



**Guidance Document on the
Use of Pandemic Influenza A (H1N1) 2009
Inactivated Monovalent Vaccine
October 21, 2009**

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Inactivated Monovalent Vaccine

Preamble

The Public Health Agency of Canada (PHAC) acknowledges that the advice and recommendations set out in this statement are based upon the best currently available evidence 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) or leaflet(s) of the Canadian manufacturer. The manufacturer has 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.

These recommendations are made in the context of a federal policy decision to purchase and make available adjuvanted pandemic H1N1 vaccine for most of the Canadian population. A limited amount of unadjuvanted vaccine will be available only for specific target groups.

Development of a pandemic vaccine for Canadians and the process for expedited regulatory authorization for its use have been based on the extensive groundwork accomplished through pandemic planning activities over several years by both the vaccine manufacturer and the Canadian regulatory authority. These activities were undertaken to ensure that when a pandemic occurred a safe and effective vaccine against the pandemic strain could be made available as early as possible. Because of the short time frame for the production of vaccine following the appearance of the pH1N1 virus and the expedited authorization for sale, the clinical trials that will inform these recommendations are still in progress. Thus, the recommendations made herein are based on those data available at the time of writing. As new data become available, adjustments may be made to the guidance provided. Any new recommendations will be posted on the PHAC web site as they are approved.

INTRODUCTION

This statement provides a summary of the epidemiology of pandemic H1N1 human influenza (pH1N1), as well as information on the pH1N1 vaccine and its recommended usage. Information on the use of the trivalent inactivated influenza vaccine for the 2009-2010 influenza season is published separately and readers are referred to the National Advisory Committee on Immunization (NACI) statement for more detailed information on that vaccine (<http://www.phac-aspc.gc.ca/naci-ccni/index-eng.php>).

EPIDEMIOLOGY

In April 2009 a novel influenza A virus (pH1N1) was determined to be the cause of outbreaks of respiratory illness in Mexico and influenza illness in two children in the United States.^{1,2} Within weeks, infection spread to other parts of North America and to many areas of the world. In response to the spread of the new virus, the World Health Organization (WHO) declared pandemic influenza Phase 6 on June 11, 2009. The novel virus, A/California/7/2009, has been characterized as a re-assorted H1N1 strain of multiple origins.

It contains genetic elements from North American swine influenza, North American avian influenza, human influenza, and a Eurasian swine influenza.

Canada reported its first six cases of pH1N1 on April 26, 2009. The first wave of the pandemic peaked in Canada during the first three weeks of June, but activity has occurred at a lower level over the summer and early fall. By mid-July, over 10,000 laboratory-confirmed cases had been reported.³ This figure is a significant underestimate of the actual number of cases for several reasons. First, a large proportion of those affected did not seek medical attention and remained undetected. Second, beginning in early June only hospitalized cases were tested in a number of provinces/territories. Because no seroprevalence survey results have been reported yet in Canada, an estimate of the proportion of the population affected in the first wave of the pandemic is difficult to ascertain.

One of the main characteristics of this pandemic is that it has affected a smaller proportion of the elderly compared with seasonal influenza.⁴ In the first wave, 54.4% of laboratory-confirmed pH1N1 cases in Canada occurred in persons less than 20 years old, and only a small proportion of cases (1.6%) occurred in those 65 years and older.⁵

As of September 26, 2009, 1,479 people had been hospitalized with pH1N1 influenza in Canada, including 292 cases (19.7% of those hospitalized) admitted to an intensive care unit (ICU), 153 (10.3% of those hospitalized) requiring mechanical ventilation, and 78 deaths.⁵ Most pH1N1 infections have caused mild to moderate clinical illness. However, certain populations have had more severe disease than average. In Canada, these populations include persons with chronic underlying medical conditions, pregnant women, children under 5 years of age (particularly those under 2 years of age), and persons living in remote communities with poorer access to timely medical care.⁵ Although these populations have had higher relative risk of severe disease than the general Canadian population, the absolute risk of severe disease is still small, and the overall severity of clinical illness associated with infection during this pandemic to date has not been significantly higher than has been observed with seasonal influenza. Estimates of case fatality in the U.S. have been as low as 0.05%.⁶ Nevertheless, it is recognized that the proportion of cases that are severe is difficult to estimate accurately when the true extent of cases in the population is not known.

The chronic health conditions that have been associated with increased risk of severe pH1N1 illness are similar to those associated with poor outcomes following seasonal influenza^{4,5,7} (see Recommended Recipients section below). Chronic respiratory conditions (including asthma) have been by far the most frequently reported underlying conditions associated with pH1N1 hospitalization, both for children and adults⁵. In Canada, as of September 26, 2009, rates of severe outcomes (death and/or admission to the ICU) in reported cases with underlying medical conditions have been about five times those without such conditions.⁵ In contrast to seasonal influenza, severe complications from pH1N1 infection have developed, albeit infrequently, in some young, previously healthy individuals.

It is estimated that pregnancy increases the risk of hospitalization and of severe outcomes (ICU admissions or deaths) from pH1N1 by four to five fold,^{5,8} although the absolute risk remains small. The risk appears to be related to the stage of pregnancy, in that over two-thirds of hospitalized cases occur in the third trimester.^{5,61}

Children less than 2 years of age have the highest hospitalization, ICU admission, and ventilation rates of all age groups. People living in remote areas, particularly First Nations, Inuit and Metis populations, have also experienced higher rates of hospitalization and severe outcomes (ICU admission and death).

