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**Guidance Document on the
Use of Pandemic Influenza A (H1N1) 2009
Inactivated Monovalent Vaccine
Revised November 13, 2009**

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1.0 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).

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 has been purchased for pregnant women.

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.

Changes in this revised guidance statement include the following:

- *Inclusion of guidance for use of Influenza A (H1N1) 2009 Pandemic Monovalent Vaccine (Without Adjuvant) prepared by GlaxoSmithKline (GSK). A separate guidance document is available for use of Panvax[®], unadjuvanted vaccine from CSL Biotherapies Inc.;*
- *Updated information on clinical trial results for Arepanrix[™] H1N1 in children and adults, including seniors, and co-administration with seasonal vaccine;*
- *Updated information on the number of doses needed;*
- *Additional detail on recommendations for pH1N1 vaccine use in pregnancy;*
- *Updates to the Epidemiology section.*

2.0 INTRODUCTION

This statement provides a summary of the epidemiology of pandemic H1N1 human influenza (pH1N1), as well as information on the pH1N1 vaccines approved for use in Canada and their 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/publicat/ccdr-rmtc/09vol35/acs-dcc-6/index-eng.php>).

3.0 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. 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.

In early September 2009 pH1N1 activity started to increase again, with the timing of the onset of the second pandemic wave varying across Canada. As of October 31, 2009, national surveillance indicators (number of regions reporting widespread or localized influenza activity, number of reported outbreaks and influenza-like illness consultation rates) were still increasing.⁴ A similar trend was seen in hospitalizations, with over two-thirds (661/948) of Canadian hospitalizations in September and October occurring in the last week of October.

One of the main characteristics of this pandemic is that it has affected a smaller proportion of the elderly compared with seasonal influenza.⁵ 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.⁶

As of October 31, 2009, 2,440 people had been hospitalized with pH1N1 influenza in Canada, including 443 cases (18.2% of those hospitalized) admitted to an intensive care unit (ICU), 230 (9.4% of those hospitalized) requiring mechanical ventilation, and 100 deaths.⁶ 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 1 year of age), and persons living in remote communities with poorer access to timely medical care.⁶ 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%.⁷ 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^{5,6,8} (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 adults.⁶ In Canada, as of October 31, 2009, rates of severe outcomes (death and/or admission to the ICU) in reported cases with underlying medical conditions have been about four times those without such conditions.⁶ 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,^{6,9} although the absolute risk remains small. The risk appears to be related to the stage of pregnancy, in that three-quarters of hospitalized cases occur in the third trimester.⁶

Children less than 5 years of age (particularly those under age 1) 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.

4.0 PREPARATIONS APPROVED FOR USE IN CANADA

Arepanrix™ H1N1 (AS03-adjuvanted H1N1 pandemic influenza vaccine) is produced by GlaxoSmithKline Canada (GSK). It 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.

Influenza A (H1N1) 2009 Pandemic Monovalent Vaccine (Without Adjuvant) is an unadjuvanted pH1N1 vaccine also produced by GSK. It is an inactivated, split-virion influenza vaccine prepared from virus propagated in eggs. The H1N1 immunizing antigen is based on the strain derived from A/California/7/2009 (H1N1)v. The vaccine contains 50 µg thimerosal per 0.5 mL and also contains trace residual amounts of egg proteins, formaldehyde, sodium deoxycholate, and sucrose. Antibiotics are not used in the manufacture of this vaccine.

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.^{10,11}

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.hc-sc.gc.ca/dhp-mps/prodpharma/legislation/interimorders-arretesurgence/index-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.

5.0 IMMUNOGENICITY AND EFFICACY

To date (November 6, 2009) there are limited immunogenicity data available for the GSK pH1N1 vaccine formulations, although data on them and on vaccines produced by other manufacturers are being 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. Effectiveness data for pH1N1 vaccine will not be available until this vaccine is used in larger populations.

5.1 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 and a third study that involved adults aged 18-85 years.

In the first study,¹² 62 persons received adjuvanted vaccine containing 5.25 µg HA per dose, and 66 received the unadjuvanted vaccine containing 21 µg per dose. These antigen contents are slightly higher than in the final formulations 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.¹³⁻¹⁷ 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,¹⁸ 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 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.

The third study¹⁹ involved 120 adults aged 18-60 and 120 adults over age 60 given adjuvanted vaccine containing 3.75 µg HA per dose. Results in the 18-60 year age group were similar to the

*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.

previously reported studies, with a seroprotection rate of 97.5% measured 21 days after the first dose. The results for subjects over age 60 are described in the Older Adults section that follows.

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.¹⁰⁻¹² 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.

