dose. Regarding egg allergic individuals, after careful review NACI has concluded egg allergic individuals may be vaccinated against influenza using TIV without prior influenza vaccine skin test and with the full dose, with consideration being given to the most appropriate setting for the vaccine administration (Refer to section IV.3.1 for details). There are additional contraindications for LAIV (Refer to section IV.7 for details).

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, TIV can be administered or LAIV could be deferred until resolution of the illness.

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 vaccines or inactivated vaccines. (Refer to section IV.5 for details).

For concomitant parenteral injections, different injection sites and separate needles and syringes should be used.

Soreness at the injection site may occur after TIV and is more common with adjuvanted or intradermal vaccine. Fever and other systemic reactions are infrequent. The most common adverse events after LAIV are nasal congestion and runny nose.

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

Counselling points for providers to emphasize with clients when discussing these recommendations.

- Vaccination is the most effective way to prevent influenza.
- Each year there is a new vaccine to protect against the influenza virus strains that are expected in the coming influenza season. Even if the strains have not changed, getting influenza vaccine every year is necessary to maximize protection.
- 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 seasonal influenza vaccine for the 2013–2014 season.

The seasonal trivalent vaccine for 2013–2014, as per recommendations by the World Health Organization (WHO) for the northern hemisphere, contains:

- an A/California/7/2009 (H1N1)pdm09-like virus;
- an A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011 (A/Texas/50/2012 viruses, which are antigenically like the A/Victoria/361/2011, will be used in manufacturing the influenza vaccine); and
- a B/ Massachusetts/2/2012-like virus (Yamagata lineage).¹

The WHO recommends that, where available, seasonal quadrivalent influenza vaccines for 2013–2014 contain the above three viruses and a B/Brisbane/60/2008-like virus. Quadrivalent influenza vaccines are not authorized for use in Canada as of June 2013.

The 2013–2014 statement contains updated information from the 2012–2013 influenza season and product information for all eight influenza vaccines authorized for use in Canada, including influvac®, Fluviral®, Vaxigrip®, Intanza®, Flumist®, Agriflu®, Fluad®, and Fluzone® (refer to Table 2 for product characteristics).

There have been no changes in the recommended recipients for influenza vaccine since the Statement on Seasonal Influenza Vaccine for 2012–2013. However, this statement updates the guidance for travellers, the recommendations for administration of influenza vaccine to egg allergic persons, the recommendations for the administration of live attenuated influenza vaccine (LAIV) with other live parenteral or mucosal vaccines and clarifies the recommendation for health care workers. For further information on the administration of live vaccines, refer to the Canadian Immunization Guide (www.phac-aspc.gc.ca/publicat/cig-gci/p01-09-eng.php).

Additionally this statement contains a discussion about seasonal influenza immunization of swine and poultry workers. Please note: the provision of recommendations regarding immunization of swine workers as a means to protect swine herds is not within the scope of NACI.

For animal health concerns, the reader should refer to appropriate animal health resources.

Immunization programs should continue to focus on those persons at high risk of influenza-related complications, those capable of transmitting influenza to individuals at high risk of complications and those who provide essential community services (refer to Section V.2 and Table 4 for full details). Contrary to the recommendation regarding those who provide regular child care to children noted in the interim statement, NACI recommends influenza vaccination for those who provide regular care to children ≤59 months of age, whether in or out of the home. Full details, including recommendations for persons with immune compromising and other chronic health conditions, can be found in the remainder of the 2013–2014 statement.

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 that have 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 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). 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 vaccine to stimulate antibody protection across B lineages requires further evaluation and may be dependent upon age and/or prior antigenic experience with both B lineages.⁵⁻⁷
II. Methods


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; as well as other aspects of influenza immunization.

In developing this statement, the Influenza Working Group (IWG) of NACI reviewed the annual influenza vaccine recommendations as well as 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. Additionally, in December 2012, the IWG consulted with animal health experts to inform the discussion regarding seasonal influenza immunization for swine and poultry workers. The findings of the work of the IWG were presented to and considered by NACI for inclusion in the 2013–14 statement. Details regarding the methodology associated with this work can be found in Appendix 1 of this statement.

The evidence and proposed recommendations were presented to NACI on February 7 and May 6, 2013. Following thorough review of the evidence, the committee voted on specific recommendations. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are described in the 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. 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. 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 should be noted that influenza testing is not often sought to confirm an influenza diagnosis or may be sought late. This makes it difficult to assess the true burden of influenza in terms of incidence, deaths and hospitalizations. It is estimated, however, that in a given year up to 20,000 hospitalizations related to influenza may occur, and that approximately 4000 deaths attributable to influenza occur annually.

III.2 NATIONAL INFLUENZA SURVEILLANCE DURING THE 2012–2013 SEASON

III.2.1 Disease Distribution

National influenza surveillance is coordinated through the Centre for Immunization and Respiratory Infectious Diseases (CIRID) at the Public Health Agency of Canada (the Agency). The FluWatch program collects data and information from various sources to provide a national picture of influenza activity. Each of the different sources gives a helpful angle on influenza, but none is complete. All capture a very small minority of the influenza infections that take place in Canada each year, and each has a bias towards certain ages, severity, people with co-morbidities, et cetera. Detailed methodology for FluWatch has been described previously. The information in this statement is based on surveillance data from August 26 2012, to April 20 2013, unless otherwise specified. Data are preliminary and numbers may fluctuate because of delayed reporting. For more current information, readers should refer to the FluWatch reports (www.phac-aspc.gc.ca/fluwatch/aiisr-raisi-eng.php).
Influenza activity in Canada remained low from September to October 2012, with only a few regions reporting increased influenza activity (in the western provinces and in Ontario). Influenza activity increased throughout the month of November in most regions across Canada except in the Atlantic Provinces. Nationally, the peak of the influenza season occurred at the end of December, 2012, and has been declining since that time. Since the start of the season, 1078 outbreaks of influenza or influenza-like illness (ILI) have been reported, of which the majority were in long-term care facilities (61.1% or 659/1078).

Influenza A has predominated since the start of the season, however the proportion of positive influenza B detections has been increasing steadily since mid-January. As of April 2013, 88.0% (26,764/30,405) of the influenza detections were for influenza A viruses (of which 34.5% were A(H3), 4.4% were A(H1N1)pdm09 and 61.1 % were A(unsubtyped); and 12.0 % were for influenza B viruses.

Detailed information on age and type/subtype has been received for 23,293 cases to date this season (Table 1).