The highest mortality rates have been observed in people over 45 years of age.

PREPARATIONS APPROVED FOR USE IN CANADA

Arepanrix™ H1N1 (AS03-adjuvanted H1N1 pandemic influenza vaccine), the pandemic vaccine currently authorized for use in Canada, is produced by GlaxoSmithKline Canada (GSK). Arepanrix™ H1N1 is a two-component vaccine consisting of an H1N1 immunizing antigen (as a suspension) and an AS03 adjuvant (as an oil-in-water emulsion). The H1N1 antigen (an inactivated, split-virion, influenza A H1N1 virus antigen) is based on the strain derived from A/California/7/2009 (H1N1)v, the strain officially recommended by the WHO for the manufacture of vaccines during the current influenza pandemic. The antigen component of the vaccine is a purified, detergent-split, inactivated, monovalent virus, propagated in eggs.

After the two components have been combined and mixed, each 0.5 mL dose of **Arepanrix™ H1N1** contains 3.75 µg haemagglutinin (HA) derived from A/California/7/2009 (H1N1) v, 5 µg thimerosal, and the three components of AS03, namely squalene, a natural, biodegradable oil (10.69 mg), DL- α -tocopherol (vitamin E oil, 11.86 mg), and polysorbate 80 (Tween 80), an emulsifier (4.86 mg). The vaccine contains trace residual amounts of egg proteins, formaldehyde, sodium deoxycholate, and sucrose.

A second vaccine, which is an unadjuvanted formulation also produced by GSK, is in production but is not yet available. This statement provides background information relevant to both vaccines. When the unadjuvanted preparation becomes available, an addendum to this statement will be issued.

Both formulations of the pH1N1 vaccine are produced in a similar manner to the production of seasonal influenza vaccine. The use of an adjuvant allows a comparable immune response but at a significantly lower antigen dose, thus allowing faster production of more doses of vaccine. Adjuvant use is also expected to broaden the immune response and provide some cross protection against virus drift.^{9,10}

While the oil-in-water adjuvant (AS03) has not previously been used in an authorized vaccine in Canada, clinical research trials using this adjuvant have been conducted in this country, the U.S., and Europe. These studies have resulted in a body of data about the safety and immunogenicity of AS03-containing vaccines.

A prototype AS03 adjuvanted vaccine (Prepandrix™) was developed in the pre-pandemic period using an H5N1 strain and has been approved for use in the European Union, Australia, and several Asian countries. During this period, Health Canada inspected the vaccine manufacturing facilities, evaluated data on the vaccine production process, and reviewed results from both animal and human studies conducted with the prototype vaccine. In

addition, the safety and effectiveness of the AS03 adjuvant to be used with the vaccine was assessed by Health Canada. Once the pH1N1 virus emerged as the pandemic virus, the manufacturer initiated vaccine production using the strain recommended by the WHO.

Health Canada has provided detailed information on the process used to approve pH1N1 vaccine, which is available at http://www.phac-aspc.gc.ca/alert-alerte/h1n1/vacc/faq_rg_h1n1-reg-eng.php.

GSK's pH1N1 vaccine Pandemrix™, which is produced using a similar but not identical process to that for Arepanrix™ H1N1, was approved for use in 27 European countries on September 30, 2009, by the European Medicines Agency.

IMMUNOGENICITY AND EFFICACY

To date (October 21, 2009) there are limited immunogenicity data available for either of the GSK pH1N1 vaccine formulations, although data on them and on vaccines produced by other manufacturers are beginning to be released as clinical trials and pandemic immunization programs in other countries are implemented. Further data will be added to this statement as they become available, during the latter part of 2009 and the first part of 2010.

a. Adults: At the time of writing, available clinical trial data on the GSK pH1N1 vaccine are post-first-dose results from two studies involving adults aged 18-60. In the first study 62 persons received adjuvanted vaccine containing 5.25 µg HA per dose, and 66 received the unadjuvanted vaccine containing 21 µg per dose.¹¹ These antigen contents are slightly higher than in the final formulations that will be available in Canada. Blood drawn 21 days after the first dose of vaccine showed seroconversion rates of 98.4% and 95.5% for the adjuvanted and unadjuvanted vaccines respectively. Seroprotection rates were 98.4% for the adjuvanted vaccine and 97.0% for the unadjuvanted vaccine*. This response is similar to or better than responses to the first dose of adjuvanted and unadjuvanted vaccines produced by other manufacturers.¹²⁻¹⁶ There were no appreciable differences in immunogenicity between the younger (18-40) and older (41-60) age groups and no impact of prior immunization with seasonal influenza vaccine.

In the second study,⁴³ 61 participants received adjuvanted vaccine containing 3.75 µg HA per dose, and 66 received the unadjuvanted vaccine containing 15 µg HA per dose, which are the antigen contents of the final Canadian vaccines. Twenty-one days after the first dose of vaccine, seroconversion rates were 96.7% for the adjuvanted vaccine and 84.8% for the unadjuvanted vaccine. Seroprotection rates were 100% for the adjuvanted vaccine and 93.9% for the unadjuvanted vaccine.

*Seroprotection rate: proportion of subjects with HI titre $\geq 1:40$; seroconversion rate: proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of $\geq 1:40$, or who were seropositive at pre-vaccination and have a four-fold increase in titre.