5.2 Children

Preliminary results are available from the first paediatric trial assessing use of GSK adjuvanted pH1N1 vaccine.²⁰ The ongoing trial involves 200 children 6 to 35 months of age given half doses of vaccine (1.9 µg antigen and a half dose of AS03 adjuvant). Analysis of the first 51 children showed that a high immune response was elicited by 21 days after a single dose. In all children the response was above the regulatory seroprotective threshold of 1:40. Additional data are needed from ongoing studies to establish whether a single dose of adjuvanted vaccine will be sufficient in this age group and in older children.

Adjuvanted vaccines are expected to be a more effective formulation in the 6-35 month age group than unadjuvanted vaccine. A recent meta-analysis suggests that unadjuvanted seasonal influenza vaccines are of low efficacy in young children.²¹ 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.²² 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.

There is no clinical experience yet with the use of GSK unadjuvanted pH1N1 vaccine in children or adolescents. The National Institute of Allergy and Infectious Diseases (NIAID) has announced interim results from a trial in children aged 6 months to 17 years who were given two doses of unadjuvanted pH1N1 vaccine containing either 15 or 30 µg HA.²³ At 21 days after the first dose, in the majority of children 10 years and older, a single 15 µg dose of vaccine elicited a strong immune response. In contrast, a strong immune response was seen in only 25% of children aged 6-35 months and 55% of children aged 3-9 years after the first 15 µg dose. However, 21 days after the second 15 µg dose, 100% of children age 6-35 months and 94% of children age 3-9 years had a robust immune response.

5.3 Older adults

Clinical trials of the GSK adjuvanted H5N1 vaccine suggested that responses to adjuvanted vaccine in people over 60 would be higher than those achieved with unadjuvanted seasonal influenza vaccines.¹² Results are now available from a clinical trial of the GSK adjuvanted pH1N1 vaccine manufactured in Europe, which included 120 persons over 60 years of age.¹⁹ At 21 days

after the first dose of adjuvanted vaccine containing 3.75 µg HA per dose, 87.5% of subjects between 61 and 70 years of age and 86.7% of those over age 70 demonstrated a response above the regulatory threshold of 1:40 seroprotection. There is no clinical experience yet with the use of GSK unadjuvanted pH1N1 vaccine in the elderly.

5.4 Pregnant women

Initial results from an ongoing clinical trial sponsored by the NIAID²⁴ have demonstrated that healthy pregnant women mount a robust immune response to a single dose of unadjuvanted pH1N1 vaccine (Sanofi Pasteur). Preliminary analysis shows that by 21 days after vaccination, 92% of the 25 recipients of a dose containing 15 µg HA and 96% of the 25 recipients of a dose containing 30 µg HA had an immune response considered protective.

6.0 RECOMMENDATIONS FOR USE OF INFLUENZA A (H1N1) 2009 VACCINE

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.

7.0 RECOMMENDED RECIPIENTS

7.1 Persons at higher risk of complications from pH1N1 and those who care for them

7.1.1 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.^{5,6}

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 haemoglobinopathy; 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.^{25,26} 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.

7.1.2 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.²⁷

The influenza-related risk in *healthy* pregnant women has been described in several studies, and summary reviews are available.²⁸⁻³⁴ 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.^{6,9}

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.³⁵⁻³⁷ 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. A similar pattern has been seen with the pandemic strain.⁶

The antibody response to pH1N1 vaccine in pregnant women is not expected to differ from that of non-pregnant individuals. This is supported by preliminary pH1N1 vaccine clinical trial data (see IMMUNOGENICITY AND EFFICACY section). 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.³⁸ 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.

7.1.3 Healthy children 6 months to 59 months of age

Children aged 6-59 months, particularly those less than 12 months, are at increased risk of pH1N1 influenza-associated hospitalization compared with healthy older children and young adults.⁶ 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,^{21,39,40} but few trials have specifically included children 6 to 23 months of age.

7.1.4 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.

7.1.5 Persons 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.⁴¹⁻⁴⁶ Individuals who are more likely to transmit influenza to those at risk of medical complications or hospitalization due to influenza include the following:

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 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.

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 for immunization, 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 immunocompromised (who are expected to have a reduced immune response to pH1N1 vaccine).

7.2 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.

7.2.1 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.

7.2.2 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.

7.2.3 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.

7.2.4 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 re-assortment among influenza viruses in swine, poultry or humans.

7.2.5 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.

