

# An Advisory Committee Statement (ACS)

## National Advisory Committee on Immunization (NACI)<sup>†</sup>

### Statement on Seasonal Influenza Vaccine for 2011–2012

---

#### Preamble

---

*The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada with ongoing and timely medical, scientific and public health advice relating to immunization and certain prophylaxis agents. The Public Health Agency of Canada (PHAC) acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product leaflet(s). Recommendations for use and other information set out herein may differ from that set out in the product monograph(s)/leaflet(s) of the Canadian manufacturer(s). Manufacturer(s) have sought approval of the vaccine(s) and provided evidence as to 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 has been developed by the Association of Medical Microbiology and Infectious Disease Canada (AMMI Canada) and can be accessed at: <http://www.ammi.ca/pdf/UseOfAntiviralDrugs.pdf>.*

#### Table of Contents

- I. Introduction
- II. Methods
- III. Epidemiology
- IV. Seasonal Influenza Vaccine
- V. Recommendations
- VI. Strategies for Reducing the Impact of Influenza
- VII. Immunization of Health Care Workers
- VIII. Research Priorities
- IX. Surveillance Issues
- Summary Table of Information contained in the NACI Statement
- Tables
- List of Abbreviations
- References

## 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 2011-2012 season, based on evidence available at this time.

The seasonal trivalent vaccine for 2011-2012 contains the same three components as the 2010-2011 vaccine. These are an A/California/7/2009 (H1N1)-like virus, an A/Perth/16/2009 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus (B Victoria lineage).

The 2011-2012 statement contains updated epidemiological information from the 2010-2011 influenza season and product information for all eight authorized influenza vaccines, including the recently approved products: Intanza®, FluMist®, Fludax® and Fluzone®. A new table outlines the product characteristics for each vaccine. Full details, including recommendations for persons with immune compromising and other chronic health conditions, can be found in the statement.

NACI now recommends that a full dose of influenza vaccine should be used for children 6 to 35 months of age, based on evidence showing moderate improvement in antibody response without increase in reactogenicity.

Immunization programs should 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. The special considerations category from the 2010-2011 statement has been removed (including children 2 to 4 years of age) as it is felt that elevated pandemic-related risk no longer exists for the groups in this category. Two of the groups (persons with morbid obesity and Aboriginal peoples) that NACI identified for special consideration for influenza vaccine in 2010-2011 have now been added to the list of high-risk recipients for ongoing annual vaccination.

Another major change in the statement is the advice for persons with egg allergy. Egg allergy is no longer considered a contraindication for trivalent influenza vaccine. After careful review, NACI concludes that egg-allergic individuals may be vaccinated against influenza using TIV, without a prior influenza vaccine skin test, based on an assessment of risk for a severe allergic reaction to guide the method of vaccination. Details of the procedures are found in the statement. Data are not currently available to support this recommendation for LAIV.

### 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. Since 1977 the human H3N2 and human H1N1 influenza A subtypes have contributed to influenza illness to varying degrees each year. 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 variously to influenza illness each year.

Seasonal influenza vaccine is reformulated annually to include 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.<sup>(1-5)</sup> Over time, antigenic variation (antigenic drift) of strains occurs within an influenza A subtype or B lineage. Despite this antigenic drift, some cross-protection among strains belonging to the same A subtype or B lineage is expected, depending on how different the strains are. Because antigenic drift usually occurs in one or more influenza vaccine components, a new vaccine formulation is considered each year.

For the 2011-2012 season in the Northern Hemisphere, the World Health Organization (WHO) recommends that the trivalent vaccine contain A/California/7/2009(H1N1)-like, A/Perth/16/2009(H3N2)-like, and B/Brisbane/60/2008(Victoria lineage)-like antigens.<sup>(6)</sup> All three components are unchanged from the 2010-2011 seasonal influenza vaccine.

## II. Methods

Details regarding NACI's evidence-based process for developing a statement are outlined in *Evidence-Based Recommendations for Immunization: Methods of the NACI, January 2009, CCDR*, available from: <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/acs-1/index-eng.php>.

The Influenza Working Group (IWG) reviewed the annual influenza vaccine recommendations for consideration by NACI and discussed 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 the overall immunization strategy. The epidemiological analysis of the 2010-2011 season was prepared by the Influenza Surveillance Section of PHAC.

The IWG also reviewed the key questions for selective literature reviews for obesity, Aboriginal status and residence in remote locations as risk factors for severe influenza-related disease, and for vaccination of persons with egg allergy. Knowledge synthesis for the risk factor review was performed by The Canadian Agency for Drugs and Technologies in Health (CADTH) and for the egg allergy review by PHAC, and supervised by the IWG chair and the IWG. Following critical appraisal of individual studies, summary tables with ratings of the quality of the evidence, and proposed recommendations for vaccine use were developed. The CADTH rapid response report on the influenza-related risk factors noted above has been published.<sup>(7)</sup> The evidence tables for the egg allergy review are found in Table 6 of this statement.

The evidence and proposed recommendations were presented to NACI on June 2, 2011. 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 text. PHAC maintains documentation of these processes throughout knowledge synthesis and recommendation development.

## III. Epidemiology

### III.1 Disease Description

It is estimated that between 5 to 10% of the population becomes infected with influenza each year.<sup>(8)</sup> Rates of influenza infection are highest in children, but rates of serious illness and death are highest in older persons (> 65 years) and persons with underlying medical conditions.<sup>(9)</sup> The true burden of influenza is difficult to assess for several reasons. 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. In addition, influenza testing is not often sought to confirm the diagnosis or may be sought late. It is estimated, however, that in a given year up to 20,000 hospitalizations related to influenza may occur; that between 4,000 to 8,000 Canadians, mostly seniors, may die from pneumonia related to influenza; and that others may die from other serious complications of influenza.<sup>(10)</sup>

## III.2 National Influenza Surveillance in the 2011-2012 Season

### III.2.1 Disease Distribution

National influenza surveillance is coordinated through the Centre for Immunization and Respiratory Infectious Diseases (CIRID), PHAC. The FluWatch program collects data and information from seven different sources to provide a national picture of influenza activity:

- (1) laboratory-based influenza detections from public health and hospital laboratories;
- (2) strain characterization and antiviral resistance of circulating influenza viruses from the National Microbiology Laboratory (NML);
- (3) consultations of influenza-like illness (ILI) from sentinel practitioners;
- (4) number of influenza/ILI outbreaks;
- (5) regional influenza activity levels from provincial and territorial FluWatch representatives;
- (6) paediatric influenza-associated hospital admissions and mortality data through the Immunization Monitoring Program Active (IMPACT); and
- (7) adult influenza-associated hospitalizations and deaths from select hospitals across the country through the Canadian Nosocomial Infection Surveillance Program (CNISP).

Detailed methodology for FluWatch has been described previously.<sup>(11)</sup> Further enhancements, which include the seventh surveillance component above, were made to FluWatch during the 2009 H1N1 pandemic and continued during the 2010-2011 influenza season.

The information in this statement for the 2010-2011 season is based on surveillance data from 1 September, 2010, to 9 April, 2011, unless otherwise specified. Data are preliminary and numbers may fluctuate because of delayed reporting. For final surveillance numbers, readers should refer to the annual FluWatch report available from: <http://www.phac-aspc.gc.ca/fluwatch/aiisr-raisi-eng.php>.

In contrast to the 2009-2010 season during which the second wave of pandemic H1N1 2009 (pH1N1) started mid-September and peaked from late October to mid-November, the 2010-2011 influenza season returned to a more typical seasonal pattern in Canada. Laboratory detections of influenza virus started increasing in mid-November (week 45) and peaked from the end of December 2010 to early January 2011 (weeks 52 and 01). The rate of ILI consultations was within the range expected for the influenza season, following the same increase as laboratory confirmations of influenza in November/December and continuing into April 2011. The number of regions reporting widespread influenza/ILI activity was greatest in the five week period from week 51 to week 03, and several regions across Canada continued to report localized influenza/ILI activity levels into April 2011. Overall influenza activity was low during the 2010-2011 season compared to the second wave of the 2009 H1N1 pandemic and was within expected range for non-pandemic years.

Influenza A/H3N2, pH1N1 and influenza B viruses were all detected in Canada during the 2010-2011 season. During the period September 1, 2010 to April 9, 2011, 121,147 laboratory tests were conducted, of which 18,197 (15.0%) were positive for influenza: 16,106 (88.5%) were influenza A and 2,091 (11.5%) were influenza B. Subtype information was available for 39.2% of the 16,106 influenza A detections, and of those, 84.7% (5,351/6,317) were A/H3N2 and 15.3% (966/6,317) were pH1N1 viruses. No other A/H1N1 viruses were detected during the 2010-2011 season. During the later part of the season, the

proportion of influenza B specimens increased from 3.4% of influenza positive specimens in mid-January (week 03) to 59.0% in the first week of April (week 14). As has been observed in previous influenza seasons in Canada, laboratory detections peaked earlier in central and western Canada (around the first week of January, week 01) compared to the Atlantic provinces (end of February, week 08).

Through detailed case-based laboratory reporting where age data are provided, from August 29, 2010 to April 9, 2011, 51.3% (1927/3779) of cases with A/H3N2 were 65 years of age or above. In contrast, the majority of laboratory-confirmed cases with pH1N1 (94.0%, 632/672) and influenza B (89.4%, 618/691) were from persons under 65 years of age.

The NML antigenically characterized 632 influenza viruses during the period from September 1, 2010 to April 14, 2011, that were received from provincial laboratories across Canada: 228 A/H3N2, 109 pH1N1, and 295 B viruses. Of the 228 influenza A/H3N2 viruses characterized, 225 (98.7%) were antigenically related to A/Perth/16/2009, which was the influenza A/H3N2 component recommended for the 2010-2011 influenza vaccine. Of the 109 pH1N1 viruses characterized, 108 (99%) were antigenically related to the pandemic vaccine virus A/California/7/2009, which was the recommended H1N1 component for the 2010-2011 influenza vaccine. Of the 295 influenza B viruses characterized, 280 (94.9%) were antigenically related to B/Brisbane/60/08 (Victoria lineage), which was the recommended influenza B component for the 2010-2011 influenza vaccine. Fifteen (5.1%) influenza B viruses were characterized as B/Wisconsin/01/2010-like, which belongs to the Yamagata lineage. B/Wisconsin/01/2010-like viruses were antigenically and genetically different from the previous Yamagata lineage vaccine strain B/Florida/04/2006. The vast majority of influenza viruses that circulated this season were antigenically similar to the recommended components of the 2010-2011 trivalent influenza vaccine.

Since the beginning of the 2010-2011 season, weekly influenza-like illness (ILI) consultation rates were within or below expected levels except for week 3, where the ILI rates were slightly above the expected range. ILI consultations peaked in week 52, at 51 consultations per 1,000 patient visits. The highest ILI consultation rate was in children age 0 to 4 years of age at 54 consultations per 1,000 patient visits.

Of the 522 influenza or ILI outbreaks reported between September 1, 2010 and April 9, 2011, there were 293 (56.1%) influenza outbreaks reported in long-term care facilities (LTCF), 140 (26.8%) ILI outbreaks in schools, 29 (5.6%) influenza outbreaks in hospitals, and 60 (11.5%) ILI outbreaks in other facilities. Of the LTCF outbreaks where the type of influenza was identified (43.0%, 126/293), the majority were identified as influenza A (97.6%; 124/126), either influenza A/H3N2 or unsubtype.

Sixty-eight percent (353/522) of outbreaks occurred in a nine-week period between the end of December and early March. The number of outbreaks reported to April 9, 2011 in LTCFs is within the range expected for an influenza A/H3N2 season. Note that not all provinces report school outbreaks; therefore comparisons cannot be made to previous seasons.

Widespread influenza activity was reported 23 times by 10 regions in 5 provinces since the start of the season. The majority of widespread activity was reported almost continuously between early December 2010 and late March 2011 and was reported mostly in Toronto, Ontario (30% of widespread reports), and in central Quebec (30%).

Since 2004, paediatric (16 years of age and under) hospitalizations with influenza have been reported through the IMPACT network, which included 12 reporting hospitals in the 2010-2011 season. Preliminary data show that a total of 620 cases were reported from September 1, 2010 to April 9, 2011 of which 72.6% (450/620) were influenza A and 27.4% (170/620) influenza B. Among cases of influenza A, 22.4% (101/450) were A/H3N2, 4.9% (22/450) were pandemic H1N1 2009, and 72.7% (327/450) were unsubtype influenza. The largest number (64 cases) was admitted in week 52, but the overall trend was increasing towards a broad peak around weeks 05 to 08. In week 03, paediatric hospitalizations with influenza B began to increase and by week 10 (early March) accounted for more cases than influenza A.

There were 13 cases of myositis associated with either influenza A or B. These cases were geographically distributed across the country and affected all paediatric age groups.

Influenza surveillance in hospitalized adult patients continued in 2010-2011 via CNISP. CNISP conducted surveillance of laboratory-confirmed influenza in adults (patients 16 years of age and older) admitted to 35 selected tertiary care hospitals across the country. Between June 1, 2010, and April 9, 2011, CNISP reported 943 hospitalized cases of which 93.6% (883/943) were identified to have influenza A, and 6.4% (60/943) influenza B. Sixty-eight percent of cases (637/943) were identified with unsubtype influenza A, 21.3% (201/943) with A/H3N2, 4.8% (45/943) with pH1N1, and 6.4% (60/943) with influenza B. The peak in adult hospitalizations was observed in week 52 with 139 cases admitted to CNISP participating facilities.

### **III.2.2 Risk Factors for Severe Disease**

The IMPACT program provided information on age and other risk factors for severe disease in children. Detailed case information was available for 533 (86.0%) of the 620 total paediatric hospitalizations. Seventy six percent of the hospitalized cases were under 5 years of age (18.2% among 0-5 month olds; 28.1% among 6-23 month olds; 29.6% among the 2-4 year-olds), 15.2% were among children 5-9 years of age and 8.8% among children 10-16 years of age.

Overall, 196 of 533 paediatric cases (36.7%) had an underlying health condition for which seasonal influenza vaccine is recommended and of those, only 22 (11.2%) had been vaccinated. Among the 151 paediatric cases between 6-23 months of age, 41 (27.1%) had an underlying condition; only 8 (5.2%) of these 151 cases were vaccinated. Among the 157 cases between 2-4 years of age, 65 (41.4%) had an underlying health condition; only 7 of these 157 cases (4.4%) were vaccinated.

Based on available data collected from 533 paediatric cases, the median length of stay (LOS) overall was 2 days. It was higher for cases 6-23 months and 5-9 years of age (3 days), and 10-14 years of age (4 days). Cases 2-4 years of age had a median LOS of 2 days. Intensive care was required for 63 hospitalized patients, for whom the median LOS was 3 days for children 6-23 months and 5-9 years of age, 2 days for those 2-4 years of age, and 6 days for those 10-14 years of age. Antibiotic use was reported in 76.9% (410/533) of cases, whereas antiviral use was reported in 19.5% (104/533) of cases, including 11 (10.6%) of those under 6 months of age.

Among the 533 paediatric cases, 5 deaths were reported. Three occurred in cases between 6 and 23 months of age, two with pH1N1 and one with influenza B; one death occurred in a child between 2 and 4 years of age with influenza B; and one death was in a child between 10 and 16 years of age with influenza A/H3. All cases had underlying comorbidities. None were vaccinated.

The CNISP program provided information on age and other risk factors for severe disease in adults. As of March 30, 2011, additional case information had been received for 595 of the 943 adult hospitalizations. Age was reported for 594 cases, of which 55.2% (328/594) were over 75 years of age, and a further 20.9% (124/594) were between 60 and 74 years of age. Among the hospitalized adult cases, 53 (8.9%) were admitted to the intensive care unit (ICU) and 33 (5.5%) died. Among the 33 fatal cases reported, 75.8% (25/33) were over 65 years of age, 18.2% (6/33) were between 40 and 64 years of age, and 6.1% (2/33) were between 16 and 39 years of age. All fatal cases were associated with influenza A: 51.5% (17/33) unsubtype, 42.4% (14/33) A/H3N2 and 6.1% (2/33) pH1N1.

Three percent (1/33) of fatal cases, 6% (3/53) of ICU admissions, and 1% (5/595) of hospitalized adults reported from participating CNISP facilities were identified as Aboriginal. Pregnancy was identified as an underlying condition in 3% (1/33) of fatal cases, 8% (4/53) of ICU admissions, and 3% (14/595) of hospitalizations. Chronic medical conditions were

noted in 89% (531/595) of hospitalized adult cases with influenza, 94% (50/53) of ICU admissions and 100% (33) of fatal cases. A total of 974 chronic conditions were reported among the 595 hospitalized cases, resulting in a mean of 1.64 conditions per person. For ICU admissions the mean was also 1.64 chronic conditions per case, and for fatal cases a mean of 2.36 chronic conditions was reported per case. The most common comorbidities were chronic heart disease (23%), diabetes (15%) and chronic lung disease (12%).

Of the adult hospitalizations for which vaccination information was provided, 14% (83/595) had received the monovalent pH1N1 vaccine the previous year, 14% (81/595) had not, and 72% (431/595) had an unknown vaccine history for 2009-2010. Similarly, 15% (87/595) had received the 2010-2011 trivalent influenza vaccine, 22% (129/595) had not, and 64% (379/595) were unknown.

Seventy-four percent (438/595) of adult hospitalized cases were treated with antibiotics for symptoms related to influenza, and 86% (513/595) were treated with antivirals: 511 with oseltamivir and 2 with zanamivir.

The average length of stay was 8.3 days (SD 18.3, median 5, range 0-81 days) for adult hospitalized cases, 13.3 days (SD 9.5, median 11.5, range 2-49 days) for cases admitted to ICU, and 10.3 days (SD 11, median 7, range 1-57 days) for fatal cases. Among fatal cases, 16% (5/33) were admitted to the ICU for complications associated with influenza, and 16% (5/33) required mechanical ventilation for complications associated with influenza.

In summary, 73% of adult hospitalizations this season were in people aged 64 years and older, in keeping with a typical influenza A/H3N2 season, and most of the hospitalized cases had at least one underlying medical condition.