The seroconversion rate following a single dose of the GSK pH1N1 vaccines has been higher than that seen in clinical trials of the manufacturer's pre-pandemic H5N1 vaccine, which required two doses to achieve adequate protection.⁹⁻¹¹ The high seroconversion rate after the first dose of GSK pH1N1 vaccines suggests that a single dose of either the adjuvanted or unadjuvanted formulation will likely be sufficient for healthy adults. The duration of protection has not been determined.

b. Children: There are no immunogenicity data currently available in children for either Canadian pH1N1 vaccine formulation. Immunogenicity following a single dose of pH1N1 vaccine in adults cannot be extrapolated to young children. Additional data are needed from ongoing studies to establish whether a single dose could be sufficient in children and adolescents.

A clinical trial involving 388 children aged 3-9 years conducted on prototype H5N1 adjuvanted vaccines showed seroconversion rates of 96% to 100% 21 days after the second dose of vaccine, which contained either 3.75 µg or 1.8 µg HA.^{11,17} Although data regarding this vaccine cannot be extrapolated directly to the pH1N1 vaccine, it is useful to know that the AS03 adjuvant induced good antibody response in these young children, even when a reduced dose of antigen was used.

There are no immunogenicity data currently available for AS03 adjuvanted vaccines in children under age 3. However, adjuvanted vaccines may be a more effective formulation in this age group. Meta-analyses suggest that unadjuvanted seasonal influenza vaccines are of low efficacy in young children.¹⁸ Initial results in a clinical trial of an unadjuvanted pH1N1 vaccine (Sanofi Pasteur) showed only 25% seroprotection in children 6-35 months after the first dose.¹⁹ The results of a clinical trial with a different oil-in-water (MF59) adjuvanted seasonal influenza vaccine demonstrated that the adjuvanted vaccine led to greater immunogenicity than the unadjuvanted vaccine in unprimed children 6-35 months of age.²⁰ However, some caution is required in extrapolation from MF59 to AS03 formulations; these adjuvants have some similarities but also differences in composition and potential mechanisms.

c. Older adults: There are currently no immunogenicity data for GSK pH1N1 vaccines in people over age 60. Clinical trials of the GSK adjuvanted H5N1 vaccine have suggested that responses to adjuvanted vaccine in people over 60 would be higher than those achieved with unadjuvanted seasonal influenza vaccines.^{11,17} However, results from clinical trials of pH1N1 vaccines in the elderly will be required before determining whether a single dose will be sufficient.

Effectiveness data on pH1N1 vaccine will not be available until this vaccine is used in larger populations.

RECOMMENDATIONS FOR USE OF INFLUENZA A (H1N1) 2009 VACCINE

General considerations

To reduce the morbidity and mortality associated with pandemic influenza, the highest priority for pH1N1 influenza immunization programs should be those people at higher risk of influenza-related complications and those who care for them. Pandemic H1N1 vaccine is STRONGLY RECOMMENDED FOR THESE POPULATIONS. Significant illness and associated societal costs also occur as a result of pandemic influenza in people who may not be considered at high risk of complications (i.e. healthy people 5 years of age and older). Therefore, pandemic influenza vaccine is ALSO RECOMMENDED for all Canadians over 6 months of age who have no contraindication. In Canada, pH1N1 vaccine will be available for any person who needs and wants it.

It is recognized that certain populations, such as First Nations, Inuit, and Metis populations, may be more socioeconomically disadvantaged, have higher proportions of people in the higher risk groups, and have difficulties accessing medical care. Health providers are encouraged to ensure that such populations are offered pH1N1 vaccine as soon as possible.

RECOMMENDED RECIPIENTS

A. People at higher risk of complications from pH1N1 and those who care for them

Persons under the age of 65 with chronic conditions

This group is at higher risk of pH1N1 complications that require hospitalization and admission to ICU and may result in death.^{4,5}

A number of chronic health conditions are associated with increased risk of influenza-related complications, and influenza infection may 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; immunodeficiency and immunosuppression (due to underlying disease or therapy); renal disease; anemia or hemoglobinopathy; and conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration. This category also includes children and adolescents (aged 6 months to 18 years) with conditions treated for long periods with acetylsalicylic acid because of the potential increased risk of Reye syndrome associated with seasonal influenza.

In some case series in the U.S., obesity (defined as body-mass index [BMI] of ≥ 30) or morbid obesity (BMI of ≥ 40) has been noted among hospitalized patients with pH1N1 infection.^{21,22} However, the majority of these patients had other underlying medical risk factors. Studies examining whether obesity is an independent risk factor for severe infection are in progress.