7.2.6 Persons 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.

8.0 SCHEDULE AND DOSAGE

8.1 Recommended dosage schedule

The recommended dosage schedule for both types of pH1N1 influenza vaccine is presented in Table 1. Many of the recommendations in the table are 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 is a higher level of evidence noted. The recommendations are consistent with the Product Information Leaflets.^{18,47}

The majority of vaccine available for use in Canada in the 2009-10 season will be the adjuvanted formulation (Arepanrix™ H1N1). A limited quantity of unadjuvanted vaccine has been purchased for pregnant women but may also be used for other persons as indicated in the CHOICE OF PRODUCT section.

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 Dosage for Influenza A (H1N1) 2009 Monovalent Vaccine 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 group	Monovalent vaccine with AS03 adjuvant Arepanrix™		Influenza A (H1N1) 2009 Pandemic Monovalent Vaccine (without adjuvant)		Level of evidence (see Appendix)
	Dosage (mL)	No. of doses	Dosage (mL)	No. of doses	
6 to 35 months	0.25 mL	2*	Not recommended		I (Arepanrix™ H1N1)
3 years to 9 years	0.25 mL	2*	0.5 mL**	2**	III
10 years and above	0.5 mL	1	0.5 mL	1	Age 10-17 years – III (both vaccines) Age 18-60 years – I (both vaccines) Age over 60 years – I (Arepanrix™ H1N1) III (unadjuvanted)

* Data are still insufficient to determine whether one or two doses of adjuvanted vaccine will be needed in children under age 10. If two doses are given, the interval between doses should be at least 21 days.

** While dosage information is provided for unadjuvanted vaccine for children age 3-9 years (based on the seasonal vaccine dosage), note that adjuvanted vaccine is the recommended formulation for children below age 10 (see CHOICE OF PRODUCT section 9.2). The interval between doses should be at least 21 days.

The need for a second dose of adjuvanted vaccine in children under age 10 cannot be definitively determined until additional clinical trial data are available, although preliminary data are promising for young children given one dose of adjuvanted vaccine. It is anticipated that provinces and territories will provide advice on scheduling the second dose in their jurisdiction, taking into account available clinical trial data as well as additional considerations, including vaccine supply.

8.2 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 increases in adverse effects if pH1N1 vaccine is given to people with prior pH1N1 infection.

9.0 CHOICE OF PRODUCT

9.1 Pregnant women

9.1.1 Unadjuvanted vaccine

Unadjuvanted vaccine is considered the preferred option for pregnant women, given that there is extensive experience regarding the safety of unadjuvanted seasonal influenza vaccines in pregnant women and there are currently no data on the safety of the adjuvanted pH1N1 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 adjuvanted vaccine during their pregnancy.

Unadjuvanted vaccine may be administered at any stage of pregnancy.

9.1.2 Adjuvanted vaccine

Clinical data on the use of the adjuvanted pH1N1 vaccine in pregnant women are not currently available. However, for women at higher risk of complications of pH1N1 infection, this formulation should be considered if unadjuvanted vaccine is not available.

The following recommendations apply if pH1N1 activity is increasing or high in a particular region of Canada and the unadjuvanted vaccine is not available:

Pregnant women 20+ weeks' gestation:

Women should be offered adjuvanted vaccine.

Rationale: The risk of severe pH1N1 disease increases in the latter half of pregnancy, particularly in the third trimester. Where pH1N1 activity is increasing or high, the potential benefits of the vaccine for the mother (and, as a result, her unborn fetus) outweigh theoretical risks to the fetus.

Pregnant women less than 20 weeks' gestation:

- ***Pregnant women less than 20 weeks' gestation with chronic health conditions:***
Adjuvanted vaccine may be considered in women with underlying conditions that place them at higher risk of complications from pH1N1 infection.

Rationale: People with chronic health conditions are at higher risk of complications from pH1N1 infection. Consequently, pregnant women with chronic health conditions have two important risk factors for severe outcomes and thus are a high-priority group for immunization. Although the effects of the adjuvanted vaccine in early pregnancy are not known, the potential for the development of severe pH1N1 disease in women with underlying health conditions is significant and outweighs any undefined theoretical risk from the vaccine.

- **Healthy pregnant women less than 20 weeks' gestation:**
There is insufficient evidence to recommend for or against the use of adjuvanted vaccine. The risk of complications from pH1N1 infection is lower than it is in the second half of pregnancy. Women should not be denied vaccine if they want it, based on informed consent; however, they may elect to wait until an unadjuvanted vaccine is available.