### III.3 International Influenza Surveillance

Between September 2010 and January 2011, pH1N1 viruses predominated in Asia and Europe while influenza A/H3N2 viruses predominated in the Americas. Influenza B viruses co-circulated in many countries in the Northern Hemisphere and were the predominant virus in some countries. Seasonal influenza A/H1N1 viruses (other than pH1N1) were detected sporadically in very few countries. The proportion of different strains circulating varied by region and also varied within regions during the course of the influenza season. Globally, the circulating influenza strains were well matched with the recommended vaccine components of trivalent influenza vaccines for both the Northern and Southern Hemispheres.<sup>(6)</sup>

#### III.3.1 United States

The 2010-2011 influenza season started in mid-December in the United States and influenza activity became widespread in January 2011. Influenza A/H3N2, pH1N1, and influenza B viruses co-circulated in the United States with the predominant virus varying over time and by region. Influenza A predominated in all regions during January and early February, and more than 80% of subtyped influenza A viruses from November and December were influenza A/H3N2. However, the proportion of pH1N1 increased from January reaching 40.4% of subtyped influenza specimens by April 9, 2011 (week 14).<sup>(12)</sup>

The Centers for Disease Control and Prevention (CDC) antigenically characterized 1,810 influenza viruses up to April 9, 2011, of which the vast majority were similar to the components of the 2010-2011 seasonal influenza vaccine. Among the 424 pH1N1 viruses, all but one (99.8%) were A/California/7/2009-like. Of the A/H3N2 viruses tested, 97% (812/841) were characterized as A/Perth/16/2009-like. Of the 545 influenza B viruses tested, 516 (94.7%) belong to the B/Victoria lineage of viruses; 515 (99.8%) of these were characterized as B/Brisbane/60/2008-like. Twenty-nine (5.3%) of the 545 viruses were identified as belonging to the B/Yamagata lineage of viruses.<sup>(13)</sup>

Among the 91 paediatric influenza-associated deaths reported in the US, 34 (37.4%) were associated with influenza B viruses, 23 (25.3%) were associated with pH1N1 viruses, 17 (18.7%) reported were associated with influenza A (H3N2) viruses, and 17 (18.7%) were associated with unsubtyped influenza A.<sup>(13)</sup>

The highest hospitalization rates for laboratory-confirmed cases of influenza were among persons 65 years of age and older (58.1 cases / 100,000 population) and under 5 years of age (42.6 cases / 100,000). Among paediatric hospitalized patients, 50.5% had no reported underlying condition while 19.0% reported having asthma. The most common underlying conditions among hospitalized adults were cardiovascular disease (35.6%), metabolic disorders (34.5%), chronic lung disease (22.4%), and asthma (19.7%). Only 14.8% of hospitalized adults had no reported underlying condition.<sup>(13)</sup>

### **III.3.2 Europe**

In Europe pH1N1 predominated early in the season, followed by an increase in influenza B detections in many European countries in December 2010 and January 2011. In the United Kingdom (Great Britain and Northern Ireland) and Western Europe, pH1N1 activity started around week 47 and reached peaks or declined by January 2011. This pH1N1 activity subsequently increased through February and March 2011 in some countries in central and south Eastern Europe,<sup>(6)</sup> and was tapering off in all countries around week 13 (28 March to 3 April 2011).<sup>(14)</sup> Influenza B was dominant or co-dominant in 11 countries in week 13 (28 March to 3 April 2011).<sup>(14)</sup>

From week 40, 2010 to week 13, 2011, 66.7% of influenza detections from sentinel and non-sentinel specimens reported to the European Centre for Disease Prevention and Control (ECDC) were influenza A and 33.3% were influenza B viruses. Of subtyped influenza A viruses, 97.6% were pandemic H1N1 2009 and 2.4% were A/H3 viruses.<sup>(14)</sup>

In the United Kingdom (UK), outbreaks and reports of severe cases increased before ILI consultation rates rose above baseline levels. Around week 51 (ending 23 December 2010), an increasing number of severe cases were reported, particularly among people under 65 years of age with pandemic H1N1 2009, and several cases required extracorporeal membrane oxygenation (ECMO) treatment. For 7 out of 8 weeks in January-February 2011, the number of deaths in England and Wales exceeded the predicted upper limit for all-cause mortality at that time of year. Among cases with available information from the UK, 68% (340/497) of fatal cases were in a clinical risk group for vaccination, including underlying respiratory disease. Among fatal cases with information on vaccination status, 71% (135/189) had not received the 2010-2011 seasonal influenza vaccine, and 91% (51/56) cases with available information had not received the pandemic H1N1 2009 vaccine.<sup>(15)</sup>

### **III.3.3 Southern Hemisphere**

In the Southern Hemisphere, influenza activity in general was low during this period with the exception of some South American countries where widespread activity was reported. Pandemic H1N1 was reported at low levels in a few countries in southern Africa, South America and Oceania. Influenza A/H3N2 was the predominant virus in many countries in South America with widespread outbreaks occurring in September in Chile. Localized and sporadic activity was also reported in southern Africa, South America and Oceania.

In tropical areas, many countries experienced outbreaks of varying intensity of pH1N1, A/H3N2 and B viruses.

Following the early arrival of pH1N1 during the 2009 influenza season, in 2010 Australia saw a return to the usual season pattern of influenza, with peak activity in late September. In Australia, to 5 November 2010, 64% of influenza detections were pH1N1, 25% were influenza B, and 9% were A/H3N2 (the latter predominantly detected in Western Australia).<sup>(16)</sup>

The seasonal epidemic peak of influenza activity in New Zealand occurred around mid-August 2010 and activity declined by late September 2010. The majority (1684/1992, 84.5%) of influenza detections were pH1N1, with only sporadic detections of A/H3N2 (7/1992, 0.4%) and influenza B (11/1992, 0.6%).<sup>(17)</sup>

From October 2010 to April 2011, Australia experienced continued circulation of A/H3N2, particularly in the northern tropical regions of the country.<sup>(18)</sup> From March 19 to April 1, 2011, levels of influenza-like illness (ILI) in the community remained low through all surveillance systems. However, the number of laboratory-confirmed notifications was unusually high, especially in the Northern Territory and Queensland. Queensland reported circulation of mostly pH1N1 and A/H3N2, while the majority of cases in the Northern Territory were A/H3N2.<sup>(19)</sup>

### **III.3.4 Animal Influenza**

From September 1, 2010, to April 11, 2011, 44 human cases of influenza A/H5N1 (including 20 deaths) were confirmed in Egypt, Indonesia, Hong Kong SAR China, Cambodia and Bangladesh. The largest number of cases reported was from Egypt (29), followed by Indonesia (8). All cases with concluded investigations had reported exposure to sick or dead poultry.<sup>(10)</sup> From 2003 to April 11, 2011, a total of 549 human cases and 320 deaths have been confirmed from 15 countries.<sup>(21)</sup> To date, there has been no evidence of sustained human-to-human transmission due to avian influenza.<sup>(22)</sup>

According to a WHO report<sup>(23)</sup> published on the 2010 laboratory-confirmed infections with avian influenza H5N1, the majority (62.5%, 30/48) of cases were reported between January and April, coinciding with the Northern Hemisphere influenza season. Cases were reported by countries where A/H5N1 circulates endemically or sporadically in poultry, and most cases were exposed through direct or indirect contact with poultry or contaminated environments. The epidemiological and virological picture of A/H5N1 infection did not change substantially in 2010. Women were more frequently reported to have a worse outcome than men, and although children and young adults were more frequently diagnosed with A/H5N1, the disease seemed more likely to be mild in young children. Early recognition and hospitalization were statistically associated with favourable outcomes.<sup>(23)</sup>

No human cases of influenza A (H9N2) were reported during the period September 2010 to January 2011. From September 2010 to February 2011, a total of 8 zoonotic infections caused by swine A (H1N1), and swine A (H3N2) viruses were detected in China (1), Switzerland (1) and the United States of America (6).<sup>(6)</sup>

### **III.4 Antiviral Resistance**

Details of antiviral resistance patterns of circulating influenza strains performed by the routine surveillance program at the NML are reported by the FluWatch program. From September 1, 2010, to April 14, 2011, the NML tested 512 influenza A isolates (399 A/H3N2 and 113 pH1N1) for amantadine resistance. All except one A/H3N2 isolate, and all pH1N1 isolates were resistant to amantadine. The NML tested 565 influenza isolates (205 A/H3N2, 103 pH1N1, and 257 influenza B) for oseltamivir (Tamiflu®) resistance, and of these, 204 A/H3N2 viruses were sensitive to oseltamivir and one was resistant with E119V mutation. The resistant case was associated with oseltamivir use (prophylaxis or treatment not specified). Of the 103 pH1N1 isolates tested for oseltamivir resistance, 102 were sensitive and one was resistant with the H275Y mutation. The resistant case was associated with oseltamivir treatment. All 257 B viruses were sensitive to oseltamivir. Of 558 influenza viruses (200 A/H3N2, 100 pH1N1, and 258 influenza B) tested for resistance to zanamivir (Relenza®), all isolates were found to be sensitive.

In the United States, from October 1, 2010 to April 9, 2011, 0.3% (2/627) A/H3N2 isolates and 0.7% (18/2,561) of pH1N1 isolates were found to be resistant to oseltamivir. No

resistance to oseltamivir was detected among influenza B specimens tested, and no resistance to zanamivir in any specimen was detected.<sup>(13)</sup>

Worldwide (to April 6, 2011), there have been 447 cases of oseltamivir-resistant pH1N1 viruses reported to WHO, all carrying the H275Y substitution. Among these, 27% of cases of oseltamivir-resistant influenza occurred in patients with immune compromising conditions, 37% were associated with prophylaxis or treatment with oseltamivir, 12% had no known association with drug use, including known or suspected cases of person-to-person transmission, and 24% of cases had insufficient clinical information or investigations were ongoing.<sup>(24)</sup>

Between week 40, 2010 and week 13, 2011, the European Surveillance System (TESSy) reported that 4.6% (91/1984) of pH1N1 viruses tested were resistant to oseltamivir, all carrying the H275Y substitution. Of specimens from patients for whom exposure to antivirals was known, 31% (17/55) were from patients who had not been treated with oseltamivir. These patients were probably infected with resistant viruses carrying the H275Y substitution.<sup>(15)</sup> Similarly, in the United Kingdom 3 of 27 cases of oseltamivir-resistant pH1N1 were not associated with prophylaxis or treatment, suggesting the potential for changing epidemiology of oseltamivir-resistant A/H1N1.<sup>(25)</sup>

Around the world, high levels of resistance to the adamantanes (amantadine and rimantadine) persisted among pH1N1 and A/H3N2 viruses during the 2010-2011 season.<sup>(13)</sup>

## IV. Seasonal Influenza Vaccine

### IV.1 Preparations Authorized for Use in Canada

#### IV.1.1 Overview

There are currently eight seasonal trivalent influenza vaccines authorized for use in Canada, of which seven are inactivated and one is a live attenuated vaccine. This statement describes the use of all eight vaccines. More detail for Intanza®, FluMist®, and Flud® vaccines may be found in supplementary NACI statements for each product.<sup>(26-28)</sup>

Full details of the composition of each vaccine 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 below and in Table 1.

The products are all manufactured by a process involving chicken eggs, which may result in the vaccine containing trace amounts of residual egg protein. All influenza vaccines currently available in Canada are considered safe for use in persons with latex allergy.

The publicly funded programs for 2011-2012 will make six of the eight authorized vaccines available to some extent. These are Fluviral® (GSK), Vaxigrip® and Intanza® (sanofi), FluMist® (AstraZeneca), and Agriflu® and Flud® (Novartis). Please consult your province or territory for specifics on the products provided in your jurisdiction.

#### IV.1.2 Trivalent Inactivated Influenza Vaccine (TIV)

Trivalent inactivated influenza vaccine, given by the intramuscular (IM) route, has been the traditional type of influenza vaccine used in Canada. There are now six TIV products authorized for IM injection, five without adjuvant and one with adjuvant. Each 0.5 mL vaccine dose of these vaccines contains 15 µg of influenza haemagglutinin (HA) of each of the three virus strains (two type A strains and one B strain). A seventh TIV product is for intradermal use only.

Historically whole cell TIV vaccines were used but they were replaced by split virus vaccines in order to reduce adverse reactions. Split virus vaccines are treated to disrupt the integrity

of the virus without diminishing the antigenic properties of the haemagglutinin and neuraminidase; they contain essentially the same elements as whole virus vaccines and in the same proportions. In recent years, subunit vaccines have also become available in Canada. Subunit vaccines are highly purified products containing surface antigen only, with most (if not all) of the internal viral components removed compared to split vaccines. Split virus and subunit vaccines are standardized to contain the same HA content (15 µg for each strain). The amount of neuraminidase in the vaccines is not standardized.

#### ***TIV without adjuvant***

The five inactivated IM influenza vaccines (without adjuvant) are as follows:

- Fluviral® (GlaxoSmithKline) is a split virus inactivated vaccine authorized for use in adults and children 6 months of age or older.
- Vaxigrip® (sanofi pasteur) is a split virus inactivated vaccine authorized for use in adults and children 6 months of age or older.
- Fluzone® (sanofi pasteur) is a split virus inactivated vaccine for use in adults and children 6 months of age or older. Fluzone® was re-authorized for use in Canada in spring 2011.
- Agriflu® (Novartis) is a surface antigen, inactivated subunit vaccine authorized for use in adults and children 6 months of age or older.
- Influvac® (Abbott) is a surface antigen, inactivated subunit vaccine authorized for use in persons ≥18 years of age.

#### ***MF59-adjuvanted TIV***

Fluad® (Novartis) is a surface antigen, inactivated subunit vaccine containing MF59 adjuvant and is authorized for use in persons ≥65 years of age. MF59 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.

#### ***TIV for intradermal use***

Intanza® (sanofi pasteur) is an inactivated split-virus vaccine for intradermal injection. There are two formulations: the product authorized for persons 18-59 years of age contains 9 µg HA (for each of the three strains) per 0.1 mL, whereas the product authorized for persons ≥ 60 years of age contains 15 µg HA (for each of the three strains) per 0.1 mL.

### **IV.1.3 Live Attenuated Influenza Vaccine (LAIV)**

FluMist® is a live attenuated influenza vaccine for administration by intranasal spray and is 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  $10^{6.5-7.5}$  fluorescent focus units (FFU) of live attenuated virus reassortants of each of three strains propagated in specific 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.

**Table 1 – Characteristics of influenza vaccines authorized in Canada, 2011-2012**

<b>Product characteristics</b>	<b>Trivalent inactivated vaccine (TIV)</b>							<b>LAIV</b>
<b>Manufacturer</b>	Abbott	GSK	Novartis		sanofi pasteur			AstraZeneca
<b>Product name</b>	Influvac®	Fluviral®	Agriflu®	Fluad®	Vaxigrip®	FluZone®	Intanza®	FluMist®
<b>Vaccine type</b>	Inactivated - subunit	Inactivated - split virus	Inactivated - subunit	Inactivated - subunit	Inactivated - split virus	Inactivated - split virus	Inactivated - split virus	Live attenuated
<b>Route of administration</b>	IM	IM	IM	IM	IM	IM	Intradermal (ID)	Intranasal spray
<b>Authorized ages for use</b>	≥ 18 years	≥ 6 months	≥ 6 months	≥ 65 years	≥ 6 months	≥ 6 months	≥ 18 years	2-59 years
<b>Antigen content (each of three strains)</b>	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	15 µg HA /0.5 mL dose	9 µg HA /0.1 mL (18-59 yrs) 15 µg HA /0.1 mL (60+ yrs)	10 <sup>6.5-7.5</sup> FFU of live attenuated reassortants /0.2 mL dose
<b>Adjuvant</b>	No	No	No	MF59 (oil-in-water emulsion)	No	No	No	No
<b>Formats available</b>	Single dose pre-filled syringes	5 mL multidose vial	Single dose pre-filled syringes	Single dose pre-filled syringes	5 mL multi-dose vial, single dose ampoule, single-dose pre-filled syringes	5 mL multi-dose vial, single dose ampoule, single-dose pre-filled syringes	Single dose pre-filled syringes with micro-injection system Two formulations (as above)	Prefilled single use glass sprayer
<b>Thimerosal</b>	No	Yes	No	No	Yes - multi-dose vials only	Yes - multi-dose vials only	No	No
<b>Antibiotics (traces)</b>	Gentamicin	None	Kanamycin Neomycin	Kanamycin Neomycin	Neomycin	Neomycin	Neomycin	Gentamicin
<b>Other clinically relevant non-medicinal ingredients*</b>	Egg protein Formaldehyde Cetyltrimethyl-ammonium bromide(CTAB) Polysorbate 80	Egg protein Formaldehyde Sodium deoxycholate Sucrose	Egg protein Formaldehyde Polysorbate 80 CTAB	Egg protein Formaldehyde Polysorbate 80, CTAB	Egg protein Formaldehyde Triton X-100	Egg protein Formaldehyde Triton X-100 Gelatin Sucrose	Egg protein Formaldehyde Triton X-100	Egg protein Gelatin hydroxylate Sucrose Arginine Monosodium glutamate

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

Abbreviations: FFU (fluorescent focus units), GSK (GlaxoSmithKline), HA (haemagglutinin), ID (intradermal), IM (intramuscular), LAIV (live attenuated influenza vaccine)

## IV.2 Efficacy and Immunogenicity

### IV.2.1 Efficacy

Multiple studies, primarily with TIV, show that influenza vaccine is efficacious, with higher efficacy demonstrated against laboratory-confirmed influenza than clinically defined outcomes without laboratory confirmation.<sup>(29)</sup> With a good match, influenza vaccination has been shown to prevent influenza illness in approximately 70% to 90% of healthy children and adults<sup>(30-34)</sup> and by about half in the elderly.<sup>(35,36)</sup> A recent meta analysis identified vaccine efficacy of 50% in healthy adults (95% CI: 27–65) during select seasons of vaccine mismatch, although mismatch is a relative term and the amount of cross-protection is expected to vary.<sup>(34,37,38)</sup>

Systematic reviews have also demonstrated that influenza vaccine decreases the incidence of pneumonia, hospital admission and death in the elderly,<sup>(39,40)</sup> and reduces exacerbations in persons with chronic obstructive pulmonary disease.<sup>(41)</sup> In observational studies, immunization reduces the number of physician visits, hospitalizations and deaths in high-risk persons <65 years of age,<sup>(42)</sup> reduces hospitalizations for cardiac disease and stroke in the elderly,<sup>(43)</sup> and reduces hospitalization and deaths in persons with diabetes mellitus.<sup>(44)</sup> Increasingly, the need for caution has been expressed in the interpretation of observational studies that use non-specific clinical outcomes and that do not take into account differences in functional status or health-related behaviours.<sup>(45-50)</sup> More studies that assess vaccine protection against laboratory-confirmed influenza and its serious complications are needed.

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 protection is still likely to occur.

With the exception of LAIV there is limited efficacy information for the newer products. While brief summaries are provided below, the individual NACI statements for Intanza®,<sup>(26)</sup> FluMist®<sup>(27)</sup> and Flud®<sup>(28)</sup> may be consulted for full details.

#### ***MF59-adjuvanted TIV***

The efficacy of Flud® 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.<sup>(28)</sup>

#### ***TIV for intradermal use***

The efficacy of Intanza® against laboratory-confirmed influenza and its serious complications has not been directly studied.<sup>(26)</sup>

#### ***LAIV***

For FluMist®, a number of studies (LAIV versus placebo and LAIV versus TIV) have been conducted in children and adults.<sup>(27)</sup> LAIV showed higher efficacy in children across all age groups when compared to placebo regardless of circulating subtype and strain match. Some protection persisted to the second year without revaccination. Three large studies in children 6 months to 18 years of age demonstrated superior efficacy of LAIV compared to TIV. LAIV also demonstrated superior efficacy to TIV against acute otitis media in children 6 to 83 months of age. In contrast to children, most comparative studies in persons 18 to 59 years of age have found that LAIV and TIV had similar efficacy or that TIV was more efficacious.<sup>(27)</sup>

## **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).<sup>(51)</sup>

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, 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.

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.<sup>(52-56)</sup> Most studies have shown that administration of a second dose of influenza vaccine to elderly individuals or other individuals who may have an altered immune response does not result in clinically significant antibody boost.<sup>(55,57-60)</sup>

### ***MF59-adjuvanted TIV***

The addition of the oil-in-water adjuvant, MF59, to the inactivated influenza vaccine is designed to improve and broaden the immune response. There is evidence from randomized controlled trials showing that Fludax® 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<sup>(28)</sup> which is the type of influenza vaccine used most often in Canada. The studies which compare Fludax® to split-virus vaccine generally compared to a vaccine called Mutagrip®, which is not available in Canada. The one study that compared Fludax® to Vaxigrip®<sup>(198)</sup> found a similar seroprotection and seroconversion rate for H3N2 and a higher immune response for H1N1 and B for Fludax® 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 Fludax®. The implication of these immunogenicity findings with regard to clinical efficacy is unknown.