Pregnant women

Pregnant women *with the chronic health conditions noted above* have a high risk of complications associated with influenza and constitute a high-priority group for immunization at any stage of pregnancy for both seasonal and pandemic influenza.²³

The influenza-related risk in *healthy* pregnant women has been described in several studies, and summary reviews are available.²⁴⁻³⁰ The epidemiological observations to date on the impact of pH1N1 on pregnant women indicate that while there is a four- to five-fold greater risk of complications compared with the general population, the absolute risk remains small.^{5,8}

Studies on seasonal influenza that have stratified analysis according to gestational age show that influenza-related risk is not evenly distributed across all trimesters of pregnancy.³¹⁻³³ In these studies, the rate of influenza-related hospitalization is not significantly greater during the first trimester of healthy pregnancy but, rather, increases later in pregnancy and is highest in the third trimester.³¹⁻³³ A similar pattern has been seen with the pandemic strain.^{5,61}

The antibody response to pH1N1 vaccine in pregnant women is not expected to differ from that of non-pregnant individuals. Transplacental passage of maternal antibody is hypothesized to protect the newborn. A randomized controlled trial (RCT) in Bangladesh provided the first RCT evidence for mother and infant protection from seasonal influenza vaccine administered in pregnancy.³⁴ It demonstrated a vaccine efficacy of 63% (95% confidence interval [CI] 5%-85%) against laboratory-confirmed influenza in the infants for six months after birth. Further evaluation is needed to determine whether these results can be extrapolated to other settings. However, the findings suggest that immunizing pregnant women with pH1N1 vaccine also may reduce the risk of infection in their young infants.

Healthy children 6 months to 59 months of age

Children aged 6-59 months, particularly those less than 24 months, are at increased risk of pH1N1 influenza-associated hospitalization compared with healthy older children and young adults.⁵ While most young children have a relatively short hospital stay, in Canada they have the highest rates of ICU admission and mechanical ventilation. Seasonal influenza immunization of older children is efficacious,^{18,35,36} but few trials have specifically included children 6 to 23 months of age.

Persons living in remote and isolated communities

Persons living in remote and isolated communities have limited access to medical care and thus may be at greater risk of complications from delayed treatment or access to intensive care. In some remote First Nations, Inuit, and Metis communities there is a higher proportion of younger people and a high concentration of persons with chronic medical conditions, with attendant increased risk of severe outcomes. The use of vaccine in isolated communities also has the potential for development of herd immunity if there is sufficient vaccine uptake, with subsequent prevention of the spread of infection in the community. It is also logistically easier to target a whole community that is small and far from others.

People who care for those at high risk of influenza-related complications or hospitalization

People who are potentially capable of transmitting influenza to those at high risk should be immunized, regardless of whether the high-risk person has been immunized. Immunization of care providers with seasonal influenza vaccine has been shown to decrease their own risk of illness, as well as death and other serious outcomes in the patients for whom they care.³⁷⁻⁴² Individuals who are more likely to transmit influenza to those at risk of medical complications or hospitalization due to influenza include the following:

i. **Health care workers**

Immunization of health care workers protects them from infection and also decreases spread of infection to vulnerable patients, thereby also preventing outbreaks in health care facilities. In addition, immunization of health care workers assists in maintaining the essential health services infrastructure required to respond to the pandemic.

This recommendation includes all health care workers involved with the pandemic response or with the delivery of essential health services, including the following:

- Those who provide direct patient care as well as those who support the provision of health care services. This includes full-time staff, part-time staff, students, regular visitors, and volunteers, i.e. all persons carrying out the health care function.

Settings include acute care, chronic care, ambulatory and community care, emergency medical services, laboratory, public health agencies, pharmacies, etc.

ii. **Household contacts and care providers**

- Of infants <6 months of age
- Of persons who are immunocompromised

This recommendation is intended to provide indirect protection for high-risk persons who cannot be immunized or may not respond to vaccine. Their household contacts (adults and children) are strongly recommended to be immunized, whether or not the high-risk individual him/herself has been immunized. This recommendation applies to household contacts of infants <6 months of age (who are at high risk of complications from influenza but for whom influenza vaccine is not approved), members of a household expecting a newborn during the influenza season, and household contacts of people who are immune-compromised (who are expected to have a reduced immune response to pH1N1 vaccine).

B. Other groups that can benefit from pandemic influenza vaccine

As noted previously, in addition to the people at higher risk outlined above, pH1N1 vaccine is also recommended for all other Canadians who have no contraindication. An effective immunization program that targets all Canadians is the cornerstone of Canada's pandemic planning and response strategy. This strategy aims at reducing morbidity and mortality, and minimizing societal disruption. By immunizing a large proportion of the population, it is anticipated that there will be less stress on the health care system and on societal infrastructure. The subcategories listed below were identified during the prior pandemic

planning process for the sequencing of vaccine administration in Canadian jurisdictions (<http://www.atlantique.phac.gc.ca/alert-alerte/h1n1/vacc/vacc-eng.php>). A rationale for the use of vaccine in each group is also provided.

Healthy children 5-18 years of age

This group has high illness rates. A proportion of all those who become ill, even those without underlying conditions, will suffer some severe complications. Vaccination of this group may reduce transmission to the broader population if high enough coverage rates are achieved.

Healthy adults 19-64 years of age

Individuals in this age group are encouraged to receive the vaccine, even if they are not in one of the aforementioned higher risk groups. Immunization provides personal protection, and by reducing infection and illness the immunization of healthy adults will allow them to continue their employment and care for their families.

First responders (e.g. police, firefighters)

First responders frequently attend emergency health situations and may be more likely to be exposed to pH1N1. They are an essential component of the health system that needs to be protected.

Poultry and swine workers

Given that pH1N1 has the ability to infect swine, poultry and humans, human contact with swine and poultry may increase the chances of transfer of pH1N1 infection to these animals. This recommendation is made according to the theoretical rationale that it may reduce the potential for reassortment among influenza viruses in swine, poultry or humans.

Adults aged 65 years and older

There is a lower attack rate of pH1N1 in this population, likely because of immunity from past exposure, and thus fewer cases of influenza are expected. However, if infected, older people have a higher risk of complications and death from influenza. The vaccine will assist in reducing the likelihood that this population will become infected and develop complications.