**TABLE 1: Cumulative numbers of positive influenza specimens by age groups reported through case-based laboratory reporting, Canada, Aug. 26, 2012 to April 20, 2013**

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Cumulative (Aug. 26, 2012 to April 20, 2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Influenza A</td>
</tr>
<tr>
<td></td>
<td>A/ H1N1pdm09</td>
</tr>
<tr>
<td>&lt;5</td>
<td>2,648</td>
</tr>
<tr>
<td>5–19</td>
<td>1,450</td>
</tr>
<tr>
<td>20–44</td>
<td>3,143</td>
</tr>
<tr>
<td>45–64</td>
<td>3,442</td>
</tr>
<tr>
<td>65+</td>
<td>9,579</td>
</tr>
<tr>
<td>Total</td>
<td>20,262</td>
</tr>
</tbody>
</table>

*This table reflects the number of specimens for which demographic information was reported. These represent a subset of all positive influenza cases reported. Five provinces have reported detailed case-by-case data since the beginning of the season (BC, AB, SK, MB and ON).*
Of the influenza A(H1N1)pdm09 cases, the largest proportions were among those 20–44 years of age (31.5%; 319/1012), followed by adults 45–64 years of age (29.6%; 300/1012). On the contrary, among the influenza A(H3N2) cases, the largest proportion was those ≥ 65 years (48.1%; 3,599/7,481). Of the influenza B cases, the largest proportions were among those 5–19 years of age (26.2%; 795/3,031) and children < 5 years of age (20.4%; 617/3,031).

During the 2012–13 season, the National Microbiology Laboratory (NML) antigenically characterized 1097 influenza viruses. The 560 influenza A(H3N2) viruses were antigenically similar to the vaccine strain A/Victoria/361/2011 and the 186 A(H1N1)pdm09 viruses were antigenically similar to the vaccine strain A/California/07/09. Among the influenza B viruses, 283 were antigenically similar to the vaccine strain B/Wisconsin/01/2010 (Yamagata lineage) and 68 were similar to B/Brisbane/60/2008 (Victoria lineage; component of the 2011–2012 seasonal influenza vaccine).

III.2.2 Severe Illness 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. 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 who are not laboratory confirmed as having influenza.

Paediatric hospitalizations and deaths

IMMUNIZATION MONITORING PROGRAM ACTIVE (IMPACT) NETWORK

Between August 26, 2012 and April 20, 2013, a total of 820 influenza-associated paediatric hospitalizations have been reported by the IMPACT network: 615 (75.0%) with influenza A (of which 121 (19.7%) were A(H3N2), 22 (3.6%) were A(H1N1)pdm09 and the remaining 472 were A(unsubtyped)); and 205 (25.0%) with influenza B. The distribution of cases by age group is as follows: 152 (18.5%) <6 months of age; 194 (23.7%) age 6–23 months; 234 (28.5%) age 2–4 years; 171 (20.9%) age 5–9 years; and 69 (8.4%) age 10–16 years. Eighty-five (10.4%) of the 820 cases were admitted to the ICU. Of the 61 ICU admissions with available data, 53 (86.9%) cases had at least one co-morbidity. One death has been reported to date this season by the IMPACT network.

PROVINCIAL/TERRITORIAL PAEDIATRIC INFLUENZA HOSPITALIZATIONS AND DEATHS

Influenza-associated paediatric hospitalizations are reported to the Agency by several provinces and territories in Canada except for British Columbia, Quebec, Nova Scotia, Nunavut and New Brunswick. Only hospitalizations that require intensive medical care are reported by Saskatchewan, and ICU admissions are not reported by Ontario.

Between August 26, 2012 and April 20, 2013, 899 paediatric hospitalizations (<20 years of age) have been reported by the provinces and territories. The majority of paediatric hospitalizations have been influenza A (736/899; 81.9%), predominately A(H3). The age breakdown is as follows: 660 (73.4%) (0–4 years), 199 (22.1%) (5–14 years) and 40 (4.4%) (15–19 years). Among the 288 cases with available information, there have been 35 hospitalizations for which admission to the ICU were required. Six paediatric deaths have been reported by the participating provinces and territories: five in children 0–4 years of age, and one child 5–14 years of age. It is important to note that the cause of death does not have to be attributable to influenza in these provincial/territorial reports; a positive laboratory test is sufficient for reporting, which differs from the method used by IMPACT. Detailed clinical information (e.g. underlying medical conditions) is not known for these cases.
Adult hospitalizations and deaths

PHAC/CIHR INFLUENZA RESEARCH NETWORK (PCIRN) SERIOUS OUTCOMES SURVEILLANCE (SOS) NETWORK

From November 4, 2012 to April 20, 2013, 1,735 influenza-associated adult hospitalizations were reported by the PCIRN-SOS network: 1,590 (91.6%) with influenza A [of which 305 were A(H3N2), 16 were A(H1N1)pdm09, and 1,269 were A(unstyped)]; 94 (5.4%) with influenza B, and the type has not been reported for 51 cases. The age distribution of hospitalizations is as follows: 1,193 (68.8%) were ≥65 years of age, 349 (20.1%) were 45–64 years, 185 (10.7%) were 20–44 years, and 8 (0.5%) were <20 years of age. ICU admission was required for 201 hospitalizations; the majority of which were adults ≥65 years of age (121; 60.2%). Of the ICU admissions, 82 (40.8%) had at least one co-morbidity, three (1.5%) had no co-morbidities, and 116 had no information to date. A total of 112 deaths have been reported: 26 with influenza A(H3N2), one with A(H1N1)pdm09, 79 with A(unstyped), and one untyped. More than 85% of the deaths (96/112) were in adults ≥65 years of age, 13 (11.6%) were adults 45–64 years of age, and 3 (2.7%) were 20–44 years of age. Fifty-one (45.5%) deaths occurred in individuals who had at least one co-morbidity. Detailed clinical information on co-morbidities is not known for the remaining cases.

PROVINCIAL/TERRITORIAL INFLUENZA HOSPITALIZATIONS AND DEATHS

As of April 20, 2013, 3,587 influenza-associated adult hospitalizations (>20 years) have been reported this season; of which 93.1% have been influenza A, predominantly A(H3). The age distribution is as follows: 400 (11.2%) (20–44 years), 758 (21.1%) (44–64 years) and 2,429 (67.7%) ≥65 years. Among the 912 cases with available data, there have been 155 (17.1%) hospitalizations for which admission to an ICU was required; the highest proportion being adults between 45–64 years of age (36.3%) followed by adults ≥65 years (33.7%). To date, 280 deaths have been reported: 236 (84.3%) were adults ≥65 years of age, 33 (11.8%) were adults between 45–64 years of age; and 11 (3.9%) were adults between 20–44 years of age. It is important to note that the cause of death does not have to be attributable to influenza in these provincial/territorial reports; a positive laboratory test is sufficient for reporting, which differs from the method used by PCIRN. Detailed clinical information (e.g. underlying medical conditions) is not known for these cases.