### ***TIV for intradermal use***

The skin is a potent immune organ and contains copious amounts of antigen-presenting dendritic cells. Influenza vaccine administered by the intradermal route is thus thought to stimulate cell-mediated immunity as well as 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.<sup>(26,61)</sup> 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 and the clinical relevance remains uncertain. No difference in immunogenicity was noted between healthy participants and those with chronic conditions.<sup>(26)</sup> In a randomized clinical trial comparing Intanza® (intradermal TIV) to Fluad®, Intanza® was shown to be non-inferior across 2 of the vaccine viral strains using the haemagglutination inhibition method and 3 strains using the single radial haemolysis method.<sup>(61)</sup>

### **LAIV**

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 as clinical efficacy studies have shown protection in the absence of a significant antibody response. Studies have demonstrated that presence of an HAI antibody response after the administration of LAIV is predictive of protection (details are provided in the FluMist® supplement statement). The immunogenicity of LAIV has been assessed in multiple studies conducted among children and adults.<sup>(27)</sup> LAIV has generally been shown to be equally, if not more immunogenic, than TIV for all three strains in children, whereas TIV was typically more immunogenic in adults than LAIV. Greater rates of seroconversion to LAIV occurred in baseline seronegative individuals compared to baseline seropositive individuals in both child and adult populations, because pre-existing immunity may interfere with response to a live vaccine.<sup>(27)</sup>

### **Paediatric considerations**

The first time that children <9 years of age receive seasonal influenza immunization, a two-dose schedule is required to achieve protection.<sup>(62-64)</sup> Several studies have looked at whether these two initial doses need to be given in the same season.<sup>(4,65,66)</sup> Englund et al.<sup>(4,66)</sup> 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 when there was a major B lineage change.<sup>(3,4)</sup> Issues related to effective prime-boost when there is a major change in influenza B lineage across sequential seasons require further evaluation.<sup>(67)</sup>

A recent RCT conducted with one TIV formulation in children 6-23 months of age during the 2008-2009 season suggests moderate improvement in antibody response without an increase in reactogenicity when two full doses (0.5 mL) versus two half doses (0.25 mL) of TIV are given to very young influenza-naïve infants 6-11 months of age.<sup>(68)</sup>

## **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 2.

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

The first time children <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 season thereafter.

Because children 6 to 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.

Infants and toddlers have a high burden of illness and their response to TIV is not as robust as older children. Some countries (e.g., in Europe) already recommend full TIV doses in these young children or are permissive of either half or full doses. NACI has reviewed published and unpublished evidence for use of full dose in infants that suggests moderate improvement in antibody response without increase in reactogenicity with use of full doses. In light of these findings and in recognition that it will simplify the administration schedule, **NACI now recommends that children 6 to 35 months of age should be given a full dose (0.5 mL)\* of TIV instead of the previously recommended half dose (0.25 mL)\*.** This recommendation applies whether the child is being given one dose of TIV or a two dose series.<sup>a</sup>

For influenza vaccines given by the intramuscular route, the deltoid muscle is the recommended site in adults and children  $\geq 12$  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. The appropriate Intanza® formulation should be chosen – 9 µg/strain for persons 18-59 years of age and 15 µg/strain for persons 60 years of age and older.

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 is sprayed into the other nostril.

---

<sup>a</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.

**Table 2. Recommended influenza vaccine dosage, by age, for the 2011-2012 Season**

Age group	Dosage				Number of doses required
	TIV without adjuvant	MF59 - adjuvanted TIV (Fluad®)	TIV for intradermal use (Intanza®)	LAIV (FluMist®)	
6-23 months	0.5 mL <sup>b</sup>	-	-	-	1 or 2*
2-8 years	0.5 mL	-	-	0.2 mL (0.1 mL per nostril)	1 or 2*
9-17 years	0.5 mL	-	-	0.2 mL (0.1 mL per nostril)	1
18-59 years	0.5 mL	-	0.1 mL (9 µg/strain)	0.2 mL (0.1 mL per nostril)	1
60-64 years	0.5 mL	-	0.1 mL (15 µg/strain)	-	1
≥65 years	0.5 mL	0.5 mL	0.1 mL (15 µg/strain)	-	1

\*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 season thereafter.

#### IV.4 Storage Requirements

Influenza vaccine should be stored at +2°C to +8°C and should not be frozen.

#### IV.5 Simultaneous Administration with Other Vaccines

Influenza vaccine, including LAIV, may be given at the same time as other inactivated or live vaccines. However, after administration of a live vaccine, such as LAIV, at least four weeks should pass before another live vaccine is administered.

Injections should be given if possible in opposite limbs. When multiple injections are given at one clinic visit, injections given on 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.<sup>(69)</sup>

<sup>b</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.

## 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  $\leq 7\%$  of healthy children who are  $< 3$  years of age. Post-vaccination fever may be observed in  $\leq 12\%$  of immunized children 1 to 5 years of age.

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. Similar rates of local and systemic reactions are seen with Fluad® after re-immunization in subsequent influenza seasons. Serious adverse events are uncommon and are comparable between Fluad® and comparator vaccines.<sup>(28)</sup>

TIV given intradermally (Intanza®) produces more frequent and more extensive injection site reactions (erythema, swelling, induration and pruritis) than vaccine given by the IM route, but 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®.<sup>(26)</sup>

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.<sup>(70,71)</sup> Large cohort studies of health databases have demonstrated that there is no association between childhood vaccination with thimerosal-containing vaccines and neurodevelopmental outcomes, including autistic-spectrum disorders.<sup>(72)</sup> Similar large-scale studies have not specifically addressed prenatal exposure to thimerosal-containing vaccines in pregnancy. 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.

During the 2000–2001 influenza season, an increased number of reports of vaccine-associated symptoms and signs that were subsequently described as “oculorespiratory syndrome” (ORS)<sup>(73)</sup> were reported nationally following receipt of TIV. The case definition is as follows: 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. The pathophysiologic mechanism underlying ORS remains unknown, but it is considered distinct from IgE-mediated allergy.

Approximately 5% to 34% of patients who have previously experienced ORS may have a recurrence attributable to the vaccine, but these episodes are usually milder than the original one, and vaccinees indicate willingness to be immunized in subsequent years.<sup>(74,75)</sup> 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.

## **LAIV**

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.<sup>(27)</sup>

Both children and adults can shed vaccine viruses after vaccination with LAIV. Studies have shown that vaccine virus can be recovered by nasal swab following vaccination (i.e. "shedding"). The frequency of shedding decreases with age, with 69%, 44%, 27%, and 17% of individuals 2-4 years, 5-8 years, 9-17 years, and 18-49 years of age shedding virus following vaccination. Shedding is rare after day 11 following vaccination, although children may shed for a mean duration of 7.6 days. 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. Serious illnesses have not been reported among unvaccinated persons who have been inadvertently infected with vaccine viruses. No transmission has been reported in a health care setting.<sup>(27)</sup>

### **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<sup>(69)</sup> for further details about administration of vaccine and management of adverse events including anaphylaxis. Vaccine considerations for persons with egg allergies are addressed in the following section.

Guillain-Barré syndrome (GBS) occurred in adults in association with the 1976 swine influenza vaccine, and evidence is consistent with a causal relation between the vaccine and GBS during that season.<sup>(76)</sup>

In an extensive review of studies since 1976, the United States Institute of Medicine concluded that the evidence was inadequate to accept or reject a causal relation between GBS in adults and influenza vaccines administered after the swine influenza vaccine program in 1976.<sup>(77)</sup> A retrospective review of the 1992 and 1993 US influenza vaccine campaigns found an adjusted relative risk of 1.7 (95% CI: 1.0–2.8;  $p=0.04$ ) for GBS associated with influenza vaccination.<sup>(78)</sup> This is consistent with a more recent Canadian study involving a self-matched case series from the Ontario health care database for the years 1992 to 2004.<sup>(79)</sup> It found the estimated relative risk of hospitalization for GBS in the period two to seven weeks after influenza vaccination, compared with the period 20 to 43 weeks after influenza vaccination, to be 1.45 (95% CI: 1.05–1.99,  $p=0.02$ ). The Ontario study also looked at the incidence of GBS in the entire Ontario population since 2000, when a universal influenza immunization program was introduced in that province; no statistically significant increase in hospital admissions because of GBS was found.<sup>(79)</sup>

These studies suggest that the absolute risk of GBS in the period following seasonal influenza vaccination is about one excess case per 1 million vaccinees above the background GBS rate. Preliminary analysis of surveillance for GBS after pH1N1 vaccination in the United States results in a similar estimate: 0.8 excess GBS cases per million doses administered.<sup>(80)</sup> The potential benefits of influenza vaccine must be weighed against this very low risk.

In a Canadian study, the background incidence of GBS due to any cause was estimated at 2.02 per 100,000 person-years in Ontario and 2.30 per 100,000 person-years in Quebec.<sup>(81)</sup> A variety of infectious agents, including *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumoniae*,<sup>(82)</sup> and influenza itself<sup>(83,84)</sup> have been associated with GBS. A consistent finding in case series is the occurrence of an infection in the six weeks before GBS diagnosis in about two-thirds of patients.<sup>(88)</sup>

Two studies suggest that influenza vaccine may have a protective effect for GBS. Tam et al.<sup>(85)</sup> conducted a nested case control study using data from the United Kingdom General Practice Research Database between 1991 and 2001. The authors found positive associations between GBS and infection with *Campylobacter spp.*, Epstein-Barr virus and ILI in the previous two months, as well as evidence of a protective effect of influenza vaccination. Stowe et al.<sup>(86)</sup> used the self-controlled case series method to investigate the relation of GBS with influenza vaccine and ILI using cases recorded in the same UK database from 1990 to 2005. The authors found a reduced risk (non-significant) of GBS after seasonal influenza vaccine rather than an increased risk but a greatly increased risk after ILI, consistent with preceding respiratory infection as a possible trigger.

#### IV.7 Contraindications and Precautions

---

Influenza vaccine should not be given to people who have had an anaphylactic reaction to a previous dose or to any of the vaccine components, with the exception of egg allergy as outlined later in this section. For more information on vaccine safety and anaphylaxis, please see the Canadian Immunization Guide at <http://www.phac-aspc.gc.ca/publicat/cig-gci/p02-03-eng.php>.

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 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.

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 as described in the previous paragraph. Health care providers who are unsure whether an individual previously experienced ORS versus an IgE-mediated hypersensitivity immune response should seek advice. 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.

Persons with serious acute febrile illness should usually not be vaccinated until their symptoms have abated. Those with mild non-serious febrile illness (such as mild upper respiratory tract infections) may be given influenza vaccine. Opportunities for immunization should not be lost because of inappropriate deferral of immunization.

It is not known whether influenza vaccination is causally associated with increased risk of recurrent GBS in persons with a previous history of GBS due to any cause. Avoiding subsequent influenza vaccination of persons known to have had GBS within eight weeks of a previous influenza vaccination appears prudent at this time.

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.

Therapy with beta-blocker medication is not a contraindication to influenza vaccination. 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.

### ***Additional LAIV (FluMist®)-specific contraindications and precautions***

FluMist® should not be administered to children <24 months of age due to increased risk of wheezing. FluMist® should not be administered to 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.

FluMist® should not be administered to 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®.

FluMist® should not be given to 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.

Because FluMist® is an attenuated live virus vaccine, it is not recommended for persons with immune compromising conditions. Because of the theoretical risk for transmission, 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.

It is also recommended that FluMist® not be administered until 48 hours after antiviral agents active against influenza (e.g. 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®), revaccination should take place at least 48 hours after the antivirals are stopped.

### ***Persons with egg allergy***

Past NACI influenza statements have advised that persons with known IgE-mediated hypersensitivity to eggs (manifested as hives, swelling of the mouth and throat, difficulty in breathing, hypotension, or shock) should not routinely receive influenza vaccine manufactured in eggs. However, a growing number of studies have demonstrated that most egg-allergic persons can safely receive inactivated influenza vaccine (TIV),<sup>(87-92)</sup> and guidelines for vaccination have been developed by a number of professional groups.<sup>(93,94)</sup>

James et al.<sup>(87)</sup> administered TIV to 83 subjects with egg allergy (27 with history of anaphylaxis to eggs) and 124 control subjects. The vaccination protocol for the egg-allergic persons was a two-step graded challenge (10%, 90%) with skin testing. All patients with egg allergy tolerated the vaccination protocol without significant allergic reactions.

Chung et al.<sup>(88)</sup> conducted a retrospective chart-review study of egg-allergic paediatric patients who received TIV under a two-stage graded protocol, with and without a skin test. None had a history of egg-induced anaphylaxis. There were no anaphylaxis or multisystem allergic reactions in the 171 patients vaccinated. Localized reactions (wheals or flares at the injection site) were seen in 29 persons and 7 experienced systemic reactions such as wheezing, eczema exacerbation, facial flushing, or hives on the face/chest. The authors concluded that 95-97% of egg-allergic patients tolerated the influenza vaccine without any serious adverse events.

In the largest study to date, Gagnon et al.<sup>(89)</sup> conducted a Canadian cohort study using monovalent pH1N1 vaccine and no vaccine skin tests. In phase one involving 830 egg-allergic individuals (and age matched controls), 758 egg-allergic individuals (without history of severe reactions) received a single dose and the remaining 72 (with a history of more severe reactions) were given two divided doses (10% and 90%). Phase two expanded the study to an additional 3640 individuals with self-reported egg allergy who were vaccinated by nurses under physician supervision. No patients developed

anaphylaxis in either study phase, although a few developed minor allergic symptoms. It is noted that the monovalent pandemic vaccine would be expected to contain less ovalbumin than seasonal TIV vaccines.

Greenhawt et al.<sup>(90)</sup> also conducted a controlled prospective study of 2009 pH1N1 vaccine administered to 105 egg-allergic individuals (25 with a history of egg-induced anaphylaxis), and 19 controls 6 months to 24 years of age. Three egg-allergic individuals (2.4%) and one control (5.2%) reported post-vaccination symptoms (rashes) which were not characteristic of an allergic reaction. All 25 individuals with a history of egg-induced anaphylaxis tolerated the vaccine without symptom development. The 110 participants who required a booster vaccination received vaccine from another lot without incident.

Schuler et al.<sup>(91)</sup> conducted a small Canadian prospective cohort study using the 2009 pH1N1 vaccine in 62 children identified as high risk for egg allergy and pH1N1 disease who were referred for vaccination by an allergist. Participants were given a total vaccine dose of 0.5 mL, with children 6 months to 9 years of age receiving two half doses (0.25 mL) four weeks apart. The first dose was administered using a two-step protocol (10% of total dose followed by the remaining dose), and the second dose, if required, as a single step. Four reactions were reported in the administration of the first dose, including a hypo-responsive episode which resolved after a short observation period in the emergency department. One reaction was reported after administration of the second dose, which was treated with medication. All reactions resolved without incident, and there were no reports of anaphylaxis.

Finally, Howe et al.<sup>(92)</sup> conducted a five year retrospective review of egg-allergic children 6-36 months of age when they first received TIV vaccine or egg allergy testing, and found that 135 of 140 (96%) received TIV without significant complications (5 were not vaccinated). Of 17 children with documented anaphylaxis to eggs, 14 safely received TIV (3 were not vaccinated). In prospective evaluation in the 2009-10 influenza season of 69 egg-allergic children and 14 non-allergic children, no serious allergic reactions were reported although 2 egg-allergic and 2 non egg-allergic children developed mild allergic symptoms. None of the children with a history of egg-induced anaphylaxis developed a reaction to TIV. Both single dose and two-step graded dosing were used based on risk assessment for a reaction.

Several of these studies evaluated the validity and predictability of an influenza vaccine skin test in the vaccination protocols and concluded that it is unnecessary and does not predict vaccine tolerance.<sup>(87,88,90,92)</sup>

Ovalbumin content in influenza vaccine manufactured in eggs may vary from year to year, between vaccine products or between lots of the same vaccine.<sup>(87,95,96)</sup> However, influenza vaccines marketed in Canada are approved under the European specification for ovalbumin content, which is currently <1.2 µg/mL, the level associated with low risks of adverse events.<sup>(89)</sup>

After careful review, NACI concludes that **egg-allergic individuals may be vaccinated against influenza using TIV, without a prior influenza vaccine skin test, based on an assessment of risk for a severe allergic reaction to guide the method of vaccination. (NACI recommendation Grade A)<sup>c</sup>**

Because of the lack of data, the use of FluMist® in egg-allergic persons is not recommended at this time. However, ovalbumin concentrations in FluMist® are documented to be very low and a study is currently underway to assess the use of

---

<sup>c</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.

FluMist® in egg-allergic persons. Its use will be re-evaluated when further data become available.

The Canadian Society of Allergy and Clinical Immunology (CSACI) defines egg allergy as immediate symptoms within 1-2 hours after exposure, such as urticaria and angioedema, respiratory, gastrointestinal or cardiovascular symptoms plus confirmatory allergy tests (skin test or egg specific IgE).<sup>(93)</sup> The risk of severe allergic reaction or anaphylaxis in egg-allergic individuals can be determined by assessing the history of reactions to egg. CSACI considers an egg-allergic individual to be at **lower risk for severe allergic reactions** if they have mild gastrointestinal or mild local skin reaction, can tolerate ingestion of small amounts of egg, or have a positive skin/specific IgE test to egg when exposure is unknown. An egg-allergic individual is considered to be at **higher risk for severe allergic reactions** if they have had a previous respiratory or cardiovascular reaction or generalized hives when exposed to egg, or have poorly controlled asthma.

Two vaccine delivery protocols can be used for egg-allergic individuals, depending on their level of risk for an allergic reaction.<sup>(93)</sup> Egg-allergic individuals at lower risk for severe allergic reaction can be vaccinated for influenza using a single vaccine dose. The two-step graded protocol is recommended for individuals who are at higher risk for severe allergic reaction. These protocols are as follows:

1. **Full dose** - A single vaccine dose without the use of a graded challenge. Individuals should be observed for 30 minutes following administration for symptom development.
2. **Two-step graded dosing** - A two-step graded process, whereby 10% of the age-appropriate dose is administered followed by 30 minutes of observation. If no symptoms develop, or symptoms are self-resolving, administer the remaining 90% with another 30 minute observation period. If sustained or severe reactions arise after the initial dose, the vaccine is withheld and the individual should be re-evaluated for receipt of the influenza vaccine.

Referral to a specialist with expertise in allergies may be necessary in occasional circumstances where there is strong concern about proceeding with the recommendations 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.

Children who are to get a second influenza vaccination during the same season can, if the first dose is tolerated well, be given a single dose of the same product used for the initial administration, which need not be from the same vaccine lot. A graded process is not needed for this second dose.

The vaccine provider should discuss the risks of potential reactions, including the potential risk for an anaphylactic reaction after the observation period. All egg-allergic individuals receiving the influenza vaccine should be observed post-vaccination for a recommended 30 minute time period, which may be extended (e.g., to 60 minutes) as a precautionary measure for higher risk individuals. Appropriate emergency treatment and resuscitative equipment should be immediately available to manage potential severe reactions or anaphylaxis.

Egg-allergic individuals should be reassessed each year prior to the administration of the influenza vaccine and immunized using a full dose or two-step graded process according to their risk of a severe reaction.

**These recommendations for egg-allergic individuals replace the advice about influenza vaccination for egg-allergic individuals in the Seventh edition (2006) of the *Canadian Immunization Guide*.**

## V. Recommendations for the 2011-2012 Seasonal Influenza Vaccine

---

### V.1 General Considerations

The national goal of the seasonal influenza immunization program in Canada is to prevent serious illness caused by influenza and its complications, including death.<sup>(97)</sup> In keeping with this, NACI recommends that priority for seasonal influenza vaccination be given to 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. However, influenza vaccine is encouraged for all Canadians who have no contraindication.

The antigenic characteristics of current and emerging influenza virus strains provide the basis for selecting the strains included in each year's vaccine. The World Health Organization (WHO) recommends that the trivalent vaccine for the 2011-2012 season in the Northern Hemisphere contain A/California/7/2009(H1N1)-like, A/Perth/16/2009(H3N2)-like and B/Brisbane/60/2008(Victoria lineage)-like antigens.<sup>(6)</sup> These are the same three components as the 2010-2011 vaccine. Vaccine producers may use antigenically equivalent strains because of their growth properties.

All manufacturers of influenza vaccines in Canada have confirmed to the Biologics and Genetic Therapies Directorate of Health Canada that the vaccines to be marketed in Canada for the 2011-2012 influenza season contain the three WHO-recommended antigenic strains.

Annual immunization against influenza is recommended for optimal protection. Protective antibody levels are generally achieved by two weeks following immunization and are then expected to wane over the following year. In most years antigenic drift occurs in one or more of the predominant influenza viruses and a new formulation—updated yearly with the most current circulating strains—provides optimal protection. Even when the vaccine strains have not changed, as in 2011-2012, annual immunization reinforces optimal protection. Although 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.<sup>(98)</sup>

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 medical officers of health. 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  $\geq 6$  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 (see Table 3).**

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 2 to 64 years). Therefore NACI also encourages influenza vaccine for all Canadians.