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

Outbreaks of pH1N1 in long-term care homes are anticipated to be uncommon owing to pre-existing immunity among elderly people. In residential care institutions for younger adults, however, pH1N1 outbreaks may be more frequent. If they occur, outbreaks in these institutions may lead to significant morbidity and mortality, since residents may have one or more chronic medical conditions and live in institutional environments that may facilitate spread of the disease.

SCHEDULE AND DOSAGE

The recommended dosage schedule for both types of influenza vaccine is presented in Table 1. Many of the recommendations there are largely based on level III evidence (opinion of scientific and medical experts), since data from most of the clinical trials of this vaccine are not yet available. If data are available, there will be a higher level of evidence noted. The recommendations are consistent with the Product Information Leaflet.⁴³

The majority of vaccine available for use in Canada in the 2009-10 season will be the adjuvanted formulation (Arepanrix™). A limited quantity of unadjuvanted vaccine will be made available only for particular risk groups.

There are limited data on and minimal prior experience with immunization of infants <6 months of age with seasonal influenza vaccines. Marked increased reactogenicity has occurred in the past with whole-virus seasonal influenza vaccine and has made that vaccine unsuitable for use in this age group. It is possible that similar side effects will be seen with a pH1N1 vaccine; consequently, pH1N1 influenza immunization is not currently recommended for children less than 6 months of age. To protect this age group, it is strongly recommended that their household contacts be immunized as noted above.

Table 1. Recommended pH1N1 Influenza Vaccine Dosage By Age for Fall 2009/Winter 2010 Season

(NOTE: the recommended number of doses for each age group may be revised if indicated by new data)

Age	Dose (mL)	Number of doses required	Level of evidence (see Appendix 1)
6 months to 9 years*	0.25	2	III
10 years and above**	0.5	1	I (age 18-60) III (other ages)
Pregnant women***	0.5	1	III

*The adjuvanted pH1N1 vaccine (Arepanrix™ H1N1) is recommended for this age group because of the potential for enhanced immunogenicity (see IMMUNOGENICITY AND EFFICACY section). Unadjuvanted vaccine may be used in children under age 3, but it may result in a poorer immune response. For either formulation, the interval between doses should be a minimum of 21 days.

**The adjuvanted pH1N1 vaccine (Arepanrix™ H1N1) is recommended for this age group. On the basis of the results of clinical trials to date, a single dose of vaccine may be sufficient. Clinical trials are ongoing, and this recommendation will be reviewed as additional data become available.

***Unadjuvanted pH1N1 vaccine is considered the preferred option for pregnant women, given that there are more safety data on the use of unadjuvanted seasonal influenza vaccines in pregnant women and there are currently no data on the safety of the adjuvanted vaccine in this group. This recommendation is made as a precaution for this population, given the potential concern of pregnant women about receiving a newly developed vaccine during their pregnancy. Unadjuvanted vaccine may be administered at any stage of pregnancy. The WHO's Strategic Advisory Committee of Experts (SAGE) has recommended that, if unadjuvanted product is not available, pregnant women should be vaccinated with another pandemic vaccine, such as an adjuvanted formulation.⁴⁴ Therefore, if unadjuvanted vaccine is not available and if pH1N1 activity is increasing or high in a particular region of Canada, pregnant women who are in the second half of pregnancy (i.e. above 20 weeks' gestation) should be offered adjuvanted vaccine.

Persons who have had pH1N1 infection or influenza-like illness

Persons who have been infected with pH1N1 will have developed a protective immune response to this virus and consequently will not receive additional benefit from pH1N1 vaccine. Therefore, vaccine is not required for persons who have had laboratory-confirmed pH1N1 infection. However, pH1N1 vaccine is recommended for persons who have experienced an influenza-like illness since March 2009 that was not a laboratory-confirmed case of pH1N1, since such an infection may have been due to other respiratory viruses. There are no expected adverse effects if pH1N1 vaccine is given to people with prior pH1N1 infection.

ROUTE OF ADMINISTRATION

Influenza vaccine should be administered intramuscularly. The deltoid muscle is the recommended site in adults and children ≥ 12 months of age. The anterolateral thigh is the recommended site in infants between 6 and 12 months of age.

ADVERSE REACTIONS

Information on adverse events following receipt of the pH1N1 vaccine is limited to preliminary data from two small clinical trials in adults. However, there are extensive data on adverse events following immunization with seasonal influenza vaccines. In addition, data are available from clinical trials of other influenza vaccines that contain the AS03 adjuvant (GSK H5N1 vaccine – Prepandrix™) or MF59, another oil-in-water adjuvant used in a seasonal influenza vaccine licensed in many countries (Flud™, Novartis).