III.3 INTERNATIONAL INFLUENZA SURVEILLANCE

Between September 2012 and January 2013, influenza activity was reported in Africa, the Americas, Asia, Europe and Oceania. Influenza A(H1N1)pdm09 viruses circulated at low levels in general except in some countries in Africa, Asia, Central and South America and Europe. Influenza A(H3N2) viruses were predominant in most of North America, some countries in northern Africa, some parts of Asia and, early in the season, in some European countries as well as China. Influenza B viruses circulated in many countries and were the predominant viruses in some.

In the northern hemisphere, influenza activity was low in September and October. Increased activity was reported in North America in November, in Europe from December onwards and in a number of countries in Asia in December or January. In the southern hemisphere, influenza activity generally declined from September onwards. Some South American countries reported regional outbreaks in September and October due to A(H1N1)pdm09, A(H3N2) and B viruses.

The majority of A(H1N1)pdm09 viruses were antigenically similar to A/California/7/2009 and the majority of A(H3N2) viruses isolated were antigenically and genetically similar to cell-propagated A/Victoria/361/2011 and A/Victoria/361/2011-like reference viruses such as A/Texas/50/2012. The proportion of B/Yamagata/16/88 lineage viruses increased in many parts of the world but B/Victoria/2/87 lineage viruses predominated in some countries, including Australia and China. While most of the viruses characterized were antigenically related viruses in the 2012–2013 trivalent vaccine, the WHO recommended a change in the influenza B composition of the next northern hemisphere vaccine formulation (for the 2013–2014 influenza season) to include a B/Massachusetts/2/2012-like virus of the Yamagata lineage, and to continue the inclusion of an A/Victoria/361/2011 (H3N2)-like virus and an A/California/7/2009 (H1N1)pdm09-like virus.
III.3.1 Novel Human Influenza Viruses (Avian or Swine origin)

Humans can become ill when infected with viruses from animal sources, such as influenza viruses of avian or swine origin. The primary risk factor for human infection appears to be direct or indirect exposure to infected live or dead animals or contaminated environments.\(^\text{14}\)

**Avian Origin Influenza Viruses in Humans**

**AVIAN INFLUENZA A(H5N1)**

Currently, the avian influenza H5N1 virus continues to circulate in poultry in some countries, especially in Asia and northeast Africa. From September 1, 2012 to March 12, 2013, the WHO reported 14 cases of human A/H5N1 avian influenza infection from six countries: Cambodia (n=9), China (n=2), Egypt (n=2), Indonesia (n=1). Of the 14 cases, 5 were in adults (> 18 years) and 9 were in children. Twelve (85.7%) of the cases required hospitalization and 12 of the 14 cases died (85.7% fatality; 5 deaths were in adults and 7 were in children). Nine cases had exposure to sick or dead poultry, three cases had exposure to animals (i.e. exposed to backyard or neighbourhood poultry) and two cases had no exposure documented. This virus continues to cause sporadic human infections with some instances of limited human-to-human transmission among very close contacts.

Since 2003, 628 confirmed cases of avian influenza H5N1 have been reported globally, including 374 deaths. However, there has been no sustained human-to-human or community-level transmission identified thus far.\(^\text{16}\)

**AVIAN INFLUENZA A(H7N9)**

On March 31, 2013, the World Health Organization (WHO) was notified of cases of human infection with influenza A(H7N9) by the China Health and Family Planning Commission of the People’s Republic of China.\(^\text{15}\) This is the first time that this virus has been detected in humans and the situation is being monitored very closely. The most recent information regarding this influenza A(H7N9) situation is available on FluWatch (www.phac-aspc.gc.ca/fluwatch).

**Swine Origin Influenza Virus in Humans**

Swine influenza viruses do not normally infect humans; however, sporadic human infections with influenza viruses that normally infect swine have occurred and are referred to as variant influenza. Three hundred and nine cases of influenza A(H3N2)v were detected in 2012 in the United States of America.\(^\text{16}\) Since 2005, there have been 348 cases of human infection with swine-origin variant viruses in the United States: 329 H3N2v, 14 H1N1v and 5 H1N2v. Most infections with variant viruses have occurred in children (persons 18 or younger) and most cases have reported direct or indirect exposure to swine prior to onset of illness. Limited transmission from close contact with an infected person has been observed in some investigations of human infections with variant viruses, but sustained human-to-human transmission has not been documented.\(^\text{16}\)

In September 2012, a case of variant influenza A(H1N1v) infection was detected in Canada. The case became ill after exposure to pigs, was hospitalized and recovered. There was no disease transmission to close contacts of the case, and no additional cases were reported.

Globally, no human cases of influenza A(H1N1)v, A(H1N2)v, A(H7N3) or A(H9N2) were detected during the period September 19, 2012 to February 18, 2013.

The current status of these viruses is provided for completeness however, they do not have an impact on the seasonal influenza vaccine.

III.4 Antiviral Resistance

Details of antiviral resistance patterns of circulating influenza strains performed by the routine surveillance program at the National Microbiology Laboratory (NML) are reported weekly by the FluWatch program.

During the 2012–13 season, NML tested 730 influenza viruses for resistance to oseltamivir, and 727 influenza viruses for resistance to zanamivir. All viruses tested were sensitive to oseltamivir and zanamivir. A total of 886 influenza A viruses (772 H3N2 and 114 H1N1) were tested for amantadine resistance and all were resistant.
IV. Seasonal Influenza Vaccine

IV.1 PREPARATIONS AUTHORIZED FOR USE IN CANADA

IV.1.1 Overview
There are eight seasonal influenza vaccines currently authorized for use in Canada, of which seven are inactivated and one is a live attenuated vaccine:

- 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 vaccines. Further detail for Intanza®, Flumist®, and Fluad® may be found in supplementary NACI statements for each product.\(^\text{[17]-[19]}\)

The antigenic characteristics of current and emerging influenza virus strains provide the basis for selecting the strains included in each year’s vaccine. The WHO has recommended a change in the virus used as an A/Victoria/361/2011-like virus. This change is required because the A/Victoria/361/2011 egg propagated vaccine virus has antigenic changes compared with the cell-propagated A/Victoria/361/2011 virus. By contrast, both the cell- and egg-propagated A/Texas/50/2012 viruses are antigenically like the A/Victoria/361/2011 cell-propagated virus. Thus, the WHO’s expert group recommends the A/Victoria/361/2011-like virus be A/Texas/50/2012.\(^\text{[1]}\)

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 three 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 allergy.