Note that the Special Considerations category in the 2010-2011 statement has been removed as the elevated pandemic-associated risks for certain groups no longer apply. Two of the groups (persons with morbid obesity and Aboriginal peoples) that were identified for special consideration in 2010 have now been added to the list of people at high risk in Table 3. With the return to a more typical profile of seasonal influenza burden, children 2-4 years of age have been removed from the Recommended Recipients table. A full NACI evidence review for healthy people 2 to 64 years of age is underway and NACI's recommendations for seasonal influenza vaccine will be communicated once completed. Provinces and territories with current universal and expanded paediatric programs for seasonal influenza vaccination may elect to continue those programs pending completion of the NACI evidence review.

**Table 3. Recommended recipients of influenza vaccine for the 2011-2012 season\***

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

- Adults (including pregnant women) and children with the following chronic health conditions:
  - cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma);
  - diabetes mellitus and other metabolic diseases;
  - cancer, immune compromising conditions (due to underlying disease and/or therapy);
  - renal disease;
  - anemia or hemoglobinopathy;
  - conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration;
  - morbid obesity (BMI $\geq$ 40); and
  - children and adolescents with conditions treated for long periods with acetylsalicylic acid.
- People of any age who are residents of nursing homes and other chronic care facilities.
- People  $\geq$ 65 years of age.
- Healthy children 6 to 23 months of age.
- Healthy pregnant women (the risk of influenza-related hospitalization increases with length of gestation, i.e. it is higher in the third than in the second trimester)
- Aboriginal peoples.

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

- Health care and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk of influenza complications.
- Household contacts (adults and children) of individuals at high risk of influenza-related complications (whether or not the individual at high risk has been immunized):
  - household contacts of individuals at high risk, as listed in the section above;
  - household contacts of infants <6 months of age as these infants are at high risk of complications from influenza but cannot receive influenza vaccine; and
  - members of a household expecting a newborn during the influenza season.
- Those providing regular child care to children <24 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 2 to 64 years without contraindication are also encouraged to receive influenza vaccine even if they are not in one of the priority 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 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** – Before the 2009 influenza pandemic, obesity had not been associated with increased risk of influenza-related complications. However, a potential association between severe pH1N1 illness and obesity was reported during the first wave of pH1N1.<sup>(99)</sup> Additional observational studies of cases in the United States, Mexico, Canada, Australia and New Zealand subsequently reported excess cases with severe disease (i.e., admitted to ICU, requiring mechanical ventilation) in the obese, particularly among those with morbid obesity (body mass index [BMI]  $\geq 40$ ).<sup>(100-103)</sup>

In their rapid response report,<sup>(7)</sup> CADTH identified two systematic reviews<sup>(104,105)</sup> that examined the relationship between obesity and severe outcomes among patients hospitalized for influenza A pH1N1 infection. Fezeu et al.<sup>(104)</sup> performed a meta-analysis on six cross-sectional studies, five of which reported on the association between morbid obesity (BMI  $\geq 40$ ) and ICU admission or death. The pooled summary estimates from these studies indicated that being morbidly obese significantly increased the risk of ICU admission or death (OR 2.01, 95% CI: 1.29-3.14,  $p < 0.002$ ). Being obese (BMI  $\geq 30$ ) was likewise associated with an over twofold increased likelihood of ICU admission or death but the result was not significant (OR 2.14, 95% CI: 0.92-4.99,  $p < 0.07$ ). The sample included 3059 adults and children.

Falagas et al.<sup>(105)</sup> reviewed 15 studies describing the first wave of pH1N1 in the Southern Hemisphere and summarized their findings descriptively. Obesity was recorded in 1.5% of patients with severe ILI, 1.8% of lab-confirmed cases, 1.6-13.3% of hospitalized cases, 28.5-44% of cases admitted to ICUs, and 14.5-21.9% of fatal cases. The proportion of morbidly obese cases among the cases that were obese was 13.3% for ILI, 16.7% for lab-confirmed cases, 33% for ICU admissions and 57.2% for those who died.

CADTH also identified 22 non-randomized studies that addressed the association between obesity and severe outcomes in pandemic influenza. While associations between morbid obesity and severe outcomes were found in many of these studies, results were not always consistent. The results are detailed in the CADTH rapid response report.<sup>(7)</sup>

A new study has examined the association between obesity and severe outcomes of seasonal influenza. Kwong et al.<sup>(106)</sup> conducted a cohort study over 12 influenza seasons on 82,545 respondents to population health surveys in Ontario and examined self-reported BMI and hospitalization for selected respiratory diseases. Obese individuals were more likely than non-obese individuals to have a respiratory hospitalization during influenza season, with risk increasing with higher BMI category. Among those with BMI  $\geq 35$ , the association was present both for those without other risk factors (OR 5.10; 95% CI 2.53-10.24) and those with one risk factor (OR 2.11; 95% CI 1.10-4.06). The authors conclude that severely obese persons with and without chronic conditions are at increased risk for respiratory hospitalizations during influenza seasons.

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 increased risk from both seasonal and pandemic influenza,

NACI recommends the inclusion of those who are morbidly obese (BMI  $\geq 40$ ) 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.

- **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 spread of the disease.

- **People  $\geq 65$  years of age.** Admissions attributable to influenza in this age group are estimated at 125 to 228 per 100,000 healthy persons,<sup>(107)</sup> and death rates increase with age.<sup>(108)</sup>

- **Healthy children 6 to 23 months of age.** Children in this age group are at increased risk of influenza-associated hospitalization compared with healthy older children and young adults. Hospitalization is most frequent in those  $< 2$  years of age with rates estimated in a variety of North American studies to be from 90 to 1,000 admissions per 100,000 healthy children.<sup>(109,110)</sup> Risk is greatest in the very young. These rates of hospitalization are similar to or greater than those of persons  $\geq 65$  years of age, although comparisons based on days of hospitalization and other severity indicators are not available and differences in the methods and setting for estimating influenza-attributable rates must also be taken into account. Influenza immunization of older children is efficacious,<sup>(30-32)</sup> but few trials have specifically included children 6 to 23 months of age. NACI recognizes that both the number of studies and the number of participants in trials of influenza vaccine in children of this age are limited, particularly related to efficacy, and that cost-effectiveness of routine immunization programs in this age group is dependent on related assumptions.<sup>(111)</sup> NACI strongly encourages further research regarding these issues. However, on the basis of existing data indicating a high rate of influenza-associated hospitalization in healthy children  $< 24$  months, NACI recommends the inclusion of children 6 to 23 months of age among high-priority recipients of influenza vaccine.

- **Pregnant women.** Women with the chronic health conditions indicated in Table 1 have a high risk of complications associated with influenza and are recommended by NACI as a high-priority group for immunization at any stage of pregnancy.

Several studies have described influenza-related risk in healthy pregnant women and summary reviews are available.<sup>(112-118)</sup> Since surrogate outcomes for influenza (e.g. hospitalization for ILI and respiratory or cardiopulmonary outcomes) rather than laboratory-confirmed influenza have been reported, it is difficult to know the true influenza-attributable risk. In some studies, it is also difficult to assess the contribution of underlying co-morbidities, since these are not always presented separately. More evaluation of the impact of seasonal influenza on the healthy pregnant woman and her fetus would be helpful.

All studies that have stratified analysis according to gestational age show that influenza-related risk is not evenly distributed across all trimesters of pregnancy.<sup>(119-121)</sup> In these studies, the rate of influenza-related hospitalization is not significantly increased during the first trimester of healthy pregnancy but, rather, increases later in pregnancy and is highest in the third trimester.<sup>(119-121)</sup> In Neuzil et al.'s frequently cited 1997 publication spanning almost 20 influenza seasons, the risk of cardiopulmonary hospitalization during the influenza season rose significantly above the non-pregnant rate only beyond 21 weeks' gestation.<sup>(119)</sup> Both Dodds et al. (Canada) and Neuzil et al. (US) reported excess influenza-related hospitalization rates of 40 and 100 per 100,000 women-months, respectively, in the third trimester, comparable to non-pregnant adults with co-morbidities.<sup>(119,120)</sup> Differences in the methods and settings for estimating influenza-attributable rates should be taken into account in making these comparisons.

The most robust epidemiologic evidence for increased influenza-related fatality in pregnancy comes from the 1918, 1957 and 2009 pandemics.<sup>(122-124)</sup> Canada experienced four fatalities in pregnant women (all in their third trimester) in the first wave of pH1N1 and the rates of hospitalization and ICU admission were much higher in pregnant women than in non-pregnant women of child-bearing age, particularly in the third trimester.<sup>(125)</sup> Increased maternal mortality during the antigenic shifts in 1968 and 1977 has not been described. With the exception of case reports and a single ecologic study in a single season in Great Britain,<sup>(126)</sup> epidemiologic evidence has not shown increased maternal mortality associated with seasonal influenza.<sup>(112,119,127-131)</sup>

The antibody response to TIV in pregnant women is not expected to differ from that of non-pregnant individuals.

Transplacental passage of maternal antibody is hypothesized to potentially protect the newborn. Several observational studies have assessed this epidemiologically with mixed results based on non-specific outcomes such as acute respiratory illness.<sup>(112,132-134)</sup>

In September 2008, Zaman et al. published the first RCT to assess effectiveness of influenza vaccine administered in the third trimester of pregnancy.<sup>(135)</sup> In this study, 340 pregnant women in Bangladesh were randomized to receive either TIV or pneumococcal polysaccharide vaccine in the third trimester. A total of 300 mothers were followed from two weeks after antenatal immunization to delivery, and 316 were followed from delivery until their infants were 24 weeks of age. During the prolonged tropical influenza season described, TIV effectiveness against respiratory illness with fever was 36% (95% CI: 4–57) in mothers and 29% (95% CI: 7–46) in their infants. Vaccine efficacy against laboratory-confirmed influenza in the infants of immunized mothers followed for six months was 63% (95% CI: 5–85). This study provides the first RCT evidence for mother/infant protection from TIV administered in pregnancy. The extent to which these results may be extrapolated to seasons with a different mix of virus strains and vaccine components, to temperate rather than tropical activity, and to different household/infant care or breastfeeding patterns warrants further evaluation. Follow-up antibody studies demonstrated that maternal immunization resulted in the presence of antibody titres against influenza A subtypes in a high proportion of mothers and their newborns.<sup>(136)</sup> Six-month follow-up data showed that passively acquired protective levels of serum antibody for influenza A subtypes may be significantly greater in the babies of vaccinees compared with babies of controls up to 20 weeks of age.

This work has been validated by results of a trial of TIV during pregnancy conducted on Navajo and Apache Indian reservations.<sup>(137)</sup> This controlled observational study followed a cohort of 1169 mother-infant pairs over three influenza seasons. Maternal influenza vaccination was associated with a 41% reduction in the risk of laboratory-confirmed influenza virus infection and a 39% reduction in the risk of ILI hospitalization for infants born to influenza-vaccinated women compared with infants born to unvaccinated mothers. Infants born to influenza-vaccinated women had significantly higher haemagglutinin inhibition antibody titres at birth and at 2-3 months of age than infants of unvaccinated mothers for all eight influenza virus strains investigated.

The safety of influenza vaccine during pregnancy has recently been reviewed.<sup>(138)</sup> Passive surveillance has not identified concern related to serious adverse events following influenza immunization in pregnant women. Analysis of adverse events in pregnant women following administration of TIV and LAIV that were reported to the US Vaccine Adverse Event Reporting System (VAERS) from 1990 to 2009 found that no unusual patterns of pregnancy complications or foetal outcomes were observed.<sup>(139)</sup> The extensive 2009 pandemic experience has been reassuring in that no safety signals were found with use of both adjuvanted and unadjuvanted pH1N1 vaccine in >100,000 pregnant women in Canada and >488,000 pregnant women in Europe.<sup>(140,141)</sup> Active studies to date have not shown evidence of harm to the mother or foetus associated with influenza

immunization,<sup>(115)</sup> but cumulative sample size to date has been small, especially during the first trimester.<sup>(131,132,142-146)</sup> Further systematic evaluation would thus be informative.

Serious maternal morbidity (namely hospitalization) during seasonal influenza supports a recommendation for seasonal TIV vaccine for healthy pregnant women since rates of influenza-associated hospitalization increase with length of gestation after the first trimester.

• **Aboriginal peoples** - Historically, Aboriginal status has been associated with increased risk of influenza-related complications including death.<sup>(147,148)</sup> Similar findings were identified during the 2009 influenza A (H1N1) pandemic. Aboriginal populations from Canada, Australia and New Zealand were noted to have a three- to eight-fold higher rate of hospitalization and death associated with pH1N1 infection compared to the overall population.<sup>(149)</sup>

Death rates related to pH1N1 among American Indian and Alaska Natives (AI/AN) were reported for 12 states populated with half of all AI/AN in the US<sup>(150)</sup> Approximately 3% of the total populations in these 12 states are AI/AN. A total of 426 pH1N1 deaths were reported by the 12 states between April 15 and November 13, 2009, of which 9.9% (n=42) occurred in AI/AN. The overall AI/AN pH1N1-related age-adjusted death rate was 3.7 per 100,000 population compared to 0.9 per 100,000 for all other racial/ethnic populations combined, resulting in a mortality rate ratio of 4.0. Age group-specific pH1N1-related death rates reported per 100,000 people in each age group were 3.5 for those aged 4 years and under, 1.1 for those aged 5 to 24 years, 4.2 for those aged 25 to 64 years, and 7.2 for persons aged 65 and older. In all age groups, AI/AN death rates were higher than in the other populations combined.

In a case control study of Manitoba-based individuals with pH1N1 infection, Aboriginals were more likely to suffer more severe disease than non-Aboriginals (OR 6.52, 95% CI: 2.04–20.8) when comparing patients admitted to the ICU (i.e., with severe disease) and those cared for in the community.<sup>(151)</sup> Similar higher risk for severe disease in Aboriginals was identified for admitted patients (OR for ICU admission=3.23, 95% CI: 1.04–10.1). This analysis was controlled for age, sex, urban versus rural status and income.

A Canadian study<sup>(101)</sup> of 168 cases of pH1N1 admitted to 38 adult ICUs and paediatric ICUs (PICUs) between April 16 and August 12, 2009, did not identify a statistically significant difference in survival based on Aboriginal status. However, an increased proportion of the Aboriginal community was noted to present with severe pH1N1 illness during the period of evaluation. An observational study<sup>(152)</sup> of 57 children admitted to nine Canadian PICUs with pH1N1 infection found that 14 (24.6%) of PICU patients were Aboriginal children, although Aboriginal people comprise only 3.8% of the Canadian population (15.5% in Manitoba). However, once hospitalized, Aboriginal children in this study were not at elevated risk for ICU admission. A retrospective review<sup>(153)</sup> of pH1N1 hospitalizations in Canada reported to PHAC found that the Aboriginal population experienced a much higher incidence of non-severe outcome (hospitalization without ICU admission or death) and severe outcomes (ICU admission or death) than the general population; however the proportion of hospitalized Aboriginal patients with a non-severe outcome versus a severe outcome did not differ significantly from that for the general 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),<sup>(150)</sup> obesity, delayed access to health care and increased susceptibility to disease because of poor housing and overcrowding.<sup>(154-156)</sup> Research into an underlying biological mechanism for severe disease in Aboriginals has generated hypotheses but is not conclusive.<sup>(151,157)</sup>

Based on the body of evidence indicating a higher rate of influenza-associated hospitalization and death among Aboriginals, NACI recommends the inclusion of Aboriginal peoples, both on and off reserve, among high-priority recipients of influenza vaccine. Special consideration to socioeconomic challenges and geographical isolation is required to overcome the logistical challenges faced to achieve this objective.<sup>(147)</sup>

### **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 of death and other serious outcomes among the patients for whom they care.<sup>(158-164)</sup>

Immunization of care providers and residents is associated with decreased risk of ILI outbreaks.<sup>(165)</sup> Individuals who are more likely to transmit influenza to those at risk of medical complications or hospitalization due to influenza include the following groups:

- **Health care and other 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.
- **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: 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 <24 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., crews on ships).**

### **V.2.3 Others**

- **People who provide essential community services.** Vaccination for these individuals should be encouraged in order to minimize the disruption of routine activities during annual epidemics. Employers and their employees should consider yearly influenza immunization for healthy working adults, as this has been shown to decrease work absenteeism due to respiratory and other 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.<sup>(166-169)</sup> Influenza immunization on a yearly basis for these workers has been recommended in some countries<sup>(170)</sup> and provinces, based on the theoretical rationale that it may prevent the infection of these individuals with human influenza strains and thus reduce the potential for human-avian re-assortment of genes should such workers become co-infected with avian influenza.<sup>(171)</sup> 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. Those who are immunized with influenza vaccine just before exposure to avian influenza will not produce protective antibodies against the human

vaccine strains for approximately 14 days. For further information on human health issues related to domestic avian influenza outbreaks, see the PHAC guidance at <http://www.phac-aspc.gc.ca/publicat/daio-enia/index.html>.

#### **V.2.4 Further Comments Regarding Influenza Immunization**

##### **• Immunization of healthy persons 2 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. Systematic reviews of randomized controlled trials in healthy children and adults show that inactivated influenza vaccine is about 70% to 90% effective in preventing laboratory-confirmed influenza infection.<sup>(30-34)</sup> A recent meta analysis of randomized controlled trials since 1966 found a vaccine efficacy in young adults of 80% (95% CI: 56–91) against laboratory-confirmed influenza when measured during select seasons of vaccine match and 50% (95% CI: 27–65) during select seasons of vaccine mismatch to circulating virus, although the amount of protection conferred is anticipated to vary with the degree of mismatch, the mix of circulating viruses and other factors.<sup>(34)</sup>

Prior to the American universal recommendation described later, the American Academy of Family Physicians and the Advisory Committee on Immunization Practices (ACIP) recommended routine annual influenza vaccination of adults  $\geq 50$  years of age. The prevalence of high-risk conditions increases at age 50 years, while the influenza immunization rate among US adults with high-risk chronic medical conditions in this age group has been low. Age-based influenza guidelines may be more successful in reaching individuals with chronic medical conditions; in one analysis, this approach has been considered cost-effective.<sup>(172)</sup>

##### **• Travellers**

Travellers with a chronic health condition or other factors that would make them recommended recipients of influenza vaccine should be immunized (see Table 3), and healthy travellers are also encouraged to receive vaccine. Vaccine products/formulations prepared specifically for use in the Southern Hemisphere are not currently 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. For further information on advising travellers about influenza prevention, consult the Committee to Advise on Tropical Medicine and Travel (CATMAT) statement (available at <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/05pdf/acs-dcc3102.pdf>).<sup>(173)</sup>

#### **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. While some comparative studies have been conducted,<sup>(174)</sup> more are needed.

The decision to include specific influenza vaccines as part of publicly funded provincial/territorial programs will depend on multiple factors such as cost-benefit evaluation and other programmatic and operational factors, such as cost, shelf-life and the development of implementation strategies.

Table 4 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 4 – Choice of influenza vaccine for selected age and risk groups (for persons without a contraindication to the vaccine)**

Recipient by age group	Vaccine types available for use*	Preferred vaccine (if any)		Comments
		Healthy	With chronic health conditions	
Children 6-23 months of age	TIV	-	-	Only TIV is available for this age group
Children 2-17 years of age	TIV LAIV	LAIV	TIV LAIV	Children with immune compromising conditions: <ul style="list-style-type: none"> <li>• LAIV not recommended</li> </ul>
Adults 18-59 years of age	TIV TIV-ID (9 µg) LAIV	TIV TIV-ID (9 µg) LAIV	TIV TIV-ID (9 µg)	Adults with immune compromising conditions: <ul style="list-style-type: none"> <li>• consider 15 µg formulation if using TIV-ID,</li> <li>• LAIV not recommended</li> </ul>
Adults 60-64 years of age	TIV TIV-ID (15 µg)	TIV TIV-ID (15 µg)	TIV TIV-ID (15 µg)	
Adults 65+ years of age	TIV TIV-ID (15 µg) MF59- adjuvanted TIV	TIV TIV-ID (15 µg) MF59- adjuvanted TIV	TIV TIV-ID (15 µg) MF59- adjuvanted TIV	
Pregnant women	TIV TIV-ID (9 µg)	TIV TIV-ID (9 µg)	TIV TIV-ID(9 µg)	

**\*Legend:** 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 for use in healthy children and adolescents 2-17 years of age. Available data indicates that LAIV would be preferred over TIV in this population, although NACI recognizes that other programmatic considerations will impact the implementation of this recommendation in publicly-funded programs.