Vaccines containing the AS03 adjuvant

Clinical trials with more than 41,000 recipients of AS03-containing vaccines (H5N1, seasonal influenza, malaria, and pH1N1 vaccines) are either under way or have been completed, but all related data have not yet been published. An integrated summary of safety from 15,400 subjects with a six-month follow-up suggests an increase in local reactogenicity in the first week following receipt of AS03-containing vaccines.⁴⁵ Published data include results from over 6,000 healthy recipients of a GSK AS03-containing prototype H5N1 influenza vaccine,^{9-11,46,47} as well as

preliminary results from two clinical trials of GSK pH1N1 vaccine.^{11,43,48}

i. GSK H5N1 adjuvanted vaccines

a) Adults: GSK AS03-adjuvanted H5N1 vaccines were generally well tolerated. Pain at the injection site was significantly more frequent in recipients of AS03 H5N1 vaccines (50%-96%) than either unadjuvanted H5N1 vaccine (38%-68%)¹⁰ or seasonal influenza vaccine (27%-65%).⁴⁶ This reaction is expected, as the adjuvant improves immunogenicity by causing an increased inflammatory reaction. Pain was more frequent in the 18-60 age group than in recipients over 60. Frequency was lower after a second dose in both age groups.⁴⁶ Other local reactions such as redness, induration, swelling, and ecchymosis occurred more frequently in AS03 H5N1 recipients than in those who received unadjuvanted H5N1 vaccine, seasonal vaccine, or placebo, but these differences were not all statistically significant.⁴⁷ Most local symptoms were of mild to moderate severity and had resolved or decreased in intensity within 48 hours of vaccine administration.

The most commonly reported systemic symptoms following receipt of AS03 H5N1 vaccine were fatigue (in 20%-41% of recipients), myalgia (23%-40%), headache (20%-35%), and arthralgia (12%-19%). All of these symptoms were more frequent than in recipients of the seasonal influenza vaccine and were less frequent in recipients over 60. Fever occurred in 2%-9%, and swelling and/or pain of the local lymph nodes occurred in about 1% of AS03 H5N1 vaccine recipients.⁴⁶ Uncommon adverse events, occurring in less than 1% of recipients, included insomnia, paresthesia, somnolence, dizziness, gastrointestinal symptoms, pruritus, and rash.¹⁷

b) Children: Data are available from a study of 388 children 3 to 9 years of age who received the GSK H5N1 vaccine.^{11,17,43} Local and systemic symptoms were generally higher in the children who received adjuvanted vaccine than in controls who received an unadjuvanted seasonal influenza vaccine. Rates were higher for most symptoms following a full dose of vaccine. After a half dose of vaccine, the most common reactions were pain (49%-68% for adjuvanted vs. 29%-58% for unadjuvanted), swelling (12%-14% for adjuvanted vs. 3%-19% for unadjuvanted), induration (10%-12% for adjuvanted vs. 3%-22% for unadjuvanted), and redness (11%-13% for adjuvanted vs. 6%-17% for unadjuvanted).⁴³ Fever of >39° Celsius occurred in 4% of children aged 3-5 years receiving the adjuvanted vaccine (0% in the unadjuvanted group) and no children aged 6-9 years (6% in unadjuvanted group). Other systemic reactions in children 3-5 years included drowsiness (8% vs. 3%), irritability (8% vs. 3%), and loss of appetite (7% vs. 3%) for the adjuvanted and unadjuvanted vaccines respectively. Other systemic reactions in children aged 6-9 were headache, myalgia, and arthralgia, but the rates were not markedly different from those in children receiving the unadjuvanted control vaccine.¹¹ There are no reactogenicity data for children under 3 years of age.

ii. GSK pH1N1 vaccines

a) Adults: Adverse event data are available for two small clinical trials in adults aged 18-60^{11,43}. The first, involving 63 people who received a 5.25 µg HA adjuvanted pH1N1 vaccine and 66 who received a 21 µg HA unadjuvanted pH1N1 vaccine, found that the incidence of local and systemic reactions after one dose was very similar to that reported for GSK H5N1 vaccines. The second trial involved 124 adults who received either adjuvanted or unadjuvanted pH1N1 vaccine with the antigen content present in the commercial Canadian vaccines (3.75 µg and 15 µg respectively).⁴⁸

Table 2 shows the preliminary reactogenicity results from that study. In both studies, local and systemic symptoms were reported more frequently in the recipients of the adjuvanted vaccine than the unadjuvanted vaccine. Almost all symptoms were mild to moderate in severity.⁴³

Table 2. Frequency of Symptoms Following a Single Dose of 3.75 µg HA + AS03 Vaccine vs. a Single Dose of 15 µg Unadjuvanted pH1N1 Vaccine⁴³

Symptom	Adjuvanted vaccine (n=62) (%)	Unadjuvanted vaccine (n=62) (%)
Pain	90.3	37.1
Redness	1.6	0.0
Swelling	6.5	0.0
Fatigue	32.3	25.8
Headache	14.3	7.6
Arthralgia (joint pain)	11.3	4.8
Myalgia (muscle ache)	33.9	8.1
Shivering	8.1	3.2
Sweating	9.7	8.1
Fever	0.0	0.0

b) Children: Data are not yet available in children; however, results of GSK clinical trials in children are expected in November 2009, and this guidance document will be updated if indicated.

MF59-adjuvanted influenza vaccines

Another oil-in-water adjuvant called MF59 is used in Fludax®, a Novartis-produced seasonal influenza vaccine approved for use in persons 65 years of age and older in the European Union since 1997. Although not directly comparable in formulation to AS03 vaccines, Fludax® has been studied in over 26,000 individuals and used in over 40 million individuals. Other than some increased local reactogenicity, it has not been associated with any safety concerns.⁴⁹ In addition, a recent randomized trial of MF59-adjuvanted versus unadjuvanted influenza vaccines in 269 children 6-35 months²⁰ found that the adjuvanted vaccine was well tolerated; it had a slightly higher local reactogenicity but similar systemic reactogenicity to the unadjuvanted vaccine.