The decision to include specific influenza vaccines 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. 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 Trivalent Inactivated Influenza Vaccine (TIV)

There are two main types of inactivated influenza vaccines, 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 seven TIV 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 TIV 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. The other six TIV products do not contain an adjuvant.

One of the TIV products (Intanza®) is administered intra-dermally; the other six TIV 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 for persons 2–59 years of age. Each 0.2 mL dose of Flumist®, (given as 0.1 mL in each nostril) contains \(10^{4.5-7.5}\) 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 2.


<table>
<thead>
<tr>
<th>Manufacturer and Product name</th>
<th>Abbott Influvac&lt;sup&gt;a&lt;/sup&gt;</th>
<th>GSK Fluviral&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Novartis Agriflu&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Novartis Fluad&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sanofi Pasteur Vaxigrip&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sanofi Pasteur Fluzone&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sanofi Pasteur Intanza&lt;sup&gt;a&lt;/sup&gt;</th>
<th>AstraZeneca FluMist&lt;sup&gt;a&lt;/sup&gt;</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>
</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></td>
</tr>
<tr>
<td>Route of administration</td>
<td>IM</td>
<td>IM</td>
<td>IM</td>
<td>IM</td>
<td>IM</td>
<td>IM</td>
<td>IM</td>
<td>ID</td>
</tr>
<tr>
<td>Authorized ages for use</td>
<td>≥ 18 years</td>
<td>≥ 6 months</td>
<td>≥ 6 months</td>
<td>≥ 65 years</td>
<td>≥ 6 months</td>
<td>≥ 6 months</td>
<td>≥ 18 years</td>
<td>2–59 years</td>
</tr>
<tr>
<td>Antigen content (each of three 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>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&lt;sup&gt;5.5-7&lt;/sup&gt; FFu of live attenuated reassortants /0.2 mL dose given as 0.1 mL in each nostril</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>
</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 with or without a needle</td>
<td>5 mL multi-dose vial, single dose ampoule, single-dose pre-filled syringes with or without a needle</td>
<td>5 mL multi-dose vial, single dose ampoule, single-dose pre-filled syringes with or without a needle</td>
<td>Single dose pre-filled syringes with micro-injection system Two formulations (as above)</td>
<td>Prefilled single use glass sprayer</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>Not reported</td>
<td>n/a</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>
</tr>
<tr>
<td>Antibiotics (traces)</td>
<td>Gentamicin</td>
<td>None</td>
<td>Kanamycin</td>
<td>Kanamycin</td>
<td>Neomycin</td>
<td>Neomycin</td>
<td>Neomycin</td>
<td>Gentamicin</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>Succrose</td>
<td>Egg protein</td>
<td>Formaldehyde</td>
<td>Polysorbate 80</td>
</tr>
</tbody>
</table>

* consult product monograph for complete listing of non-medicinal ingredients and excipients  
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

IV.2.1 Efficacy and Effectiveness

Multiple studies show that influenza vaccine is efficacious with higher efficacy demonstrated against laboratory-confirmed influenza than clinically defined outcomes.\(^{(20)}\)

In healthy children (equal to or younger than 18 or 16 years old) a systematic review and meta-analyses showed that efficacy of influenza vaccine against laboratory confirmed influenza ranged from 59% to 82%, efficacy against serologically-confirmed influenza ranged from 54% to 63% and efficacy against clinical illness ranged between 33% to 36%.\(^{(21)-(23)}\) Other studies have shown that LAIV is more efficacious than TIV in children. NACI is reviewing data comparing efficacy of LAIV vs. TIV in older children and will publish the results when completed. Further details are available in the Flumist\(^{\text{®}}\) statement (www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-7/index-eng.php) and Appendix 1 of the 2012–2013 statement.

In a systematic review, for healthy adults, inactivated influenza vaccine efficacy against laboratory-confirmed influenza was 80% (95% CI, 56 to 91) and vaccine effectiveness against influenza-like illness was 30% (95% CI, 17 to 41) when the vaccine strain matched the circulating strains and circulation was high.\(^{(24)}\) A recent meta-analysis identified vaccine efficacy of 50% in healthy adults (95% CI, 27 to 65) during select seasons of vaccine mismatch, although mismatch is a relative term and the amount of cross-protection is expected to vary.\(^{(25)-(27)}\) In the elderly, vaccine effectiveness is about half of that of healthy adults and varies depending on the outcome and the study population.\(^{(28)-(29)}\) Systematic reviews have also demonstrated that influenza vaccine decreases the incidence of pneumonia, hospital admissions and deaths in the elderly,\(^{(28)}\) and reduces exacerbations in persons with chronic obstructive pulmonary disease.\(^{(29)}\) 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,\(^{(31)}\) hospitalizations for cardiac disease and stroke in the elderly,\(^{(32)}\) and hospitalization and deaths in persons with diabetes mellitus 18 years of age and older.\(^{(33)}\) 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.\(^{(34)-(38)}\) 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 prevent 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.

A recent review by Osterholm et al. on efficacy and effectiveness of influenza vaccines has been frequently referred to over the past several months.\(^{(39)}\) In this review, the pooled efficacy of TIV in adults 18–65 years of age was 59% (95% CI, 51 to 67). The authors found no papers that met their inclusion criteria for TIV efficacy in children 2–17 years old or for adults older than 65 years. The pooled efficacy of LAIV for children 6 months to 7 years old was 83% (95% CI, 69 to 91). The authors found no papers that met their inclusion criteria for older children. Vaccine effectiveness was deemed variable according to the included data, with 35% of the analyses that were included showing significant protection against medically attended influenza. 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 as such, 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 is still lacking on several topics of relevance.

With the exception of LAIV, there is limited efficacy information for the newer products. While brief summaries are provided below, the individual NACI supplemental statements for Intanza\(^{\text{®}}\),(17) Flumist\(^{\text{®}}\),(18) and Fluad\(^{\text{®}}\) should be consulted for details.

### TIV for intradermal use (TIV-ID) (Intanza\(^{\text{®}}\))

The efficacy of Intanza\(^{\text{®}}\) against laboratory-confirmed influenza and its serious complications has not been directly studied.\(^{(17)}\)

### LAIV (Flumist\(^{\text{®}}\))

For Flumist\(^{\text{®}}\), a number of studies (LAIV versus placebo and LAIV versus TIV) have been conducted in children and adults. LAIV showed higher efficacy in children across all age groups when compared to placebo and TIV regardless of circulating subtype and strain match.\(^{(16)-(17)}\) 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.\(^{(18)}\)
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.\textsuperscript{19}(42)-(45)

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).\textsuperscript{48} Because 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 usually 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 may be lower to some influenza vaccine components among elderly recipients, a literature review identified no evidence for subsequent antibody decline that was any more rapid in the elderly than in younger age groups.\textsuperscript{47} Influenza vaccination can induce protective antibody levels in a substantial proportion of adults and children with immune compromising conditions, including transplant recipients, those with proliferative diseases of the hematopoietic and lymphatic systems, and HIV-infected patients.\textsuperscript{48}-\textsuperscript{52} 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.\textsuperscript{53}(54)-(56)

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 seems that MF59 may act differently from aluminum-based adjuvants.