There is insufficient evidence available to prefer LAIV over TIV in children with chronic health conditions.<sup>(27)</sup> 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 now three types of vaccine available for use in adults 18-59 years of age: TIV, TIV given intradermally (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.<sup>(26)</sup> There is some evidence that TIV may provide better efficacy than LAIV in healthy adults although not all studies are consistent on this point.<sup>(27)</sup>

For adults in this age group with chronic health conditions, either TIV or TIV-ID 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 hypo-responsive populations with chronic health conditions.<sup>(26)</sup> 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.<sup>(27)</sup> LAIV is not recommended for adults with immune compromising conditions.

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.

### **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 immune response to TIV-ID is statistically superior to TIV (Vaxigrip®), although the clinical significance of differences remains uncertain.<sup>(26)</sup> No difference in immunogenicity was noted in persons with chronic health conditions compared to healthy persons receiving TIV-ID (persons with immune compromising conditions were excluded from this study).<sup>(26)</sup>

### **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.<sup>(26,28)</sup>

There are no published efficacy studies available for TIV-ID or MF59-adjuvanted TIV. A few observational studies suggest that Fludax® 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.<sup>(28)</sup>

There is evidence from randomized controlled trials showing that Fludax<sup>®</sup> 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<sup>(28)</sup> The intradermal product, Intanza<sup>®</sup>, has been shown to elicit an immune response that is comparable to TIV, with or without adjuvant, administered by the intramuscular route.<sup>(26,61)</sup> In adults 60 years of age and older, data from two clinical trials with over 4800 participants demonstrated that immune response to Intanza<sup>®</sup> was statistically superior to Vaxigrip<sup>®</sup>, 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.

Given the availability of TIV, NACI does not recommend the use of LAIV, which is a live attenuated vaccine, in pregnant women.

## **VI. Strategies for Reducing the Impact of Influenza**

---

Vaccination is recognized as the cornerstone for preventing or attenuating influenza for those at high risk of serious illness or death from influenza infection and related complications.

In addition to the direct protection of vaccine recipients, there is emerging evidence that vaccination may provide indirect protection to others in the household or in the community. A recent cluster randomized trial was conducted among Hutterite communities in Canada.<sup>(175)</sup> It compared laboratory-confirmed influenza among unvaccinated persons in Hutterite communities where children were given influenza vaccine (coverage=83% among children aged 3 to 15) with communities where children received hepatitis A vaccine. Influenza vaccine effectiveness in preventing influenza in unvaccinated persons was 61% (95% CI: 8–81). Differences in social mixing patterns between Hutterite and other communities, particularly across age groups, need to be taken into account in extrapolating these findings to other settings.

School-based trials and observational studies suggest that immunization of healthy children may reduce influenza transmission<sup>(176-182)</sup> and a systematic review concluded that there was evidence that vaccinating healthy children and adolescents has the potential for reducing the impact of influenza epidemics, although limitations in study design or execution make community benefits hard to quantify.<sup>(183)</sup> Studies that looked at indirect protection of patients when HCWs are immunized are described in Section VII.

Despite the known benefits of vaccination, influenza immunization rates among recommended recipients are suboptimal. Results from the 2008 cycle of the Adult National Immunization Coverage Survey show that coverage for adults 18 to 64 years of age with a chronic medical condition is low at 35.8% (95% CI: 34.1-37.6) (unpublished data, Immunization and Respiratory Infections Division, PHAC). Results from this 2008 survey also show that non-institutionalized seniors (≥65 years) have higher coverage, with 66.5% (95% CI: 62.4-70.6) receiving influenza vaccine in the previous year. The results for both groups have declined somewhat since the 2006 survey and fall short of the 80% national targets for influenza vaccine coverage in adults <65 years of age with chronic conditions and in seniors.<sup>(97)</sup>

Kwong et al. compared influenza vaccine rates in Ontario with those in other provinces in relation to introduction of the Universal Influenza Immunization Program (UIIP) in Ontario in 2000.<sup>(184)</sup> Vaccination rate data were obtained from the 1996–1997 cycle of the

National Population Health Survey and the 2000–2001, 2003 and 2005 cycles of the Canadian Community Health Survey. Between the pre-UIIP 1996–1997 estimate and the mean post-UIIP vaccination rate, influenza vaccination rates for the household population aged  $\geq 12$  years increased 20 percentage points (from 18% to 38%) for Ontario, compared with 11 percentage points (13% to 24%) for other provinces ( $p=0.001$ ). For those  $<65$  years of age, the vaccination rate increases were greater in Ontario than in other provinces, while for those  $\geq 75$  years of age, the increase was smaller in Ontario.

Kwong et al. also studied health outcomes in Ontario compared with other provinces without a universal immunization program.<sup>(184)</sup> The authors found that influenza-associated mortality, hospitalizations and doctors' office visits decreased more in Ontario than in other provinces. The universal program was also associated with a 64% larger reduction in influenza-associated antibiotic prescriptions than in other provinces that maintained targeted programs.<sup>(185)</sup> An economic appraisal of the Ontario program found an incremental cost-effectiveness ratio of \$10,797/quality-adjusted life year (QALY) gained and concluded that universal immunization against seasonal influenza is an economically attractive intervention.<sup>(186)</sup>

In February 2010 the ACIP voted to recommend a universal influenza immunization policy for seasonal influenza vaccine for all Americans aged 6 months and older, to be implemented for the 2011–2012 season.<sup>(187,188)</sup> Reasons cited for the program expansion include supporting evidence that annual influenza vaccine is a safe and effective preventive health action with potential benefit in all age groups, existing recommendations that already cover 85% of the population, the lack of awareness of many higher risk persons of their risk factor and the occurrence of complications in some adults without previously recognized risk factors. There was also concern that pH1N1 would continue to circulate in the 2010–2011 season and that a substantial proportion of young adults would not yet have immunity to this virus, which produced higher risk of complications in this age group than is typical for seasonal influenza.

Before making expanded recommendations that may influence Canadian immunization programs nationally, NACI is committed to careful systematic review of the required and available evidence and interpretation in the context of goals and objectives previously established in Canada by a consensus process.<sup>(97)</sup> As with other new vaccines, this process will be followed in considering population-based indications for expansion of influenza immunization programs. A summary of that analysis in relation to paediatric or other program expansion will be made available when concluded. Until then, NACI continues to encourage influenza vaccine for all Canadians.

Low rates of utilization of influenza vaccine may be due to failure of the health care system to offer the vaccine and refusal by persons who fear adverse reactions or mistakenly believe that the vaccine is either ineffective or unnecessary. HCWs and their employers have a duty to actively promote, implement and comply with influenza immunization recommendations in order to decrease the risk of infection and complications among the vulnerable populations for which they care. Educational efforts aimed at HCWs and the public should address common doubts about disease risk for HCWs, their families and patients, vaccine effectiveness and adverse reactions.

The advice of a health care provider is a very important factor affecting whether a person accepts immunization. Most people at high risk are already under medical care and should be vaccinated during regular fall visits. Strategies to improve coverage include, but are not limited to, the following:

- Standing-order policies in institutions allowing nurses to administer vaccine and simultaneous immunization of staff and patients in nursing homes and chronic care facilities. In these settings, increased vaccination rates are associated with a single, non-physician staff person organizing the program; having program aspects covered by written policies; and instituting a policy of obtaining consent on admission that is durable for future years.

- Vaccinating people at high risk who are being discharged from hospital or visiting the emergency department.
- Promoting influenza vaccination in clinics in which high-risk groups are seen (e.g., cancer clinics, cardiac clinics, pulmonary clinics, obstetrics clinics).
- Providing school-based clinics in jurisdictions that provide publicly-funded vaccine to school-age children. School-based vaccination is associated with higher vaccination rates in school-age children<sup>(189)</sup> and strategies for effective school programs have been identified.<sup>(190,191)</sup>
- Using community newspapers, radio, television, other media including newer social media, and influenza information lines, and collaborating with pharmacists and specialist physicians to distribute information about the benefits and risks of influenza immunization.
- Issuing computer-generated reminders to HCWs, mailing reminder letters to patients or using other recall methods to identify outpatients at high risk.
- Issuing patient-carried reminder cards.
- Increasing the accessibility of immunization clinics for staff in institutions and for community-based elderly (e.g., mobile programs).
- Organizing activities such as vaccination fairs and competitions between institutions.
- Working with multicultural groups to plan and implement effective programs.
- Incorporating influenza vaccination within the provision of home health care.

## VII. Immunization of Health Care Workers

---

Influenza vaccination provides benefits to HCWs and to the patients they care for. Unfortunately vaccine uptake in HCWs often falls short of expectations. According to the 2008 cycle of the Adult National Immunization Coverage Survey, the coverage rate in HCWs was 67.8% (95% CI: 63.3-72.4), down slightly from the 69.9% (95% CI: 66.6-73.2) rate in the 2006 cycle (unpublished data, Immunization and Respiratory Infections Division, PHAC). This falls short of the national target of 80% for coverage in HCWs.<sup>(97)</sup>

Transmission of influenza between infected HCWs and their vulnerable patients results in significant morbidity and mortality. Studies have demonstrated that HCWs who are ill with influenza frequently continue to work, thereby potentially transmitting the virus to both patients and co-workers. In one study, 59% of HCWs with serologic evidence of recent influenza infection could not recall having influenza, suggesting that many HCWs experience subclinical infection.<sup>(192)</sup> These individuals continued to work, potentially transmitting infection to their patients. In two other studies, HCWs reported four to ten times as many days of respiratory illness as days absent from work due to respiratory illness, suggesting that many HCWs worked while they were ill and were potentially able to transmit infection.<sup>(164,193)</sup> In addition, absenteeism of HCWs who are sick with influenza results in excess economic costs and, in some cases, potential endangerment of health care delivery because of the scarcity of replacement workers.

Four randomized controlled trials conducted in long-term care settings have demonstrated that vaccination of HCW staff is associated with substantial decreases in

mortality in the residents. Potter et al.<sup>(159)</sup> found that vaccination of HCWs in geriatric medical long-term care sites was associated with reductions of total patient mortality from 17% to 10% (OR 0.56, 95% CI: 0.40–0.80) and in influenza-like illness (OR 0.57, 95% CI: 0.34–0.94). Vaccination of patients was not associated with significant effects on mortality. Carman et al.<sup>(161)</sup> studied 20 long-term elderly-care hospitals and found 13.6% patient mortality in hospitals where influenza vaccine was given to staff compared with 22.4% in no-vaccine hospitals (OR 0.58, 95% CI: 0.40–0.84,  $p=0.014$ ). Hayward et al.<sup>(158)</sup> found significant decreases in resident mortality in the first study year in UK care homes where influenza vaccine was offered to staff compared with non-intervention homes (rate difference: -5.0 per 100 residents, 95% CI: -7.0 to -2.0) and in influenza-like illness (ILI) ( $p=0.004$ ), general practice ILI consultations ( $p=0.008$ ) and in hospital admissions with ILI ( $p=0.009$ ). No differences were found during periods of no influenza activity or in a second study year. Lemaitre et al.<sup>(162)</sup> studied 40 nursing homes and found 20% lower resident mortality ( $p=0.02$ ) in homes where influenza vaccine was provided to staff compared with control homes, and a strong correlation was observed between staff vaccination coverage and all cause mortality in residents (correlation coefficient=0.42,  $p=.007$ ). In the vaccination arm, ILI in residents was 31% lower ( $p=.007$ ) and staff sick leave was 42% lower ( $p=.03$ ). A Cochrane review of studies in long-term care settings reported that pooled data from three cluster randomized controlled trials showed that vaccination of HCWs in long-term care facilities for the elderly reduced influenza-like illness (OR 0.71, 95% CI: 0.55–0.90,  $p=.005$ ) and all cause mortality (OR 0.68, 95% CI: 0.55–0.84,  $p<.001$ ).<sup>(194)</sup>

For the purposes of this document, we define a HCW as a person who provides direct patient care or indirect health services. The term “direct patient contact” is defined as activities that allow opportunities for influenza transmission between HCWs and a patient.

NACI considers the provision of influenza vaccination for HCWs who have direct patient contact to be an essential component of the standard of care for the protection of their patients. 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.

In order to protect vulnerable patients during an outbreak, it is reasonable to exclude from direct patient contact HCWs with confirmed or presumed influenza and unvaccinated HCWs who are not receiving antiviral prophylaxis. Health care organizations should have policies in place to deal with this issue.

## VIII. Research Priorities

NACI has identified the following as areas requiring further study:

- Correlates of protection (humoral and cell-mediated immunity) by age group require validation
- More studies that assess vaccine protection against laboratory-confirmed influenza and its serious consequences
- Strategies to provide optimal protection against both B lineages
- Paediatric studies: vaccine efficacy in unprimed children, optimal protection for infants
- Systematic review of the evidence related to expanded immunization of healthy children and adults
- Optimal protection for patients with immune compromising conditions
- Continuing evaluation of new vaccines, including use in populations with comorbidities (e.g., FluMist® in persons with immune compromising conditions)

- Comparative immunogenicity and efficacy where appropriate, e.g. to identify potential preferential use of specific products in adults, seniors or persons with chronic health conditions
- Strategies to improve vaccine uptake in targeted populations, including HCWs.

## IX. Surveillance Issues

Surveillance information is vital for planning and evaluating vaccination programs including influenza. Shortfalls and gaps in existing systems mean that we do not always have the information that is needed. Key surveillance issues for influenza vaccination programs are as follows:

- **Identifying the burden of disease and risk factors for severe disease** - This information is needed to plan and evaluate effective vaccination programs, including identifying high risk persons and groups who should be vaccinated. Influenza surveillance should include infections and outbreaks in the community, as well as in hospitals and long term care facilities. Surveillance in Aboriginal populations and remote and isolated communities is of particular interest.  
  
Existing surveillance systems may not provide a representative picture of what is happening with influenza across the country because of the underrepresentation of some jurisdictions and lack of detailed data from all jurisdictions on cases and outbreaks. It is difficult to determine the burden of clinical illness by age and risk group because ILI surveillance is affected by participation of sentinel physicians, biases in health care utilization and physician testing behaviour.
- **Identifying and characterizing circulating influenza strains** – This information is needed for vaccine effectiveness studies, and for the annual vaccine WHO strain selection process, among other uses. Unfortunately there is variation across the country in the proportion of specimens undergoing strain characterization, and inconsistency in viral sequencing and sources of specimens for sequencing (i.e. hospital versus community).
- **Monitoring vaccine uptake and effectiveness** - The limitations of current program information systems to capture vaccination status (e.g., lack of integrated laboratory and health information systems and lack of vaccination registries) present challenges, along with the virus itself, in conducting surveillance of influenza vaccination programs, particularly for monitoring vaccine uptake and effectiveness. Vaccine coverage information is needed in risk groups, HCWs and the general population (where a universal recommendation exists). Canadian research initiatives, have established several sentinel methods (using sentinel physicians or hospitals) to study influenza vaccine effectiveness.<sup>(195-197)</sup> Such initiatives need to become part of our ongoing national surveillance systems, particularly as the variety of influenza vaccines continues to grow. Vaccine uptake and effectiveness studies also need to be able to capture differences between different vaccine products.
- **Monitoring vaccine safety** - The increasing variety of influenza vaccines highlights the need to strengthen vaccine safety surveillance and our ability to capture product-specific results. Improved information on the type of influenza vaccine given to patients (e.g. through billing codes), better electronic records, and capacity for data linkage studies would allow more comprehensive analysis of safety and response to signals raised by passive systems.

## Summary of Information in this Statement

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

**Table 5: Summary of information contained in this NACI Statement**

<p><b>1. What –</b> The disease and the vaccine</p>	<p>Influenza is a respiratory infection caused by influenza A and B viruses and occurs in Canada every year, generally during late fall and the winter months. Infection typically starts with a headache, chills and cough, followed rapidly by fever, loss of appetite, muscle aches and fatigue, running nose, sneezing, watery eyes and throat irritation. Nausea, vomiting and diarrhea may also occur, especially in children.</p> <p>Most people will recover from influenza within a week or ten days, but some - including those 65 years of age and older and adults and children with chronic conditions, such as diabetes and cancer - are at greater risk of more severe complications, such as pneumonia. Additional information about influenza can be accessed at: <a href="http://www.phac-aspc.gc.ca/im/vpd-mev/influenza-eng.php">http://www.phac-aspc.gc.ca/im/vpd-mev/influenza-eng.php</a></p> <p>There are currently eight seasonal trivalent influenza vaccines authorized for use in Canada. Your province or territory will advise which vaccines will be made available for the publicly-funded program in your jurisdiction.</p> <p>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.</p> <p>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.</p> <p>Influenza vaccine is safe and well-tolerated and may be given to persons starting from six months of age (note product-specific age indications and contraindications).</p>
<p><b>2. Who to immunize</b></p>	<p>Immunization programs should focus on:</p> <ul style="list-style-type: none"> <li>• <i>those at high risk of influenza-related complications</i> - adults and children with underlying health conditions, including morbid obesity; residents of nursing homes and other chronic care facilities; people ≥ 65 years of age; healthy children 6 to 23 months of age; pregnant women; and Aboriginal peoples;</li> <li>• <i>those capable of spreading influenza to individuals at high risk of complications</i> - health care providers in facilities and</li> </ul>

	<p>community settings; household contacts of high-risk persons and infants &lt;6 months of age; those providing child care to children &lt; 24 months of age; and those providing services in closed settings to the high risk (e.g. crew on a ship); and</p> <ul style="list-style-type: none"> <li>• <i>those who provide essential community services.</i></li> </ul> <p>NACI also encourages influenza vaccine for all Canadians, because significant illness and societal costs also occur in people not considered to be at high risk of complications.</p>
<p><b>3. How –</b> Dose and schedule; contraindications and precautions; co-administration</p>	<p>Children who have been previously immunized with seasonal influenza vaccine and adults are to receive one dose of influenza vaccine. Children 6 months to &lt;9 years of age receiving seasonal influenza vaccine for the first time should be given two doses, with a minimum interval of four weeks. The route of administration and dosage varies by product (see statement for details). For intramuscular TIV, the dose is now 0.5 ml IM for all age groups.</p> <p>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 GBS within eight weeks of influenza vaccination should not receive a further dose. NACI now advises that most persons with egg allergy may be safely vaccinated with inactivated influenza vaccine (TIV) (See section IV.7 of this statement for details). Vaccination should be deferred in persons with serious acute febrile illness.</p> <p>There are additional contraindications for LAIV (See the above statement for details).</p> <p>Influenza vaccine, including LAIV, may be given at the same time as other inactivated or live vaccines. However, after administration of a live vaccine at least four weeks should pass before another live vaccine is administered.</p> <p>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.</p> <p>Influenza vaccine should be stored at 2-8°C and not be frozen.</p>
<p><b>4. Why –</b> Counselling points for providers to emphasize with clients when discussing these recommendations</p>	<p>Vaccination is the most effective way to prevent influenza.</p> <p>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 reinforces optimal protection.</p> <p>Annual influenza vaccination is encouraged for all Canadians, particularly those at high risk of influenza complications, those who could spread influenza to someone at risk and those who provide essential community services.</p> <p>Influenza vaccine is safe and well-tolerated.</p>