Other considerations

Influenza vaccination cannot cause influenza because the vaccine does not contain live virus.

Allergic responses to influenza vaccine are a rare consequence of hypersensitivity to some vaccine components, such as residual egg protein, which is present in minute quantities.

Guillain-Barré syndrome (GBS) occurred in adults in association with the 1976 US swine influenza vaccine, and evidence is consistent with a causal relation between the vaccine and GBS during that season.⁵⁰ In a review of studies since 1976, the US 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 1976.⁵¹

In Canada, the background incidence of GBS due to any cause has been estimated at 2.02 per 100,000 person-years in Ontario and 2.30 per 100,000 person-years in Quebec.⁵² A variety of infectious agents, including influenza, have been associated with GBS.^{53,54} A Canadian study involving a self-matched case series from Ontario for the years 1992 to 2004 estimated a relative risk of hospitalization for GBS in the period 2 to 7 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, $p = 0.02$),⁵⁵ suggesting that the absolute risk of GBS in the period after vaccination is about one excess case per 1 million vaccinations above the background GBS rate. However, two recent self-controlled case series analyses of the UK General Practice Research Database found no evidence of an increased risk of GBS after influenza vaccination.^{56,57}

It is important to note that the above GBS studies relate to unadjuvanted seasonal influenza vaccines. The extent to which the results may apply to adjuvanted pH1N1 vaccine is uncertain.

Both the adjuvanted and unadjuvanted preparations of pH1N1 vaccine contain minute quantities of thimerosal, which is used as a preservative.^{58,59} 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.⁶⁰ Similar large-scale studies have not specifically addressed prenatal exposure to thimerosal-containing vaccines in pregnancy; however, thimerosal-containing influenza vaccines have been used for years in pregnant women, and no adverse effects have been noted.

The use of adjuvant in a vaccine formulation results in a greater immune response to the vaccine and/or allows smaller doses of vaccine antigen to be used to achieve a similar response. There is a theoretical possibility that the altered inflammatory response associated with the use of adjuvants such as AS03 could result in a small number of immunologically mediated adverse events. Such events could also be induced by natural infection or by the vaccine antigen itself without adjuvant. Regardless of the theoretical trigger, if such events occur they are expected to be rare and may only occur in individuals with a genetic predisposition or a particular underlying or comorbid condition. Events such as these would only become apparent through careful post-marketing surveillance.

CONTRAINDICATIONS

Influenza vaccine should not be given to any person who has had an anaphylactic reaction to any component of the vaccine. In addition, 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 be routinely vaccinated with influenza vaccine. Egg-allergic individuals who are at risk of the complications of influenza should be evaluated by an allergy specialist, as vaccination might be possible after careful evaluation, skin testing, and graded challenge or desensitization. If such an evaluation is not possible, the risk of an allergic reaction to the vaccine must be weighed against the risk of influenza disease. The *Canadian Immunization Guide*'s recommendations for those with a known hypersensitivity to eggs can be found at <http://www.phac-aspc.gc.ca/publicat/cig-gci/p02-04-eng.php>. Modification of protocols for immunizing egg-allergic people is being considered in light of the benefits and risks of immunization with pH1N1 vaccine, and guidance will be updated as new recommendations are made by other expert groups (see http://www.csaci.ca/include/files/CSACI_H1N1_Statement.pdf).

Since the rubber stoppers used for the GSK pH1N1 vaccines do not contain latex, latex allergy is not a contraindication to receipt of these vaccines.

PRECAUTIONS

Persons with serious acute febrile illness usually should 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.

Avoiding subsequent influenza vaccination of persons known to have had GBS within 8 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.

There is no evidence to suggest that oculorespiratory syndrome (ORS) will be a concern following immunization with pH1N1 vaccine. Therefore, people who have experienced ORS following receipt of seasonal influenza vaccine may be immunized with pH1N1 vaccine, unless the ORS was severe enough to result in hospitalization.

SIMULTANEOUS ADMINISTRATION OF OTHER VACCINES

Preliminary data on a small number of people who received an unadjuvanted pH1N1 vaccine at the same time as seasonal influenza vaccine suggest that simultaneous administration results in an acceptable immune response to the pH1N1 vaccine.¹⁶ While there are currently no data on the simultaneous administration of adjuvanted pH1N1 vaccine with other vaccines, acceptable immune responses are similarly anticipated.

Pandemic influenza vaccine may be administered concurrently (but in the opposite arm) with seasonal influenza vaccine and/or other vaccines. If not given concurrently, there is no minimum interval required between the two influenza vaccines. If pH1N1 vaccine is administered at the same time as other vaccines, the latter should be given in a different limb than that used for the pH1N1 vaccine because of the higher frequency of local reactions to the adjuvanted pH1N1 vaccine. Simultaneous administration may present logistical advantages in some situations but makes it more difficult to attribute adverse reactions to one or the other vaccine.

STORAGE AND RECONSTITUTION

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

Arepanrix™ H1N1 consists of two containers: one multidose vial containing the antigen (suspension) and a second multidose vial containing the adjuvant (emulsion). The antigen suspension is a translucent to whitish opalescent suspension that may sediment slightly. The emulsion is a whitish homogeneous liquid.

Prior to administration, the two components should be mixed. The entire contents of the adjuvant emulsion must be withdrawn and added to the antigen suspension and mixed.