These studies show that MF59 acts locally in the muscle fibres to create a local immune-stimulatory environment at the injection site.\textsuperscript{57} 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.\textsuperscript{58} MF59 further facilitates the internalization of antigen by these dendritic cells.\textsuperscript{59}(60) 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.\textsuperscript{59}

There is evidence from randomized controlled trials showing that Fluad® induced higher immunogenicity and broader cross-reactivity in adults 65 years of age and older compared to the non-adjuvanted subunit vaccines, with similar but less consistent results 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 to a vaccine called
Mutagrip®, which is not available in Canada. The one
study that compared Fluad® to Vaxigrip® found a similar
seroprotection and seroconversion rate 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 clinical trial comparing Intanza®
(intradermal TIV) to Fluad®, Intanza® was shown to be
non-inferior. 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. 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)
(www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/

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. LAIV has generally been shown to be equally,
if not more immunogenic, than TIV for all three strains in
children and adolescents 2 to 17 years of age, whereas
TIV was typically more immunogenic in adults than LAIV.
Greater rates of seroconversion to LAIV occurred in
baseline seronegative individuals compared to baseline
seropositive individuals in both child and adult
populations, because pre-existing immunity may interfere
with response to a live vaccine. For further details consult the NACI supplemental statement for FluMist®
(www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/
acs-dcc-7/index-eng.php). [18]

Paediatric considerations
The first time that children <9 years of age receive seasonal
influenza immunization, a two-dose schedule is required to
achieve protection. Several studies have looked at
whether these two initial doses need to be given in the
same season. 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. 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. Issues related to effective prime-
boost when there is a major change in influenza B lineage
across sequential seasons requires further evaluation.
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 suggests
moderate improvement in antibody response in infants,
without an increase in reactogenicity, with the use of full
vaccine doses. 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 (www.phac-aspc.gc.ca/publicat/

LAIV has generally been shown to be equally, if not more,
immunogenic than TIV for all three strains in
children 2–17 years of age, whereas TIV was typically more immunogenic
in adults than LAIV.

Immunization with currently available influenza vaccines
is not recommended for infants <6 months of age.
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 note 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 3.

NACI recommends that children 6 to 35 months of age should be given a full dose (0.5 mL) of TIV as is recommended for older children and adults. The first time children 6 months to ≤ 9 years of age receive seasonal influenza vaccine, whether TIV or LAIV, a two-dose schedule is required with a minimum interval of four weeks between doses. Pending further evidence, 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 (www.phac-aspc.gc.ca/publicat/cig-gci/assets/pdf/p01-eng.pdf). 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 3: Influenza vaccine: Recommended dosage and route, by age, for the 2013–2014 Season

<table>
<thead>
<tr>
<th>Age group</th>
<th>TIV without adjuvant&lt;sup&gt;i&lt;/sup&gt; IM</th>
<th>MF59—adjuvanted TIV (Fluad&lt;sup&gt;ii&lt;/sup&gt;) IM</th>
<th>TIV for intradermal use (Intanza&lt;sup&gt;ii&lt;/sup&gt;) ID</th>
<th>LAIV (FluMist&lt;sup&gt;iii&lt;/sup&gt;)&lt;sup&gt;* IN</th>
<th>Number of doses required</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–23 months</td>
<td>0.5 mL</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)&lt;sup&gt;iv&lt;/sup&gt;</td>
<td>0.2 mL (0.1 mL per nostril)</td>
<td>1</td>
</tr>
<tr>
<td>60–64 years</td>
<td>0.5 mL</td>
<td>0.1 mL (15 µg/strain)&lt;sup&gt;iv&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>≥65 years</td>
<td>0.5 mL</td>
<td>0.5 mL</td>
<td>0.1 mL (15 µg/strain)&lt;sup&gt;iv&lt;/sup&gt;</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

TIV—Trivalent inactivated vaccine
LAIV—Live attenuated influenza vaccine
IM = Intramuscular
ID = Intradermal
IN = Intranasal

<sup>i</sup> 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.

<sup>ii</sup> Influvac<sup>®</sup> ≥ 18 years, Fluviral<sup>®</sup> ≥ 6 months, Agriflu<sup>®</sup> ≥ 6 months, Vaxigrip<sup>®</sup> ≥ 6 months and Fluzone<sup>®</sup> ≥ 6 months.

<sup>iii</sup> Unless contraindicated, NACI recommends the use of LAIV as the preferred product for healthy children and adolescents 2–17 years of age. If LAIV is not available, TIV should be used as it is safe, efficacious and effective in this group.

<sup>iv</sup> 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.

<sup>v</sup> 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

Regarding egg-allergic individuals, 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, with the following conditions.⁶ Those with mild reactions such as hives, or those who tolerate eggs in baked goods may be vaccinated in regular vaccination clinics. Those who have suffered from anaphylaxis with respiratory or cardiovascular symptoms should be vaccinated in a medical clinic, allergy office or hospital where appropriate expertise and equipment to manage respiratory or cardiovascular compromise is present. These individuals should always be kept under observation for 30 minutes.⁷¹(⁷²)

Referral to a specialist with expertise in allergies may be necessary in occasional circumstances where there is strong concern about proceeding with the recommendation above and the individual is at risk of complications from influenza. If the individual is not in a high-risk group, the need for vaccination may be reassessed.

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

* 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

There have been no studies done on the possibility of interference between LAIV and other live vaccines. Based on expert opinion, 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 as 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.⁷³

The administration of LAIV with or at any time before or after live attenuated or inactivated vaccines is a change since the 2012–2013 influenza statement when 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 (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. Different administration sets (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.⁷⁴

IV.6 ADVERSE EVENTS

TIV

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 (Fluviral®, Vaxigrip®, and Fluzone®) contain minute quantities of thimerosal, which is used as a preservative. 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. 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, difficulty breathing, difficulty swallowing, 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. Since this 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 at 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.

**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 at www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-4/index-eng.php.