## Tables

**Table 6 – Evidence tables for egg allergy**

STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of key Findings Using Text or Data (95% CI)	Level of Evidence	Quality
James JM, Zeiger RS, Lester MR, et al. Safe administration of influenza vaccine to patients with egg allergy. <i>J Pediatr.</i> 1998 Nov;133(5):624-8. <sup>(87)</sup>	Annual influenza vaccine (IM) Parke Davis Same lot number for the corresponding year at all the study sites for skin prick testing and vaccine administration.	Multicentre clinical trial, non-randomized, active controlled  1994-1997	N = 207 Cases n = 83 Controls n = 124  ≥ 6 months of age  Case – confirmed egg allergy via testing or history of serious allergic reaction to egg  Control – negative test results regardless of history of reaction to egg  Egg allergy screened via skin testing, medical history and/or blinded oral challenge  Skin prick tests performed on all participants.	<b>Vaccination Protocol</b> Cases 2 step delivery - 10% dose, 30 minute observation, 90% dose if no concerning reactions, and 60 minute observation  Controls 1 step delivery - full dose and 60 minute observation  Follow-up phone call 24 and 48 hours to assess delayed adverse reactions to the vaccine  <b>Outcome</b> Vaccine-related adverse events  Reactions reported from 8 cases and 4 controls No significant reactions, all resolved uneventfully  Safety (percentage) to receive this vaccine Cases: 100% (95.7, 100) Controls: 100% (97.1, 100)  34/70 (48.6%) subjects ≤ 8 years old with egg allergy returned for booster in a single full dose without reactions  <b>Ovalbumin/ovomucoid assessment</b> Ovalbumin/ovomucoid content = 0.1, 1.2, and 0.02 µg /mL, respectively in the 1994-95, 1995-96, and 1996-97 influenza vaccines.  Concentration varied within and between manufacturer lots (0.02-1.2 µg /mL, and 1-42µg /mL)	II-3	Good

STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of key Findings Using Text or Data (95% CI)	Level of Evidence	Quality
Chung EY, Huang L, Schneider L. Safety of influenza vaccine administration in egg-allergic patients. <i>Pediatrics</i> . 2010 May;125(5):e1024-30. <sup>(88)</sup>	Vaccines from the 2002–2003 through 2008–2009 influenza seasons.	Retrospective cohort (chart review)  2002–2003 through 2008–2009 influenza Seasons	N=261  vaccine skin test: n=55 (negative) n=91 (positive)  no vaccine test: n=115  6mths to 18 yrs  Have egg allergy and received influenza vaccine skin test and/or graded influenza vaccine (individuals with egg-induced anaphylaxis or severe egg allergy are implicitly excluded)	<b>Vaccination Protocol</b> 2-step delivery: 10% dose, 30 minute observation , 90% dose if no reaction/mild self-resolving reaction, and 30 minute observation Negative skin test required before receiving vaccine for influenza seasons between 2002-2003 and 2006-2007  <b>Outcome</b> Vaccine tolerance – lack of local (wheal, flare at site of infection) or systemic (urticaria, eczema exacerbation, wheeze) adverse reaction Vaccine with a negative skin test (n=53) -tolerance rate: 78.6% (65.6, 88.4) Vaccine without skin test (n=115) -tolerance rate: 79.1% (70.6, 86.2) (Skin test removed from protocol between 2006-2007 and 2008-2009)  Overall tolerance rate ratio (non-skin test: skin test) = 1.12 (0.99, 1.25) Tolerance rate ratio for no systemic reaction = 1.01 (0.97, 1.06)  Outcome similar between groups with and without skin test without occurrence of anaphylaxis of multisystem allergic reaction	II-3	Good
Gagnon R, Primeau MN, Des Roches A, et al. Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. <i>J Allergy Clin Immunol</i> .	AS03 adjuvanted monovalent pH1N1 influenza vaccine  Arepanrix™ (GSK)  0.25 mL for <10 years of age; 0.5 mL for	2 stage cohort study, multicenter  Age matched control group  Phase 1: University hospital (Oct 28 - Dec 15, 2009)	<b>Phase 1</b> N: 1223 Cases n = 830 Controls n = 393  Case: egg allergy confirmed by skin prick test and/or serum levels  Control: no egg allergy  <b>Phase 2</b>	<b>Vaccination Protocol</b> If low risk for anaphylaxis: 1 step delivery - Full dose and 60 minute observation  If high risk for anaphylaxis: 2 step delivery - 10% dose, 30 minute observation, 90% dose if no concerning reactions, and 60 minute observation  <b>Outcome:</b> Anaphylactic reaction  <b>Phase 1</b> Cases: 9% (n=54) cases required divided doses.  Cases:	II-2	Good

STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of key Findings Using Text or Data (95% CI)	Level of Evidence	Quality
2010 Aug;126(2):3 17-23. <sup>(89)</sup>	≥10 years of age  < 0.015 µg /mL ovalbumin per delivered vaccine  < 1.2 µg /mL egg protein	Phase 2: Province-wide (Nov 17, 2009- Feb 10, 2010)	N: 3640  Case: self- reported egg allergy  Excluded those with history of egg intolerance	No anaphylactic reaction Anaphylaxis reaction risk = 0/830 (0, 0.4). After 60 minutes: 2% reported reactions After 24 hours: 13.7% reported reactions  Controls: No anaphylactic reaction After 60 minutes: 3.1% reported reactions After 24 hours: 14.7% reported reactions  Signs and symptoms reported were similar between groups with a higher proportion of cases reporting dermatologic/mucosal reactions and (2.2% vs. 0.8%) and fewer cases reporting respiratory reactions (3.7% vs. 5.6%)  <b>Phase 2</b> Cases: No anaphylactic reaction 0.05% (n=2) treated with epinephrine. 1.9% mild signs/symptoms compatible with allergic reaction  Anaphylaxis after influenza immunization is a theoretic risk; vaccination of patients with egg allergy with an adjuvanted monovalent pH1N1 influenza vaccine resulted in no cases of anaphylaxis and on that basis appears safe		
Greenhawt MJ, Chernin AS, Howe L, et al. The safety of the H1N1 influenza A vaccine in egg-allergic individuals. <i>Ann Allergy Asthma</i>	pH1N1  Sanofi Pasteur (USA)  Novartis (England)	Prospective, controlled trial  October 2009 to February 2010	N: 124 n <sub>egg-allergic</sub> = 105 n <sub>control</sub> = 19  6 months and 24 years of age  Case: Convincing clinical history of egg allergy with skin prick wheal size	<b>Vaccination protocol</b> All received skin prick and intradermal test  Skin test positive cases If skin test positive, 2 step delivery - 10% dose, 30 minute observation, 90% dose if no concerning reactions, and 30 minute observation  Skin test negative cases & Controls 1 step delivery - Full dose and 30 minute observation  <b>Outcome</b> Vaccine tolerance	II-2	Good

STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of key Findings Using Text or Data (95% CI)	Level of Evidence	Quality
<i>Immunol.</i> 2010 Nov;105(5):3 87-93. <sup>(90)</sup>			3mm or larger when compared to a negative control, or test score 2+ or greater and/or ImmunoCAP class II or greater to egg white, ovomucoid or ovalbumin  Control: No documentation of clinical egg allergy or sensitization	25 individuals (23.8%) had a history of anaphylaxis attributable to egg  Skin prick tests positive in 3 (2.4%) of participants with no effect on outcome  Intradermal tests positive in 41 (33.1%) of participants with no effect on outcome (most resulted from 1 particular lot)  100% received pH1N1 vaccine with 41 individuals on a 2-step graded vaccine challenge. (Includes 13 of 25 individuals with a history of egg anaphylaxis)  Vaccine (including booster) tolerated without developing symptoms of a significant allergic reaction for both vaccination protocols  97% (91.9, 99.1) tolerance without development of rash for both egg-allergic and control groups  <b>Ovalbumin content</b> Lots ranged from 0.0058 to 0.05 µg /mL, but not found to be clinically significant  Positive intradermal skin test increased for each 0.01- µg /mL increase in vaccine ovalbumin content (OR 1.05 (1.02-1.08), p = .0002)		
Schuler JE, King WJ, Dyneka NL et al. Administration of the adjuvanted pH1N1 vaccine in egg-allergic children at high risk for	Adjuvanted pH1N1 vaccine  Arepanrix™  Two 0.25 mL doses four weeks apart for children 6	Prospective observational cohort  2009/2010 season	N=62  Children (age range 10 months to 16 years)  Identified as at high risk for egg allergy and pH1N1 disease, and referred to allergist	<b>Vaccination Protocol</b> First dose using 2-step delivery: 10% of overall total dose (0.05 mL for both age groups), 30 minute observation period, remaining dose if no concern reactions arose (0.2 mL in children 6 months to 9 years; 0.45 mL in children ≥10 years), 1 hour observation period  Second dose for children 6 months to 9 years tolerating the first dose using single step delivery: 0.25 mL, 1 hour observation period  <b>Outcome</b> First dose – Initial test dose No reactions noted	II-2	Good

STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of key Findings Using Text or Data (95% CI)	Level of Evidence	Quality
influenza A/H1N1 disease. <i>Can J Public Health</i> . 2011; 102(3):196-99. <sup>(91)</sup>	months to 9 years; Single 0.5 mL dose for children ≥10 years			<p>First dose – Remaining dose -2 children developed hives -1 child developed vasovagal response requiring symptomatic management</p> <p>First dose – Post-vaccination observation period -1 child with hypo-responsive episode with uneventful recovery after short observation in emergency department</p> <p>Second dose – Post-vaccination observation period -1 child developed erythema and itching of face (did not have reaction to first dose)</p> <p>-14/44 eligible received second dose at study clinic; 27/44 received a second dose; 17 lost to follow-up</p> <p>No anaphylactic reactions reported</p>		
Howe LE, Conlon AS, Greenhawt MJ, et al. Safe administration of seasonal influenza vaccine to children with egg allergy of all severities. <i>Ann Allergy Asthma Immunol</i> . 2011 May;106(5):446-7. <sup>(92)</sup>	TIV	Retrospective chart review  October 2004 to February 2009	N=135 n <sub>anaphylaxis</sub> =17  Children age 6-36 months at first immunization or testing with objective evidence of egg allergy	<p><b>Vaccination protocol</b> Single full dose or two-dose (10% / 90%)</p> <p><b>Outcome</b> Vaccine tolerance</p> <p>Increased likelihood of using single full dose protocol over time (p&lt;0.006)</p> <p>96% (135) patients received TIV without significant complications.</p> <p>14 (82.4%) individuals with egg-induced anaphylaxis received vaccine without incident (others opted not to get vaccine)</p> <p>4% were not vaccinated per physician or parent preference after a positive TIV skin test result</p> <p>21% (28 out of 135) safely received their first TIV without skin testing</p>	II-3	Fair

STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of key Findings Using Text or Data (95% CI)	Level of Evidence	Quality
				7 patients reported minor reactions (wheal or erythema at the injection site, hives, and diarrhea)		
	pH1N1 Sanofi Pasteur	Prospective cohort with control group  2009 to 2010 season	N=83 n <sub>egg-allergic</sub> =69 n <sub>control</sub> =14  Children age 6-36 months at first immunization or testing  Case: Egg-allergic  Control: Non egg-allergic	<b>Vaccination protocol</b> Single full dose if skin test negative, and for booster if needed Two-step (10% dose, 30 minute observation, 90% dose and 30 minute observation) if skin test positive  <b>Outcome</b> Vaccine tolerance  49% (34) received full strength skin prick testing to TIV 18% (6) positive test results had vaccine administered in 2 steps  99% (68 of 69) EAC tolerated single dose as a first or booster dose  No serious allergic reactions to TIV 2 egg-allergic children had lip or mouth itching and scattered hives 2 non egg-allergic controls had hives and fever or rash  13 with history of egg-induced anaphylaxis, with 12 (92%) tolerating single dose of TIV and 1 receiving two-step vaccine without need for booster  <b>Ovalbumin content</b> Samples of influenza lots ranged from 0.3 to 1.087 µg /mL.	II-3	Fair
Li JT, Rank MA, Squillace DL, et al. Ovalbumin content of influenza vaccines and pH1N1 mono-valent vaccines (varying manufacturer	Samples of 2009 seasonal influenza vaccines and pH1N1 mono-valent vaccines (varying manufacturer	Assays  Bigger sample and higher sensitivity	N=58  n <sub>seasonal</sub> =35  n <sub>H1N1</sub> =23	Ovalbumin concentration (median) <ul style="list-style-type: none"> <li>Seasonal vaccine was 350 ng/mL (range, 0.5-1002).</li> <li>pH1N1 vaccine was 21 ng/mL (range, &lt;1-76).</li> </ul> <b>Specific vaccines</b> <ul style="list-style-type: none"> <li>Fluzone (Sanofi Pasteur) showed higher levels compared with other seasonal influenza vaccines</li> <li>pH1N1 (Sanofi Pasteur) showed higher levels compared with other pH1N1 vaccines; significant lot-to-lot variability for the 2 Sanofi Pasteur vaccines.</li> <li>FluMist contained less than 1 ng/mL ovalbumin.</li> </ul>	n/a	n/a

STUDY DETAILS					SUMMARY	
Study	Vaccine	Study Design	Participants	Summary of key Findings Using Text or Data (95% CI)	Level of Evidence	Quality
Jun;125(6):1412-3. <sup>(95)</sup>	ers and lots) assayed for ovalbumin content			All pH1N1 vaccine lots have low levels of ovalbumin, up to 76 ng/mL in our study  Intranasal LAIV contain very low levels of ovalbumin and may be suitable for administration to patients with egg allergy who do not have asthma.		
Waibel KH, Gomez R. Ovalbumin content in 2009 to 2010 seasonal and H1N1 monovalent influenza vaccines. <i>J Allergy Clin Immunol.</i> 2010 751.e1;125(3):749; Mar-751. <sup>(96)</sup>	Samples of 2009-2010 seasonal influenza vaccines and pH1N1 monovalent vaccines (varying manufacturers and lots) assayed for Ovalbumin content  Sensitivity range of 0.5 to 4 ng/mL	Assays  2009-2010 season	N =11  n <sub>seasonal</sub> =6  n <sub>H1N1</sub> =5	Ovalbumin content of different brands and lots: - For ovalbumin content <i>stated</i> at $\leq 2 \mu\text{g} / \text{mL}$ : <i>Actual</i> content: - nasal vaccines: 0.001 to 0.007 $\mu\text{g} / \text{mL}$ - injectable vaccines: 0.018 to 0.41 $\mu\text{g} / \text{mL}$  - For ovalbumin content <i>stated</i> as maximum 10 $\mu\text{g} / \text{mL}$ : <i>Actual</i> content: 0.064-1.411 $\mu\text{g} / \text{mL}$ (higher than vaccines from the other manufacturers)  Very little lot-to-lot variability	n/a	n/a

Legend: SPT: Skin Prick Testing; TIV: trivalent inactivated influenza vaccine; LAIV: live attenuated influenza vaccine

**Table 7. Levels of evidence based on research design**

I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

**Table 8. Quality (internal validity) rating of evidence**

Good	A study (including meta-analyses or systematic reviews) that meets all design-specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.
I	NACI concludes that there is <b>insufficient</b> evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

\* General design specific criteria are outlined in Harris et al., 2001<sup>4</sup>.

**Table 9: NACI recommendation for immunization - Grades**

A	NACI concludes that there is <b>good</b> evidence to recommend immunization.
B	NACI concludes that there is <b>fair</b> evidence to recommend immunization.
C	NACI concludes that the existing evidence is <b>conflicting</b> and does not allow making a recommendation for or against immunization; however other factors may influence decision-making.
D	NACI concludes that there is <b>fair</b> evidence to recommend against immunization.
E	NACI concludes that there is <b>good</b> evidence to recommend against immunization.
I	NACI concludes that there is <b>insufficient</b> evidence (in either quantity and/or quality) to make a recommendation, however other factors may influence decision-making.

<sup>4</sup> Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20:21-35.

## List of Abbreviations

ACIP	Advisory Committee on Immunization Practices (US)
AI/AN	American Indian and Alaska Natives
AMMI	Association of Medical Microbiology and Infectious Disease
BMI	Body mass index
ca	Cold-adapted
CADTH	Canadian Agency for Drugs and Technologies in Health
CATMAT	Committee to Advise on Tropical Medicine and Travel
CCDR	Canada Communicable Disease Report
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CIRID	Centre for Immunization and Respiratory Infectious Diseases
CNISP	Canadian Nosocomial Infection Surveillance Program
CSACI	Canadian Society of Allergy and Clinical Immunology
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal membrane oxygenation
FFU	Fluorescent focus units
GBS	Guillain-Barré syndrome
HA	Haemagglutinin antigen
HCW	Health care worker
HIV	Human immunodeficiency virus
ICU	Intensive care unit
ID	Intradermal
IgE	Immune globulin E
IgG	immune globulin G
ILI	Influenza-like illness
IM	Intramuscular
IMPACT	Immunization Monitoring Program, Active
IWG	Influenza Working Group
LAIV	Live attenuated influenza vaccine
LOS	Length of stay
LTCF	Long-term care facility
mL	Millilitre
NACI	National Advisory Committee on Immunization
NAI	Neuraminidase inhibitors
NML	National Microbiology Laboratory
OR	Odds ratio
ORS	Oculorespiratory syndrome
pH1N1	Pandemic H1N1 2009
PHAC	Public Health Agency of Canada
PICU	Paediatric intensive care unit
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
TESSy	The European Surveillance System
TIV	Trivalent inactivated influenza vaccine
TIV-ID	Trivalent inactivated influenza vaccine administered intradermally
µg	Microgram
UIIP	Universal Influenza Immunization Program (Ontario)
UK	United Kingdom
VAERS	Vaccine Adverse Event Reporting System (USA)
WHO	World Health Organization

<sup>†</sup> This statement was prepared by Dr. S. Tamblyn with contributions from CADTH and Ms. E. Wong, and approved by NACI and the Public Health Agency of Canada.

<sup>†</sup> **Members:** Dr. J. Langley (Chair), Dr. B. Warshawsky (Vice-Chair), Dr. C. Cooper, Dr. N. Crowcroft, Ms. A. Hanrahan, Dr. B. Henry, Dr. D. Kumar, Dr. S. McNeil, Dr. C. Quach-Thanh, Dr. B. Seifert, Dr. D. Skowronski, , Dr. Wendy Vaudry, Dr. Richard Warrington,

**Liaison Representatives:** Dr. J. Brophy (Canadian Association for Immunization Research and Evaluation), Dr. A. Mawle (U.S. Center for Disease Control and Prevention), Dr. Heather Morrison, (Council of Chief Medical Officers of Health) Ms. S. Pelletier (Community Hospital Infection Control Association), Dr. A. Opavsky (Association of Medical Microbiology and Infectious Disease Canada), Ms. K. Pielak (Canadian Nursing Coalition for Immunization), Dr. P. Plourde (Committee to Advise on Tropical Medicine and Travel), Dr. S. Rechner (College of Family Physicians of Canada), Dr. M. Salvadori (Canadian Paediatric Society), Dr. V. Senikas (Society of Obstetricians and Gynaecologists of Canada), Dr. N. Sicard (Canadian Public Health Association).