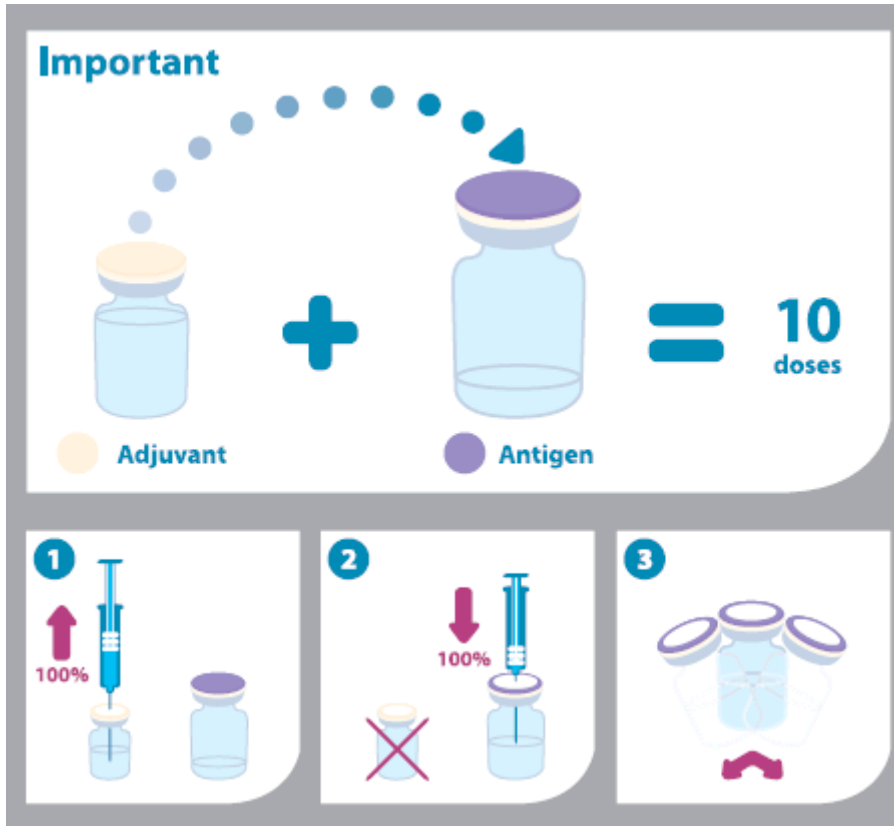
Instructions for mixing and administration of the vaccine (as depicted in the pictogram below):

1. Before mixing the two components the vials should be brought to room temperature, and the emulsion and suspension should be shaken and inspected visually for any abnormal physical appearance.
2. The vaccine is mixed by withdrawing the entire contents of the vial containing the emulsion by means of a syringe and by adding it to the vial containing the antigen suspension.
3. After the addition of the emulsion to the suspension, the mixture should be well shaken. The mixed vaccine is a whitish emulsion. In the event of other variation being observed, discard the vaccine.
4. The volume of Arepanrix™ H1N1 (5 mL) after mixing corresponds to 10 doses of vaccine.
5. The vial should be shaken prior to each administration.
6. Each vaccine dose of 0.5 mL is withdrawn into a syringe for injection. The vaccine should be allowed to reach room temperature before use.
7. The needle used for withdrawal must be replaced by a needle suitable for intramuscular injection.

After mixing, the vaccine should be used within 24 hours. Although it is recommended to maintain the mixed product between 2°C and 8°C, it may be kept at room temperature during this period if required. However, if the product is refrigerated, it must be brought to room temperature

before withdrawal. The chemical and physical in-use stability has been demonstrated for 24 hours at 30°C.

Any unused product or waste material should be disposed of in accordance with local requirements.



RESEARCH AND EVALUATION PRIORITIES

Because of the need for a pandemic vaccine as soon as possible, data are not yet available from all the clinical trials under way. In addition, there is a need for additional research to answer questions not addressed in the basic immunogenicity and safety studies conducted by the manufacturer. Extensive monitoring of vaccine safety and effectiveness is also required, given the scope of the pandemic vaccination program.

Additional research questions to be addressed include the following:

- a more complete determination of the relative advantages and disadvantages of the adjuvanted and unadjuvanted formulations across the age spectrum;
- studies of both formulations in special populations, such as Aboriginal people, persons with chronic health conditions, and pregnant women;
- the relative protection against drifted pH1N1 afforded by adjuvanted versus unadjuvanted

- preparations;
- duration of immunity following immunization, for both one- and two-dose recipients, and in all age groups;
 - effectiveness of immunization in pregnancy for the protection of young infants;
 - safety and immunogenicity of adjuvanted vaccine in infants less than 6 months of age;
 - immunogenicity following co-administration of pH1N1 and seasonal influenza vaccines.

Detailed pharmacovigilance plans to address vaccine safety have been developed by the Public Health Agency of Canada, in collaboration with the provinces and territories. In addition, a recently funded PHAC/Canadian Institutes of Health Research Influenza Research Network (PCIRN) with over 200 Canadian collaborators is supporting key areas of pandemic vaccine research and evaluation. The five PCIRN themes are rapid trials, extended safety evaluation, vaccine effectiveness, measurement of vaccine uptake, and enhancement of program implementation.

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Appendix I: Schema for ranking individual study design – National Advisory Committee on Immunization

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.