**LAIV (Flumist®)**

LAIV (Flumist®) is made from attenuated viruses that are able to replicate efficiently only at temperatures present in the nasal mucosa. The most common adverse events experienced by LAIV recipients are nasal congestion and runny nose. In a large efficacy trial, wheezing occurred in LAIV recipients at rates above those in TIV recipients only in children <24 months of age.

Studies on FluMist® have shown that vaccine virus can be recovered by nasal swab in children and adults following vaccination (i.e. "sheddng"). 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, the NACI FluMist supplemental statement is available at www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-7/index-eng.php.

**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 for further details about administration of vaccine and management of adverse events including anaphylaxis.

In a review of studies 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. 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. The risk of GBS associated with influenza vaccination must be balanced against the risk of GBS associated with influenza infection itself.
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 (Refer to Section IV.3.1).

For more information on vaccine safety and anaphylaxis, please refer to the Canadian Immunization Guide (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 aspirin or aspirin-containing therapy because of the association of Reye’s syndrome with aspirin and wild-type influenza infection. It is recommended that aspirin-containing products in children <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 and/or therapy, 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, difficulty breathing) within 24 hours of influenza vaccination, an apparent significant allergic reaction to the vaccine or any other symptoms (e.g., throat constriction, difficulty swallowing) that raise concern regarding the safety of re-immunization. This advice may be obtained from local medical officers of health or other experts in infectious disease, allergy/immunology and/or public health.

In view of the considerable morbidity and mortality associated with influenza, a diagnosis of influenza vaccine allergy should not be made without confirmation (which may involve skin testing) from an allergy/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. Persons who experienced ORS with lower respiratory tract symptoms should have an expert review. For more information on ORS refer to CCDR 2005 Volume 31. Health care providers who are unsure whether an individual previously 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. For a more detailed review of evidence concerning GBS and influenza vaccine, previous editions of the NACI’s annual influenza statement may be consulted.

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, TIV 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 isolation) for at least two weeks following vaccination, because of the theoretical risk for transmission.

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 (AEFs) can provide important safety data on licensed/authorized vaccines, including the identification of previously unknown AEFs and/or an increase in the frequency or severity of previously identified vaccine-related reactions. In Canada post market safety data is 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 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 has shown seasonal influenza vaccines to have a safe and stable AEFI profile with no unexpected events. One exception was for 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 is similar to that of previous seasons.

Early in the 2012/2013 season, distribution of Agriflu® and Flud® 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 for the 2013–2014 Seasonal Influenza Vaccine

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 issues. 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. Health care workers (HCWs) 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 getting 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 without contraindications.

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 and those who provide essential community services (refer to Table 4).

These groups remain the priority for influenza vaccination programs in Canada. However, significant illness and societal costs also occur with seasonal influenza in people who may not be considered at high risk of complications (i.e. healthy people aged 5 to 64 years). Therefore NACI also encourages influenza vaccine for all Canadians aged 6 months and older.

The NACI IWG is in the process of examining the evidence regarding a recommendation for influenza immunization for:

- healthy people 5–18 years of age; and
- healthy people 19–64 years of age.

Further details regarding the outcomes of these analyses will be provided when complete.

Recommendations regarding seasonal influenza immunization for swine and poultry workers

NACI has conducted a literature review and consulted with animal health experts concerning influenza immunization for swine and poultry workers. For animal health concerns, the reader should refer to appropriate animal health resources. Further information regarding this review can be found in Appendix 1 of this document. From this review and consultation:

- NACI concludes that there is insufficient evidence at this time to specifically recommend routine influenza immunization for swine workers (NACI recommendation grade I); however NACI encourages influenza vaccine for all Canadians age 6 months and older.
- NACI continues to recommend immunization against seasonal influenza for people in direct contact during culling operations involving poultry infected with avian influenza (NACI recommendation grade I); however NACI encourages influenza vaccine for all Canadians age 6 months and older.

TABLE 4: Recommended recipients of influenza vaccine for the 2013–2014 season*

<table>
<thead>
<tr>
<th>People at high risk of influenza-related complications or hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (including pregnant women) and children with the following chronic health conditions:</td>
</tr>
<tr>
<td>- cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma);</td>
</tr>
<tr>
<td>- diabetes mellitus and other metabolic diseases;</td>
</tr>
<tr>
<td>- cancer, immune compromising conditions (due to underlying disease and/or therapy);</td>
</tr>
<tr>
<td>- renal disease;</td>
</tr>
<tr>
<td>- anemia or hemoglobinopathy;</td>
</tr>
<tr>
<td>- conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration;</td>
</tr>
<tr>
<td>- morbid obesity (BMI≥40); and</td>
</tr>
<tr>
<td>- children and adolescents with conditions treated for long periods with acetylsalicylic acid.</td>
</tr>
<tr>
<td>People of any age who are residents of nursing homes and other chronic care facilities.</td>
</tr>
<tr>
<td>People ≥65 years of age.</td>
</tr>
<tr>
<td>All children 6 to 59 months of age.</td>
</tr>
<tr>
<td>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)</td>
</tr>
<tr>
<td>Aboriginal peoples.</td>
</tr>
</tbody>
</table>
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.

* Note: Healthy persons aged 5 to 64 years who do not have contraindications to influenza vaccine are also encouraged to receive influenza vaccine even if they are not in one of the recommended recipient groups.

V.2.1 People at High Risk of Influenza-Related Complications or Hospitalization

Adults (including pregnant women) and children with the following chronic health conditions.

A number of chronic health conditions are associated with increased risk of influenza-related complications and influenza can lead to exacerbation of the chronic disease. These conditions especially include cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma), but also diabetes mellitus and other metabolic diseases; cancer; immune compromising conditions (due to underlying disease and/or therapy); renal disease; anemia or hemoglobinopathy; and conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration. This category also includes children and adolescents (aged 6 months to 18 years) with conditions treated for long periods with acetylsalicylic acid because of the potential increased risk of Reye’s syndrome associated with influenza.

Morbid obesity

NACI recognizes that information on the association between obesity and influenza-related complications continues to evolve and encourages further research. However, on the basis of data indicating an increased risk of hospitalisations and complications, from both seasonal and pandemic influenza, NACI recommends the inclusion of those who are morbidly obese (BMI ≥40), with and without other chronic health conditions, among high-priority recipients of influenza vaccine. Offering vaccine to other obese adults may also be considered. NACI notes that it is not an expectation that a person’s weight or BMI be measured in order to implement this recommendation. For details on the evidence reviewed to inform this recommendation refer to the Statement on Seasonal Influenza Vaccine for 2011–2012 (www.phac-aspc.gc.ca/publicat/ccdr-rmtc/11vol37/acs-dcc-5/index-eng.php).