**Ex-Officio Representatives:** Lt.-Col. Dr. J. Anderson (Department of National Defence), Dr. Ezzat Farzad (First Nations and Inuit Health Branch – Office of Community Medicine), Dr. A. Klein (Biologics and Genetic Therapies Directorate), Dr. J. Laroche (Centre for Immunization and Respiratory Infectious Disease), Dr. B. Law (Centre for Immunization and Respiratory Infectious Diseases), Ms. D. Poulin (Centre for Immunization and Respiratory Infectious Diseases), Dr. M. Tepper (Department of National Defence), Dr. P. Varughese, (Centre for Immunization and Respiratory Infectious Disease)

**Additional Influenza Working Group Members:** Dr. P. Van Buynder, Dr. B. Cholin, Dr. G. DeSerres, Dr. I. Gemmill, Dr. S. Halperin

## References

- (1) Levandowski RA, Gross PA, Weksler M et al. Cross-reactive antibodies induced by a monovalent influenza B virus vaccine. *J Clin Microbiol.* 1991;29(7):1530-2.
- (2) Heckler R, Baillot A, Engelman H et al. Cross-protection against homologous drift variants of influenza A and B after vaccination with split vaccine. *Intervirology.* 2007;50(1):58-62.
- (3) Walter EB, Neuzil KM, Zhu Y et al. Influenza vaccine immunogenicity in 6 to 23-month-old children: are identical antigens necessary for priming? *Pediatrics.* 2006;118:e570-8.
- (4) Englund JA, Walter EB, Gbadebo A et al. Immunization with trivalent inactivated influenza vaccine in partially immunized toddlers. *Pediatrics.* 2006;118(3):e579-85.
- (5) Levandowski RA, Regnery HL, Staton E et al. Antibody responses to influenza B viruses in immunologically unprimed children. *Pediatrics.* 1991;88(5):1031-6.
- (6) World Health Organization. Recommended composition of influenza virus vaccines for use in the 2011-2012 northern hemisphere influenza season. *Wkly Epidemiol Rec.* 2011;86(10):81-91. Available from: <http://www.who.int/wer/2011/wer8610.pdf>
- (7) Canadian Agency for Drugs and Technologies in Health. The association between obesity, Aboriginal or indigenous people, Indian or Alaskan Natives living in North America and residence in remote locations and severe outcomes with seasonal and pandemic influenza: a review of the clinical evidence. Ottawa:CADTH;2011. (Rapid response report). Available from: <http://www.cadth.ca/en/products/rapid-response?q=The+Association+between+Obesity%2C+Aboriginal+or+Indigenous+People%2C+Indian+or+Alaskan+Natives+Living+in+North+America+and+Residence+in+Remote+Locations+and+Severe+Outcomes+with+Seasonal+and+Pandemic+Influenza%3A+A+Review+of+the+Clinical+Evidence>
- (8) European Centre for Disease Control. ECDC risk assessment: 2009 influenza A(H1N1) pandemic. Version 7-17 December 2009. Available from: [http://www.ecdc.europa.eu/en/healthtopics/Documents/0908\\_Influenza\\_AH1N1\\_Risk\\_Assessment.pdf](http://www.ecdc.europa.eu/en/healthtopics/Documents/0908_Influenza_AH1N1_Risk_Assessment.pdf)
- (9) Nguyen-Van-Tam JS. Epidemiology of Influenza. In: Nicholson KG, Webster RG, Hay AJ, eds. *Textbook of Influenza.* London: Blackwell Science;1998. p.181-206.
- (10) Schanzer D, Tam TW, Langley JM, et al. Influenza-attributable deaths, Canada 1990-1999. *Epidemiol Infect.* 2007;135:1109-16. Epub 2007 Feb 16.
- (11) Reyes F, Macey JF, Aziz S, et al. Influenza in Canada: 2005-2006 season. *Can Commun Dis Rep.* 2007;33(3):21-41. Available from: <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07vol33/dr3303a-eng.php>
- (12) Centers for Disease Control and Prevention. Update: Influenza Activity --- United States, October 3, 2010--February 5, 2011. *Morbidity and Mortality Weekly Report (MMWR).* 2011;60:175-81. Available from: <http://www.cdc.gov/mmwr/PDF/wk/mm6006.pdf>

- (13) Centers for Disease Control and Prevention. FluView. 2010-11 Influenza Season Week 14 ending 9 April 2011. Available from: <http://www.cdc.gov/flu/weekly/weeklyarchives2010-2011/weekly14.htm> .
- (14) European Centre for Disease Prevention and Control. Surveillance report. Biweekly influenza surveillance overview. 8 Apr 2011. Available from: [http://ecdc.europa.eu/en/publications/Publications/110408\\_SUR\\_Weekly\\_Influenza\\_Surveillance\\_Overview.pdf](http://ecdc.europa.eu/en/publications/Publications/110408_SUR_Weekly_Influenza_Surveillance_Overview.pdf).
- (15) Health Protection Agency (United Kingdom). Weekly National Influenza Report. Weeks 49 (9 Dec, 2010), 51 (23 Dec, 2010), 06 (10 Feb, 2011), and 14 (7 Apr, 2011). Available from: [http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb\\_C/1222154877315](http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1222154877315)
- (16) Australia Department of Health and Ageing. Influenza Surveillance Report No. 44, 2010, Reporting period Oct 30 – Nov 5, 2010. Available from: <http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-ozflu-no44-10.htm>.
- (17) New Zealand Ministry of Health. Influenza Weekly Update 2010/39. Sep27 – 3 Oct, 2010. Available from: [http://www.surv.esr.cri.nz/PDF\\_surveillance/Virology/FluWeekRpt/2010/FluWeekRpt201039.pdf](http://www.surv.esr.cri.nz/PDF_surveillance/Virology/FluWeekRpt/2010/FluWeekRpt201039.pdf)
- (18) World Health Organization. Global Alert and Response (GAR). Influenza update. 8 Apr 2011. Available from: [http://www.who.int/csr/disease/influenza/2011\\_04\\_08\\_GIP\\_surveillance/en/index.html](http://www.who.int/csr/disease/influenza/2011_04_08_GIP_surveillance/en/index.html)
- (19) Australia Department of Health and Ageing. Influenza Surveillance Report No. 1, 2011, Reporting period Mar 19 – Apr 1, 2011. Available from: <http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-ozflu-no1-11.htm>
- (20) World Health Organization. Global Alert and Response (GAR). Avian Influenza Situation Updates. Available from: [http://www.who.int/csr/disease/avian\\_influenza/updates/en/index.html](http://www.who.int/csr/disease/avian_influenza/updates/en/index.html)
- (21) World Health Organization. Global Alert and Response (GAR). Cumulative number of confirmed human cases of avian influenza A/(H5N1) reported to WHO. 11 Apr 2011. Available from : [http://www.who.int/entity/csr/disease/avian\\_influenza/country/cases\\_table\\_2011\\_04\\_11/en/index.html](http://www.who.int/entity/csr/disease/avian_influenza/country/cases_table_2011_04_11/en/index.html)
- (22) World Health Organization. Global Alert and Response (GAR). Current WHO phase of pandemic alert for avian influenza H5N1. Available from: [http://www.who.int/csr/disease/avian\\_influenza/phase/en/index.html](http://www.who.int/csr/disease/avian_influenza/phase/en/index.html)
- (23) World Health Organization. Update on human cases of highly pathogenic avian influenza A(H5N1) virus infection, 2010. Wkly Epidemiol Rec. 2011;86(10):161-6. Available from: <http://www.who.int/wer/2011/wer8617.pdf>
- (24) World Health Organization. Update on oseltamivir resistance in influenza A(H1N1)2009 viruses. Apr 6 2011. Available from:

- [http://www.who.int/csr/disease/influenza/2011\\_04\\_08\\_weekly\\_web\\_update\\_oseltamivir\\_resistance.pdf](http://www.who.int/csr/disease/influenza/2011_04_08_weekly_web_update_oseltamivir_resistance.pdf)
- (25) Lackenby A, Gilad JM, Pebody R, et al. Continued emergence and changing epidemiology of oseltamivir-resistant influenza A(H1N1)2009 virus, United Kingdom, winter 2010/11. *Euro Surveill.* 2011;16(5):pii=19784. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19784>
- (26) National Advisory Committee on Immunization (NACI). An Advisory Committee Statement (ACS). Recommendations on the use of intradermal trivalent inactivated influenza vaccine (TIV-ID): Update to the Statement on Seasonal Trivalent Inactivated Influenza Vaccine (TIV) for 2010-2011. Available from: <http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php#rec>.
- (27) National Advisory Committee on Immunization (NACI). An Advisory Committee Statement (ACS). Recommendations on the use of live, attenuated influenza vaccine (FluMist®): Supplemental Statement of Seasonal Influenza Vaccine for 2011-2012. Available from: <http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php#rec>.
- (28) National Advisory Committee on Immunization (NACI). An Advisory Committee Statement (ACS). MF59-adjuvanted trivalent influenza vaccine (Fluad®): Supplemental Statement of Seasonal Influenza Vaccine for 2011-2012. Available from: <http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php#rec>.
- (29) Langley JM, Faughnan ME. Prevention of influenza in the general population. *CMAJ.* 2004;171(10):1213-22.
- (30) Smith S, Demicheli V, Di Pietrantonj C et al. Vaccines for preventing influenza in healthy children. *Cochrane Database Syst Rev.* 2006;2006(1):CD004879.
- (31) Negri E, Colombo C, Giordano L et al. Influenza vaccine in healthy children: a meta-analysis. *Vaccine.* 2005;23(22):2851-61.
- (32) Manzoli L, Schioppa F, Boccia A et al. The efficacy of influenza vaccine for healthy children: a meta-analysis evaluating potential sources of variation in efficacy estimates including study quality. *Pediatr Infect Dis J.* 2007;26(2):97-106.
- (33) Demicheli V, Rivelli D, Deeks JJ et al. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev.* 2004;2004(3):CD001269.
- (34) Jefferson TO, Rivetti D, Di Pietrantonj C et al. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev.* 2007;2007(2):CD001269.
- (35) Govaert TM, Thijs CT, Masurel N et al. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. *JAMA.* 1994;272(21):1661-5.
- (36) Praditsuwan R, Assantachai P, Wasi C et al. The efficacy and effectiveness of influenza vaccination among Thai elderly persons living in the community. *J Med Assoc Thai.* 2005;88(2):256-64.
- (37) Ohmit SE, Victor JC, Rotthoff JR et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. *N Engl J Med.* 2006;355(24):2513-22.

- (38) Herrera GA, Iwane MK, Cortese M et al. Influenza vaccine effectiveness among 50–64-year-old persons during a season of poor antigenic match between vaccine and circulating influenza virus strains: Colorado, United States, 2003–2004. *Vaccine*. 2007;25(1):154–60.
- (39) Rivetti D, Jefferson T, Thomas R et al. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev*. 2006;2006(3):CD004876.
- (40) Nichol KL, Nordin JD, Nelson DB et al. Effectiveness of influenza vaccine in the community-dwelling elderly. *N Engl J Med*. 2007;357:1373–81.
- (41) Poole PJ, Chacko E, Wood-Baker RW et al. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2006;2006(1):CD002733.
- (42) Hak E, Buskens E, van Essen GA et al. Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions: the PRISMA study. *Arch Intern Med*. 2005;165(3):274–80.
- (43) Nichol KL, Nordin J, Mullooly J et al. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *N Engl J Med*. 2003;348(14):1322–32.
- (44) Looijmans-Van den Akker I, Verheij TS, Buskens E et al. Clinical effectiveness of first and repeat influenza vaccination in adult and elderly diabetic patients. *Diabetes Care*. 2006;29(8):1771–6.
- (45) Orenstein EW, De Serres G, Haber MJ et al. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. *Int J Epidemiol*. 2007;36:623–31.
- (46) Simonsen L. Commentary: observational studies and the art of accurately measuring influenza vaccine benefits. *Int J Epidemiol*. 2007;36:631–2.
- (47) Jackson LA, Jackson ML, Nelson JC et al. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. *Int J Epidemiol*. 2006;35:337–44.
- (48) Jackson LA, Nelson JC, Berson P et al. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. *Int J Epidemiol*. 2006;35:345–52.
- (49) Simonsen L, Taylor RJ, Viboud C et al. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. *Lancet Infect Dis*. 2007;7:658–66.
- (50) Simonsen L, Viboud C, Taylor RJ. Effectiveness of influenza vaccination [letter]. *N Engl J Med*. 2007;357:2729–30.
- (51) Thomas PG, Keating R, Hulse-Post DJ, et al. Cell-mediated protection in influenza infection. *Emerg Infect Dis*. 2006;12:48–54.
- (52) Anema A, Mills E, Montaner J et al. Efficacy of influenza vaccination in HIV-positive patients: a systematic review and meta-analysis. *HIV Med*. 2008;19:419–23.

- (53) Cooper C, Hutton B, Fergusson D et al. A review of influenza vaccine immunogenicity and efficacy in HIV-infected adults. *Can J Infect Dis Med Microbiol.* 2008;19:419–23.
- (54) Scharpe J, Evenepoel P, Maes B et al. Influenza vaccination is efficacious and safe in renal transplant recipients. *Am J Transplant.* 2008;8(2):332–7.
- (55) Manuel O, Humar A, Chen MH et al. Immunogenicity and safety of an intradermal boosting strategy for vaccination against influenza in lung transplant recipients. *Am J Transplant.* 2007;7(11):2567–72.
- (56) Englehard D, Nagler A, Hardan I et al. Antibody response to a two-dose regimen of influenza vaccine in allogenic T cell-depleted and autologous BMT recipients. *Bone Marrow Transplant.* 1993;11:1–5.
- (57) Buxton JA, Skowronski DM, Ng H et al. Influenza revaccination of elderly travelers: antibody response to single influenza vaccination and revaccination at 12 weeks. *J Infect Dis.* 2001;184:188–91.
- (58) Ljungman P, Nahi H, Linde A et al. Vaccination of patients with haematological malignancies with one or two doses of influenza vaccine: a randomised case study. *Br J Haematol.* 2005;130:96–8.
- (59) McElhaney JE, Hooton JW, Hooton N et al. Comparison of single versus booster dose of influenza vaccination on humoral and cellular immune responses in older adults. *Vaccine.* 2005;23:3294–300.
- (60) Gross PA, Weksler ME, Quinnan GV et al. Immunization of elderly people with two doses of influenza vaccine. *J Clin Microbiol.* 1987;25:1763–5.
- (61) Van Damme P, Arnou R, Fiquet A, et al. Evaluation of non-inferiority of intradermal versus adjuvanted seasonal influenza vaccine using two serological techniques: a randomized comparative study. *BMC Infect Dis.* 2010;10:134
- (62) Ritzwoller DP, Bridges CB, Shetterley S et al. Effectiveness of the 2003–2004 influenza vaccine among children 6 months to 8 years of age, with 1 vs 2 doses. *Pediatrics.* 2005;116(1):153–9.
- (63) Neuzil KM, Jackson LA, Nelson J et al. Immunogenicity and reactogenicity of 1 versus 2 doses of trivalent inactivated influenza vaccine in vaccine-naïve 5-8-year-old children. *J Infect Dis.* 2006;194:1032–9.
- (64) Shuler CM, Iwamoto M, Bridges CB. Vaccine effectiveness against medically-attended, laboratory-confirmed influenza among children aged 6 to 59 months, 2003–2004. *Pediatrics.* 2007;119:587–95.
- (65) Allison MA, Daley MF, Crane LA et al. Influenza vaccine effectiveness in healthy 6- to 21-month-old children during the 2003–2004 season. *J Pediatr.* 2006;149(6):755–62.
- (66) Englund JA, Walter EB, Fairchok MP et al. A comparison of 2 influenza vaccine schedules in 6- to 23-month-old children. *Pediatrics.* 2005;115(4):1039–47.
- (67) Skowronski dM, Hottes TS, De Serres G et al. Influenza B/Victoria antigen induces strong recall of B/Yamagata but lower B/Victoria response in children primed with two doses of B/Yamagata. *Ped Inf Dis J.* 2011 [In press]

- (68) Skowronski DM, Hottes TS, Chong M, et al. Randomized controlled trial of dose-response to influenza vaccine in children 6-23 months of age. *Pediatrics*. Epub 2011 July 18. Doi: 10.1542/peds.2010-2777).
- (69) National Advisory Committee on Immunization (NACI). *Canadian Immunization Guide*. 7th ed. Ottawa: Public Works and Government Services Canada; 2006. Available from: <http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php>.
- (70) National Advisory Committee on Immunization (NACI). Statement on thimerosal. *Can Commun Dis Rep*. 2003;29(ACS-1):1-12.
- (71) National Advisory Committee on Immunization (NACI). Thimerosal: updated statement. *Can Commun Dis Rep*. 2007;33(ACS-6):1-13.
- (72) Gerber JS, Offit PA. Vaccines and autism: a tale of shifting hypotheses. *Clin Infect Dis*. 2009;48:456-61.
- (73) National Advisory Committee on Immunization (NACI). Supplementary Statement for the 2002-2003 influenza season: Update on oculo-respiratory syndrome in association with influenza vaccination. *Can Commun Dis Rep*. 2002;28(ACS-6):1-8.
- (74) Skowronski DM, Strauss B, Kendall P et al. Low risk of recurrence of oculo-respiratory syndrome following influenza revaccination. *CMAJ*. 2002;167(8):853-8.
- (75) De Serres G, Skowronski DM, Guay M et al. Recurrence risk of oculo-respiratory syndrome after influenza vaccination: randomized controlled trial of previously affected persons. *Arch Intern Med*. 2004;164(20):2266-72.
- (76) Langmuir AD, Bregman DJ, Kurland LT et al. An epidemiologic and clinical evaluation of Guillain-Barré syndrome reported in association with the administration of swine influenza vaccines. *Am J Epidemiol*. 1984;119(6):841-79.
- (77) Institute of Medicine. *Immunization Safety Review: Influenza Vaccines and Neurological Complications*. Washington, D.C.: Institute of Medicine of the National Academies; 2008.
- (78) Lasky T, Terracciano GJ, Magder L et al. The Guillain-Barré syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *N Engl J Med*. 1998;339(25):1797-802.
- (79) Juurlink DN, Stukel TA, Kwong J et al. Guillain-Barré syndrome after influenza vaccination in adults: a population-based study. *Arch Intern Med*. 2006;166(20):2217-21.
- (80) Prothro C, Kudish K, Fielin M et al. Preliminary results: surveillance for Guillain-Barre syndrome after receipt of influenza A (H1N1) 2009 monovalent vaccine - United States, 2009-2010. *MMWR*. 2010;59:657-61.
- (81) McLean M, Duclos P, Jacob P et al. Incidence of Guillain-Barré syndrome in Ontario and Quebec, 1983-1989, using hospital service databases. *Epidemiology*. 1994;5(4):443-8.

- (82) Hughes RA, Cornblath DR. Guillain-Barré syndrome. *Lancet*. 2005;366(9497):1653-66.
- (83) Sivadon-Tardy V, Orlikowski D, Porcher R et al. Guillain-Barré syndrome and influenza virus infection. *Clin Infect Dis*. 2009;48(1):48-56.
- (84) Lehmann HC, Hartung HP, Kieseier BC, et al. Guillain-Barré syndrome after exposure to influenza virus. *Lancet Infect Dis* 2010;10:643-51.
- (85) Tam CC, O'Brien SJ, Petersen I et al. Guillain-Barré syndrome and preceding infection with campylobacter, influenza and Epstein-Barr virus in the general practice research database. *PLoS One*. 2007 Apr 4;2(4):e344.
- (86) Stowe J, Andrew N, Wise L et al. Investigation of temporal association of Guillain-Barré Syndrome with influenza vaccine and influenzalike illness using the United Kingdom General Practice Research database. *Am J Epidemiol*. 2009;169:382-8.
- (87) James JM, Zeiger RS, Lester MR, et al. Safe administration of influenza vaccine to patients with egg allergy. *J Pediatr*. 1998;133:624-8.
- (88) Chung EY, Huang L, Schneider L. Safety of influenza vaccine administration in egg-allergic patients. *Pediatrics*. 2010;125:e1024-30.
- (89) Gagnon R, Primeau M, Des Roches A et al, on behalf of the PHAC-CIHR Influenza Research Network (PCIRN). Safe vaccination of egg-allergic patients with an adjuvanted pandemic H1N1 vaccine. *J Allergy Clin Immunol*. 2010;126(2): 317-23 E pub 2010 Jun 25.
- (90) Greenhawt MJ, Chernin AS, Howe L, et al. The safety of the H1N1 influenza A vaccine in egg allergic individuals. *Ann Allergy Asthma Immunol*. 2010;105:387-93.
- (91) Schuler JE, King WJ, Dayneka NL, et al. Administration of the adjuvanted pH1N1 vaccine in egg-allergic children at high risk for influenza A/H1N1 disease. *Can J Public Health*. 2011;102:196-9.
- (92) Howe LE, Conlon AS, Greenhawt MJ, et al. Safe administration of seasonal influenza vaccine to children with egg allergy of all severities. *Ann Allergy Asthma Immunol*. 2011;106(5):446-7. Epub 2011 Feb 24.
- (93) Canadian Society of Allergy and Clinical Immunology. Statement: administration of H1N1 and seasonal influenza vaccine to egg allergic individuals. 2009. Available from: [http://www.csaci.ca/include/files/CSACI\\_H1N1\\_Statement.pdf](http://www.csaci.ca/include/files/CSACI_H1N1_Statement.pdf).
- (94) Greenhawt MJ, Li JT (eds). Administering influenza vaccine to egg allergic recipients: a focused practice parameter update. *Ann Allergy Asthma Immunol*. 2011;106:11-6.
- (95) Li JT, Rank MA, Squillace DL, et al. Ovalbumin content of influenza vaccines. *J Allergy Clin Immunol*. 2010;125:1412-3; author reply 1413-4. E pub 2010 May 7.
- (96) Waibel KH, Gomez R. Ovalbumin content in 2009 to 2010 seasonal and H1N1 monovalent influenza vaccines. *J Allergy Clin Immunol*. 2010 Jan;125:749-51, 751 e1. E pub 2010 Jan 8.