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, and mortality rates increase with increased age.

All children 6 to 59 months of age.

On the basis of existing data, NACI recommends the inclusion of all children 6 to 59 months of age among recommended recipients of influenza vaccine.

NACI has reviewed the burden of illness, and influenza vaccine effectiveness, efficacy, immunogenicity and safety for children 24 to 59 months of age, and as a result, includes this age group among recommended recipients of seasonal influenza vaccine.


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, evidence of adverse neonatal outcomes associated with maternal respiratory hospitalization or influenza during pregnancy, and evidence that vaccination of pregnant women protects their newborns from influenza and influenza-related hospitalization, 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. Support for the hypothesis that infants are protected by transplacental antibody transfer from vaccinated mothers has recently been published. Omer et al. provides a recent review of the evidence of the benefit of maternal influenza vaccination for pregnant women and their infants. The safety of influenza vaccine during pregnancy has recently been reviewed. Active studies of influenza vaccination during pregnancy have not shown evidence of harm to the mother or fetus associated with influenza immunization. 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. 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. The antibody response to TIV in pregnant women is not expected to differ from that of non-pregnant individuals.

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.

Historically, Aboriginal status has been associated with increased risk of influenza-related complications including death. This has also been seen with the recent 2009 H1N1 pandemic, during which Indigenous populations from Canada, Australia, New Zealand and United States (US) were reported to have hospitalisation and mortality rates three- to six-fold higher compared to the overall population. It has been proposed that the increased risk of severe influenza outcomes in the Aboriginal population is a consequence of multiple factors including high prevalence of chronic health conditions (e.g., diabetes, chronic lung disease, end-stage kidney disease), obesity, delayed access to health care and increased susceptibility to disease because of poor housing and overcrowding. Research into an underlying biological mechanism for severe disease in Aboriginal peoples has generated hypotheses but is not conclusive.

For further details on the evidence reviewed to inform this recommendation refer to the Statement on Seasonal Influenza Vaccine for 2011–2012.

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 an 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. Immunization of care providers and residents is associated with decreased risk of ILI outbreaks. 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 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.

Household contacts (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 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. Although seasonal influenza immunization will not prevent avian influenza infection, some countries and provinces, have recommended influenza immunization on a yearly basis for these workers based on the rationale that preventing infection with human influenza strains may reduce the theoretical potential for human-avian re-assortment of genes should such workers become co-infected with human and avian influenza viruses. 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 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. Refer to the Agency’s guidance for further information regarding recommendations during a domestic avian influenza outbreak (www.phac-aspc.gc.ca/publicat/daio-enia/index-eng.php).

V.2.4 Further Comments Regarding Influenza Immunization

Immunization of healthy persons 5 to 64 years of age
Individuals in this age group are encouraged to receive the vaccine, even if they are not in one of the aforementioned priority groups. For information on influenza vaccine efficacy and effectiveness refer to section IV.2, above.
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 travellers with a chronic health condition or other factors that would make them part of the recommended recipients of influenza vaccine due to increased risk of complications following influenza infection. In addition, NACI encourages influenza immunization for all Canadians over 6 months of age which would also apply to travellers.

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 in favour or against re-vaccination (i.e. boosting) of travellers to the Southern Hemisphere between April and October if they had already been vaccinated in the preceding fall/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 5 summarizes NACI’s current recommendations for the choice(s) of influenza vaccine in specific age and risk groups. More details along with brief supporting rationale are outlined in the following text.

Table 5: 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>Preferred vaccine for healthy persons</th>
<th>Preferred vaccine for persons with chronic health conditions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 6–23 months of age</td>
<td>TIV</td>
<td>-</td>
<td>-</td>
<td>Only TIV is available for this age group</td>
</tr>
<tr>
<td>Children 2–17 years of age</td>
<td>TIV, LAIV</td>
<td>LAIV</td>
<td>No preference</td>
<td>Children with immune compromising conditions:</td>
</tr>
<tr>
<td>Adults 18–59 years of age</td>
<td>TIV, TIV-ID (9 µg), LAIV</td>
<td>No preference</td>
<td>TIV, TIV-ID (9 µg)</td>
<td>Adults with immune compromising conditions:</td>
</tr>
<tr>
<td>Adults 60–64 years of age</td>
<td>TIV, TIV-ID (15 µg)</td>
<td>No preference</td>
<td>No preference</td>
<td></td>
</tr>
<tr>
<td>Adults 65+ years of age</td>
<td>TIV, TIV-ID (15 µg), MF59-adjuvanted TIV</td>
<td>No preference</td>
<td>No preference</td>
<td></td>
</tr>
<tr>
<td>Pregnant women</td>
<td>TIV, TIV-ID (9 µg)</td>
<td>No preference</td>
<td>No preference</td>
<td>LAIV not recommended</td>
</tr>
</tbody>
</table>

TIV = trivalent inactivated influenza vaccine (for IM administration); TIV-ID = trivalent inactivated influenza vaccine for intradermal injection; LAIV = live attenuated influenza vaccine
Children 6 to 23 months of age

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

Children 2 to 17 years of age

Both TIV and LAIV (FluMist™) can be used in children between 2 and 17 years of age, with or without chronic health conditions.

Based on effectiveness, efficacy and immunogenicity data, NACI recommends LAIV as the preferred product for use in healthy children and adolescents 2–17 years of age. If LAIV is not available, TIV should be used as it is safe, efficacious and effective in this group.

NACI recommends that LAIV can be used in children 24 months and older with stable, non-severe asthma and in children with chronic health conditions (excluding those with immune compromising conditions and severe asthma (see definition below). Based on expert review, it is expected that LAIV should be as safe, immunogenic and efficacious in immune competent children with chronic health conditions as it is in healthy children. However, at this time there is insufficient evidence available to prefer LAIV over TIV in children with chronic health conditions.(18)

LAIV is not recommended for children with immune compromising conditions or those 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, but can be given to children with stable, non-severe asthma.

Adults 18 to 59 years of age

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

Clinical trial data have shown that TIV-ID (9 µg/strain) is statistically non-inferior to TIV (Vaxigrip®) for all three influenza strains assessed.(17) There is some evidence that TIV may provide better efficacy than LAIV in healthy adults although not all studies are consistent on this point.(18)

For adults in this age group with chronic health conditions, either TIV or TIV-ID (9 µg/strain) may be used. Data are limited on the use of TIV-ID in this population; however, they suggest that TIV-ID is safe and at least as immunogenic as TIV in vaccine hyporesponsive populations with chronic health conditions.(17) 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.(18) LAIV is not recommended for adults with immune compromising conditions.

For information related to health care workers refer to section VI.