- (97) Public Health Agency of Canada. Final Report of Outcomes from the National Consensus Conference for Vaccine-Preventable Diseases in Canada. *Can Commun Dis Rep.* 2008;34S2:28–32. Available from: <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/08vol34/34s2/index-eng.php>.
- (98) Skowronski DM, Tweed SA, De Serres G. Rapid decline of influenza vaccine-induced antibody in the elderly: is it real, or is it relevant? *J Infect Dis.* 2008;197:490–502.
- (99) Intensive-care patients with severe novel influenza A (H1N1) virus infection—Michigan, June 2009. *MMWR Morb Mortal Wkly Rep.* 2009;58(27):749–52.
- (100) Jain S, Kamimoto L, Bramley AM et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. *N Engl J Med.* 2009;361(20):1935–44.
- (101) Kumar A, Zarychanski R, Pinto R et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA.* 2009;302(17):1872–9.
- (102) The ANZIC Influenza Investigators. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med.* 2009;361(20):1925–34.
- (103) Morgan OW, Bramley A, Fowlkes A et al. Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. *PLoS One.* 2010;5(3):e9694.
- (104) Fezeu L, Julia C, Bitu, et al. Obesity is associated with higher risk of intensive care admission and death in influenza A(H1N1) patients: a systematic review and meta-analysis. *Obes Rev.* 2011 E pub 2011 Apr 4.
- (105) Falagas ME, Koletsi PK, Baskouta E. Pandemic A9H1N10 2009 influenza: review of the Southern Hemisphere experience. *Epidemiol Infect.* 2011;139:27-40.
- (106) Kwong JC, Campitelli MA, Rosella LC, et al. Obesity and respiratory hospitalizations during influenza seasons in Ontario, Canada, a cohort study. *Clin Infect Dis.* 2011. In press.
- (107) Simonsen L, Fukuda K, Schonberger LB et al. The impact of influenza epidemics on hospitalizations. *J Infect Dis.* 2000;181:831–7.
- (108) Schanzer DL, Tam TW, Langley JM et al. Influenza-attributable deaths, Canada, 1990–1999. *Epidemiol Infect.* 2007;1–8.
- (109) Schanzer DL, Langley JM, Tam TW. Hospitalization attributable to influenza and other viral respiratory illnesses in Canadian children. *Pediatr Infect Dis J.* 2006;25(9):795–800.
- (110) Izurieta HS, Thompson WW, Kramarz P et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med.* 2000;342(4):232–9.
- (111) Skowronski DM, Woolcott JC, Tweed SA et al. Potential cost-effectiveness of annual influenza immunization for infants and toddlers: experience from Canada. *Vaccine.* 2006;24(19):4222–32.

- (112) Black SB, Shinefield HR, France EK et al. Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. *Am J Perinatol*. 2004;6:333-9.
- (113) Schanzer DL, Langley JM, Tam TW. Influenza-attributed hospitalization rates among pregnant women in Canada 1994-2000. *J Obstet Gynaecol Can*. 2007;29:622-9.
- (114) Tuyishime JD, De Wals P, Moutquin JM et al. Influenza-like illness during pregnancy: results from a study in the eastern townships, province of Quebec. *J Obstet Gynaecol Can*. 2003;25:1020-5.
- (115) MacDonald NE, Riley LE, Steinhoff MC. Influenza immunization in pregnancy. *Obstet Gynecol*. 2009; 114:206-8.
- (116) Skowronski DM, De Serres G. Is routine influenza immunization warranted in early pregnancy? *Vaccine*. 2009; 27:4754-70.
- (117) McNeil SA, Halperin B, MacDonald NE. Influenza in pregnancy: the case for prevention. *Adv Exp Med Biol*. 2009; 634:161-83.
- (118) Mak TK, Mangtani P, Leese J et al. Influenza vaccination in pregnancy: current evidence and selected national policies. *Lancet Infect Dis*. 2008;8:44-52.
- (119) Neuzil KM, Reed GW, Mitchel EF et al. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am J Epidemiol*. 1997;148:1094-8.
- (120) Dodds L, McNeil SA, Fell SB et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *CMAJ*. 2007;176:463-8.
- (121) Hartert TV, Neuzil KM, Shintani AK et al. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. *Am J Obstet Gynecol*. 2003;189:1705-12.
- (122) Rasmussen SA, Jamieson DJ, Breese JS. Pandemic influenza and pregnant women. *Emerg Infect Dis*. 2008;14:95-100.
- (123) Siston AM, Rasmussen SA, Honein MA et al. Pandemic 2009 influenza A (H1N1) virus illness among pregnant women in the United States. *JAMA*. 2010;303:1517-25.
- (124) Louie JK, Acosta M, Jamieson DJ et al, for the California Pandemic (H1N1) Working Group. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N Engl J Med*. 2010;362:27-35.
- (125) Helferty M, Vachon J, Tarasuk J, et al. Incidence of hospital admissions and severe outcomes during the first and second waves of pandemic (H1N1) 2009. *CMAJ*. 2010;182:1981-7. E pub 2010 Nov 8.
- (126) Ashley J, Smith T, Dunell K. Deaths in Great Britain associated with the influenza epidemic of 1989/90. *Pop Trends*. 1991;65:16-20.

- (127) Mullooly JP, Barker WH, Nolan TF. Risk of acute respiratory disease among pregnant women during influenza A epidemics. *Public Health Rep.* 1986;101:205–10.
- (128) Schoenbaum SC, Weinstein L. Respiratory infection in pregnancy. *Clin Obstet Gynecol.* 1979;22:293–300.
- (129) Widelock D, Csizmas L, Klein S. Influenza, pregnancy and fetal outcome. *Public Health Rep.* 1963;78:1–11.
- (130) Houseworth J, Langmuir AD. Excess mortality from epidemic influenza, 1957–1966. *Am J Epidemiol.* 1974;100:40–8.
- (131) Callaghan WM, Chu SY, Jamieson DJ. Deaths from seasonal influenza among pregnant women in the United States, 1998–2005. *Obstet Gynecol.* 2010;115:919–23.
- (132) Hulka JF. Effectiveness of polyvalent influenza vaccine in pregnancy: report of a controlled study during an outbreak of Asian influenza. *Obstet Gynecol.* 1964;23:830–7.
- (133) Munoz FM, Greisinger AJ, Wehmanen OA et al. Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol.* 2005;192:1098–106.
- (134) France EK, Smith-Ray R, McClure D et al. Impact of maternal influenza vaccination during pregnancy on the incidence of acute respiratory illness visits among infants. *Arch Pediatr Adolesc Med.* 2006;160:1277–83.
- (135) Zaman K, Roy E, Arifeen SE et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med.* 2008;359:1–10.
- (136) Steinhoff MC, Omer SB, Roy E et al. Influenza immunization in pregnancy—antibody responses in mothers and infants. *N Engl J Med.* 2010;362:1644–5.
- (137) Eick AA, Uyeki TM, Klimov A, et al. Maternal influenza vaccination and effect on influenza virus infection in young infants. *Arch Pediatr Adolesc Med.* 2011;165:104–11. Epub 2010 Oct 4.
- (138) Tamma PD, Ault KA, del Rio C et al. Safety of influenza vaccination during pregnancy. *Am J Obstet Gynecol.* 2009;201:547–52.
- (139) Moro PL, Broder K, Zheteyeva Y, et al. Adverse events in pregnant women following administration of trivalent inactivated influenza vaccine and live attenuated influenza vaccine in the Vaccine Adverse Event Reporting System, 1990–2009. *Am J Obstet Gynecol.* 2011;204:146.e1–7. E pub 2010 Oct 20.
- (140) Public Health Agency of Canada. Vaccine surveillance report—adverse events following immunization. Update: 2010 Apr 27. Available from: <http://www.phac-aspc.gc.ca/alert-alerte/h1n1/vacc/addeve-eng.php>.
- (141) European Medicines Agency. Fifteenth Pandemic Pharmacovigilance update. 8 April 2010. Available from: <http://www.ema.europa.eu/pdfs/influenza/21323810en.pdf>

- (142) Heinonen OP, Shapiro S, Monson RR et al. Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. *Int J Epidemiol.* 1973;2:229–35.
- (143) Heinonen OP, Slone D, Shapiro S. Immunizing agents. In: Kaufman DW, editor. *Birth defects and drugs in pregnancy.* Boston (MA): Littleton Publishing Sciences Group; 1977. p. 314–21.
- (144) Sumaya CV, Gibbs RS. Immunization of pregnant women with influenza A/New Jersey/76 virus vaccine:reactogenicity and immunogenicity in mother and infant. *J Infect Dis.* 1979;140:141–6.
- (145) Englund JA, Mbawuikie IN, Hammill H et al. Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. *J Infect Dis.* 1993;68:647–56.
- (146) Deinard AS, Ogburn Jr P. A/NJ/8/76 influenza vaccination program:effects on maternal health and pregnancy outcome. *Am J Obstet Gynecol.* 1981;140:240–5.
- (147) Groom AV, Jim C, Laroque M et al. Pandemic influenza preparedness and vulnerable populations in tribal communities. *Am J Public Health.* 2009;99 Suppl 2: S271–8.
- (148) Samet JM, Key CR, Kutvirt DM et al. Respiratory disease mortality in New Mexico's American Indians and Hispanics. *Am J Public Health.* 1980;70(5): 492–7.
- (149) La Ruche G, Tarantola A, Barboza P et al. for the Epidemic Intelligence Team at InVS. The 2009 pandemic H1N1 influenza and indigenous populations of the Americas and the Pacific. *Euro Surveill.* 2009;14(42):1–6.
- (150) Deaths related to 2009 pandemic influenza A (H1N1) among American Indian/Alaska Natives – 12 states, 2009. *MMWR Morb Mortal Wkly Rep.* 2009;58(48):1341–4.
- (151) Zarychanski R, Stuart TL, Kumar A et al. Correlates of severe disease in patients with 2009 pandemic influenza (H1N1) virus infection. *CMAJ.* 2010;182:257–64.
- (152) Jouvét P, Hutchison J, Pinto R et al. Critical illness in children with influenza A/pH1N1 2009 infection in Canada. *Paediatr Crit Care Med.* 2010;11:603-9.
- (153) Campbell A, Rodin R, Kropp R, et al. Risk of severe outcomes among patients admitted to hospital with pandemic (H1N1) influenza. *CMAJ.* 2010;182:349-55. E pub 2010 Feb 16.
- (154) International Center for Education Statistics. Individuals, families and children in poverty. In: *Status and trends in the education of American Indians and Alaska Natives.* 2008. Available from: [http://nces.ed.gov/pubs2008/nativetrends/ind\\_1\\_6.asp](http://nces.ed.gov/pubs2008/nativetrends/ind_1_6.asp).
- (155) Canada. Royal Commission on Aboriginal Peoples: People to people, nation to nation. Highlights from the report of the Royal Commission on Aboriginal peoples. 1996. Available from: <http://www.ainc-inac.gc.ca/ap/pubs/rpt/rpt-eng.asp>
- (156) Clark M, Riben P, Nowgesic E. The association of housing density, isolation and tuberculosis in Canadian First Nations communities. *Int J Epidemiol.* 2002;31:940–3.

- (157) Larcombe L, Rempel JD, Dembinski I et al. Differential cytokine genotype frequencies among Canadian Aboriginal and Caucasian populations. *Genes Immun.* 2005;6:140-4.
- (158) Hayward AC, Harling R, Wetten S et al. Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. *BMJ.* 2006;333(7581):1241.
- (159) Potter J, Stott DJ, Roberts MA et al. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. *J Infect Dis.* 1997;175(1):1-6.
- (160) Pearson ML, Bridges CB, Harper SA. Influenza vaccination of health-care personnel: recommendations of the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006;55(RR-2):1-16.
- (161) Carman WF, Elder AG, Wallace LA et al. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. *Lancet.* 2000;355(9198):93-7.
- (162) Lemaitre M, Meret T, Rothan-Tondeur M et al. Effect of influenza vaccination of nursing home staff on mortality of residents: a cluster-randomized trial. *J Am Geriatr Soc.* 2009;57:1580-6.
- (163) Wilde JA, McMillan JA, Serwint J et al. Effectiveness of influenza vaccine in health care professionals: a randomized trial. *JAMA.* 1999;281(10):908-13.
- (164) Saxen H, Virtanen M. Randomized, placebo-controlled double blind study on the efficacy of influenza immunization on absenteeism of health care workers. *Pediatr Infect Dis J.* 1999;18(9):779-83.
- (165) Shugarman LR, Hales C, Setodji CM et al. The influence of staff and resident immunization rates on influenza-like illness outbreaks in nursing homes. *J Am Med Dir Assoc* 2006;7(9):562-7.
- (166) Bridges CB, Lim W, Hu-Primmer J et al. Risk of influenza A (H5N1) infection among poultry workers, Hong Kong, 1997-1998. *J Infect Dis.* 2002;185(8):1005-10.
- (167) Puzelli S, Di Trani L, Fabiani C et al. Serological analysis of serum samples from humans exposed to avian H7 influenza viruses in Italy between 1999 and 2003. *J Infect Dis.* 2005;192(8):1318-22.
- (168) Tweed SA, Skowronski DM, David ST et al. Human illness from avian influenza H7N3, British Columbia. *Emerg Infect Dis.* 2004;10(12):2196-9.
- (169) Skowronski DM, Li Y, Tweed SA et al. Protective measures and human antibody response during an avian influenza H7N3 outbreak in poultry in British Columbia, Canada. *CMAJ.* 2006;176(1):47-53.

- (170) Department of Health UK. Flu vaccination for poultry workers. Department of Health UK; 2007. Available from: [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAnd-Guidance/DH\\_063041](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAnd-Guidance/DH_063041).
- (171) Gray GC, Trampel DW, Roth JA. Pandemic influenza planning: Shouldn't swine and poultry workers be included? *Vaccine*. 2007 25(22):4376–81.
- (172) Turner DA, Wailoo AJ, Cooper NJ et al. The cost-effectiveness of influenza vaccination of healthy adults 50–64 years of age. *Vaccine*. 2006;24(7):1035–43.
- (173) CATMAT. Statement on travel, influenza and prevention. *Can Commun Dis Rep*. 2005;31(ACS-2):1–8.
- (174) Beyer WEP, Nauta JJP, Palache AM, et al. Immunogenicity and safety of inactivated influenza vaccines in primed populations: A systematic literature review and meta-analysis. *Vaccine*. 2011, doi:10.1016/j.vaccine.2011.05.040.
- (175) Loeb M, Russell ML, Moss L et al. Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial. *JAMA*. 2010;303:943–50.
- (176) Monto AS, Davenport FM, Napier JA et al. Modification of an outbreak of influenza in Tecumseh Michigan, by vaccination of schoolchildren. *J Infect Dis*. 1970;122(1):16–25.
- (177) Esposito S, Marchisio P, Cavagna R et al. Effectiveness of influenza vaccination of children with recurrent respiratory tract infections in reducing respiratory-related morbidity within the households. *Vaccine*. 2003;21(23):3162–8.
- (178) Piedra PA, Gaglani MJ, Kozinetz CA et al. Herd immunity in adults against influenza-like illnesses with use of the trivalent-live attenuated influenza vaccine (CAIV-T) in children. *Vaccine*. 2005;23(13):1540–8.
- (179) Reichert TA, Sugaya N, Fedson DS et al. The Japanese experience with vaccinating school children against influenza. *N Engl J Med*. 2001;344(12):889–96.
- (180) Hurwitz ES, Haber M, Chang A et al. Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts. *JAMA*. 2000;284(13):1677–82.
- (181) Rudenko LG, Slepishkin AN, Monto AS et al. Efficacy of live attenuated and inactivated influenza vaccines in schoolchildren and their unvaccinated contacts in Novgorod, Russia. *J Infect Dis*. 1993;168(4):881–7.
- (182) King JC Jr, Stoddard JJ, Gaglani MJ et al. Effectiveness of school-based influenza vaccination. *N Engl J Med*. 2006;355(24):2523–32.
- (183) Jordan R, Connock M, Albon E et al. Universal vaccination of children against influenza : are there indirect benefits to the community? A systematic review of the evidence. *Vaccine*. 2006;24:1047–62.
- (184) Kwong JC, Stukel TA, Lim W et al. The effect of universal influenza immunization on mortality and health care use. *PLoS Med*. 2008;5(10); 1440–52.

- (185) Kwong JC, Maaten S, Upshur REG et al. The effect of universal influenza immunization on antibiotic prescriptions: an ecological study. *Clin Infect Dis*. 2009;49:750–6.
- (186) Sander B, Kwong JC, Bauch CT et al. Economic appraisal of Ontario’s universal influenza immunization program: a cost-utility analysis. *PLoS Med*. 2010;7:e10000256.
- (187) Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR*. 2010;59(No. RR-8):1-62.
- (188) Poland GA, Morse D. Improving the public health: the U.S. recommendation for universal influenza immunization. *Vaccine*. 2010;28:2799–800.
- (189) Kwong JC, Ge H, Rosella LC, Guan J, Maaten S et al. School-based influenza vaccine delivery, vaccination rates, and healthcare use in the context of a universal influenza immunization program: An ecological study. *Vaccine* 2010;28:2722-2729.
- (190) Cawley J, Hull HF, Rousculp MD. Strategies for implementing school-located influenza vaccination of children: a systematic literature review. *J Sch Health* 2010;80:167-75.
- (191) Hull HF, Ambrose CS. Current experience with school-located influenza programs in the United States. A review of the medical literature. *Human Vaccines* 2011;7:153-60.
- (192) Elder A, O'Donnell B, McCrudden E et al. Incidence and recall of influenza in a cohort of Glasgow healthcare workers during the 1993–4 epidemic: results of serum testing and questionnaire. *BMJ*. 1996;313:1241–2.
- (193) Lester RT, McGeer A, Tomlinson G et al. Use of, effectiveness of and attitudes regarding influenza vaccine among housestaff. *Infect Control Hosp Epidemiol*. 2003;24:839–44.
- (194) Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who work with the elderly. *Cochrane Database of Systematic Reviews* 2010, Issue 2. Art. No.: CD005187. DOI: 10.1002/14651858.CD005187.pub3.
- (195) Skowronski DM, De Serres G, Dickinson J, et al. Component-specific effectiveness of trivalent influenza vaccine as monitored through a sentinel surveillance network in Canada, 2006-2007. *J Infect Dis*. 2009;199:168-79.
- (196) Skowronski DM, Janjua NZ, De Serres G, et al. Effectiveness of AS03 adjuvanted pandemic H1N1 vaccine: case-control evaluation based on sentinel surveillance system in Canada, autumn 2009. *BMJ*. 2011;342:c7297. Epub 2011 Feb 3.
- (197) PCIRN/CIHR Influenza Research Network (PCIRN). Vaccine Effectiveness: SOS network. Available from: <http://www.pcirn.ca/research-themes/vaccine-effectiveness.html>

- (198) Squarcione S, Sgricia S, Biasio LR, et al. Comparison of the reactogenicity and immunogenicity of a split and subunit-adjuvanted influenza vaccine in elderly subjects. *Vaccine*. 2003;21:1268-1274.