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 and TIV-ID (15µg/strain). NACI concludes that there is insufficient evidence to make a recommendation for the preferential use for either TIV or TIV-ID in this age group as there are no efficacy studies for TIV-ID.

Data from two clinical trials in adults 60 years of age and above suggest that the immune response to TIV-ID, in both healthy participants and those with chronic conditions, is statistically superior to TIV (Vaxigrip®), although the clinical significance of differences remains uncertain.(17) For further details, consult the NACI intanza® addendum.

Adults ≥65 years of age

Three types of vaccine are available for use in adults ≥65 years of age: TIV, TIV-ID (15µg/strain) and MF59-adjuvanted TIV. At this time, NACI concludes there is insufficient evidence to make a recommendation for the preferential use of any of these vaccines in adults ≥65 years of age.(17)(19) There are no published efficacy studies available for TIV-ID. For MF59-adjuvanted TIV, a few observational studies suggest that Fluad® 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. (19)(42–45)
There is evidence from randomized controlled trials showing that Fluad® induced higher immunogenicity and broader cross-reactivity in adults 65 years of age and older compared to the non-adjuvanted subunit vaccines, with similar but less consistent results shown in terms of improvement in antibody response relative to split-virus vaccine. 

The intradermal product, Intanza®, has been shown to elicit an immune response that is non-inferior to TIV, with or without adjuvant, administered by the intramuscular route, with some variation in results according to the serological method used. In adults 60 years of age and older, data from two clinical trials with over 4800 participants demonstrated that immune response to Intanza® was statistically superior to Vaxigrip®, although differences in seroprotection rates were small.

The clinical significance of these findings for both TIV-ID and MF59-adjuvanted TIV, in terms of protection against laboratory-confirmed influenza illness, is not known.

**Pregnant women**

Both TIV and TIV-ID (9 µg) are available for use in pregnant women. NACI has no preference for the use of either product. 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 who have direct patient contact 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 who have direct patient contact to be immunized against influenza implies failure in their duty of care to patients.

NACI recommends that TIV, 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.

In order 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.
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices (US)</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AEFI</td>
<td>Adverse event following immunization</td>
</tr>
<tr>
<td>AI/AN</td>
<td>American Indian and Alaska Natives</td>
</tr>
<tr>
<td>AMMI</td>
<td>Association of Medical Microbiology and Infectious Disease</td>
</tr>
<tr>
<td>AOM</td>
<td>Acute otitis media</td>
</tr>
<tr>
<td>ARI</td>
<td>Acute respiratory infection</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>ca</td>
<td>Cold-adapted</td>
</tr>
<tr>
<td>CADTH</td>
<td>Canadian Agency for Drugs and Technologies in Health</td>
</tr>
<tr>
<td>CAEFISS</td>
<td>Canadian Adverse Events Following Immunization Surveillance System</td>
</tr>
<tr>
<td>CATMAT</td>
<td>Committee to Advise on Tropical Medicine and Travel</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>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CIRID</td>
<td>Centre for Immunization and Respiratory Infectious Diseases</td>
</tr>
<tr>
<td>CNISP</td>
<td>Canadian Nosocomial Infection Surveillance Program</td>
</tr>
<tr>
<td>CSACI</td>
<td>Canadian Society of Allergy and Clinical Immunology</td>
</tr>
<tr>
<td>ECDC</td>
<td>European Centre for Disease Prevention and Control</td>
</tr>
<tr>
<td>ECMO</td>
<td>Extracorporeal membrane oxygenation</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency department</td>
</tr>
<tr>
<td>FFU</td>
<td>Fluorescent focus units</td>
</tr>
<tr>
<td>GBS</td>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>HA</td>
<td>Haemagglutinin</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>HCW</td>
<td>Health care worker</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>HRR</td>
<td>Hazard rate ratio</td>
</tr>
<tr>
<td>ICD</td>
<td>International classification of diseases</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>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>IRR</td>
<td>Incidence rate ratio</td>
</tr>
<tr>
<td>LAIV</td>
<td>Live attenuated influenza vaccine</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of stay</td>
</tr>
<tr>
<td>LRI</td>
<td>Lower respiratory infection</td>
</tr>
<tr>
<td>LTCF</td>
<td>Long-term care facility</td>
</tr>
<tr>
<td>MAARI</td>
<td>Medically attended acute respiratory illness</td>
</tr>
<tr>
<td>MAE</td>
<td>Medically attended event</td>
</tr>
<tr>
<td>mL</td>
<td>Millilitre</td>
</tr>
<tr>
<td>MCO</td>
<td>Managed care organization</td>
</tr>
<tr>
<td>NA</td>
<td>Neuraminidase</td>
</tr>
<tr>
<td>NACI</td>
<td>National Advisory Committee on Immunization</td>
</tr>
<tr>
<td>NE</td>
<td>Not estimated</td>
</tr>
<tr>
<td>NML</td>
<td>National Microbiology Laboratory</td>
</tr>
<tr>
<td>OME</td>
<td>Otitis media with effusion</td>
</tr>
<tr>
<td>OPV</td>
<td>Oral poliovirus vaccine</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>ORS</td>
<td>Oculorespiratory syndrome</td>
</tr>
<tr>
<td>OTC</td>
<td>Over the counter</td>
</tr>
<tr>
<td>PCV7</td>
<td>Heptavalent pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</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>PICU</td>
<td>Paediatric intensive care unit</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>RE</td>
<td>Reactogenicity event</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td>RTI</td>
<td>Respiratory tract infection</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>Reverse transcription polymerase chain reaction</td>
</tr>
<tr>
<td>rRT-PCR</td>
<td>Real-time reverse transcription polymerase chain reaction</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>TESSy</td>
<td>The European Surveillance System</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>UIIP</td>
<td>Universal Influenza Immunization Program (Ontario)</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>URI</td>
<td>Upper respiratory infection</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 effectiveness</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
References


(73) C. Czerkinsky and J. Holmgren. mucosal delivery routes for optimal immunization: targeting immunity to the right tissues. 2012 [cited 1 August 2013].


(110) Public Health Agency of Canada. Vaccine surveillance report—adverse events following immunization. 2010 Apr 27.


(117) Aboriginal Affairs and Northern Development Canada. Royal Commission on Aboriginal peoples: People to people, nation to nation. Highlights from the report of the Royal Commission on Aboriginal peoples. 1996.


(133) Department of Health UK. Flu vaccination for poultry workers. 2007.

(134) Gray GC, Trampi DW, Roth JA. Pandemic influenza planning: shouldn’t swine and poultry workers be included?. Vaccine. 2007;25(22):4376–81.