9.2 Children aged 6 months to 9 years

The adjuvanted pH1N1 vaccine (Arepanrix™ H1N1) is recommended for children aged 6 months to 9 years because of its enhanced immunogenicity compared with unadjuvanted vaccine in this age group (see IMMUNOGENICITY AND EFFICACY section). Furthermore, according to the product information leaflet, preliminary data with other similar, unadjuvanted vaccines suggest that for the 6-35 month age group, unadjuvanted vaccine may not be suitable against this pandemic strain.⁴⁷

9.3 Persons aged 10 to 64 years

The adjuvanted pH1N1 vaccine (Arepanrix™ H1N1) is recommended for persons aged 10 years and above. According to the results of clinical trials to date, a single dose of vaccine appears to be sufficient. Clinical trials are ongoing, and this recommendation will be reviewed as additional data become available. If adjuvanted vaccine is not available, however, unadjuvanted vaccine may be used for persons 10 to 64 years of age who are not immunocompromised.

9.4 Persons aged 65 years and above

The adjuvanted pH1N1 vaccine (Arepanrix™ H1N1) is recommended for persons aged 65 years and above because of its enhanced immunogenicity (see IMMUNOGENICITY and EFFICACY section).

10. 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.

11. ADVERSE REACTIONS

Information on adverse events following receipt of the pH1N1 vaccine is limited to preliminary data from small clinical trials and from reported post-market surveillance from Sweden.

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).

11.1 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.⁴⁸ Published data include results from over 6,000 healthy recipients of a GSK AS03-containing prototype H5N1 influenza vaccine,^{10-12,49,50} as well as preliminary results from four clinical trials of GSK pH1N1 vaccine.^{12,18-20,51}

11.2 GSK H5N1 adjuvanted vaccines

11.2.1 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%)¹¹ or seasonal influenza vaccine (27%-65%).⁴⁹ 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.⁴⁹ 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.⁵⁰ 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.⁴⁹ Uncommon adverse events, occurring in less than 1% of recipients, included insomnia, paresthesia, somnolence, dizziness, gastrointestinal symptoms, pruritus, and rash.⁵²

11.2.2 Children

Data are available from a study of 388 children 3 to 9 years of age who received the GSK H5N1 vaccine.^{12,18,52} Local and systemic symptoms were generally more common 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).¹⁸ 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 the 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.¹² There are no reactogenicity data for children under 3 years of age.

11.3 GSK pH1N1 vaccines

11.3.1 Adults

Adverse event data are available from two small clinical trials in adults aged 18-60.^{12,18} 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).¹⁸ 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. Similar safety observations were recently made in another study using the Canadian manufactured vaccine.⁴⁷

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 Vaccine¹⁸

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

A third study,¹⁹ is assessing the use of a 3.75 µg HA adjuvanted pH1N1 vaccine in 240 subjects aged 18- 85 years, half of whom are over age 60. Preliminary results of the analysis performed 21 days after the first dose showed that tolerability of the vaccine was similar to that of H5N1 vaccine. Local reactions such as pain, redness and swelling at the injection site were observed, but no severe reactions have been reported to date. General reactions such as low-grade fever, headache and muscle ache were also observed and were in line with, or slightly more often seen than, after administration of GSK's current unadjuvanted seasonal influenza vaccines.

11.3.2 Children

Preliminary results are available from the first paediatric trial²⁰ assessing use of GSK adjuvanted pH1N1 vaccine in 200 children 6 to 36 months of age given half doses of vaccine (1.9 µg antigen and a half dose of AS03 adjuvant). Analysis of the first 51 children found the tolerability of this vaccine to be similar to that seen in the H5N1 clinical trial program. There are no safety data for the use of GSK unadjuvanted vaccine in children, although the profile is expected to be similar to that of seasonal vaccine.

11.3.3 Post-market results

Post-market results are available from Sweden for Pandemrix™, GSK's adjuvanted H1N1 vaccine manufactured in Europe.⁵³ As of October 29, about 1.4 million doses had been distributed in Sweden. Almost 200 adverse drug reaction reports were received from health care professionals. The majority were expected reactions, such as soreness, redness, and pain at the injection site and 'flu-like symptoms such as fever, shivering, fatigue, headache, body aches, and malaise. There were fewer reports of nausea, vomiting, stomach pain, diarrhea, dizziness, rashes, and insomnia. About 20 reports were identified as serious reactions that had a causal relation with the vaccination; the majority were allergic reactions, including anaphylactic

reaction, angioedema, and urticaria. Besides this, paresthesia (three cases), facial palsy, sensibility disorder, hypertension, and absence attacks (one case each) were reported.

There were five reports of death with a temporal association to vaccination, all in persons with known chronic disease. Although investigations are not complete in all cases, there is nothing from what is known to support a causal association with vaccination in any of these cases. On average, 200-300 deaths occur daily in Sweden. More than 450 consumer reports have also been received, 90% of which described non-severe, expected, and known reactions. According to the Swedish Medical Products Agency the adverse drug reaction profile does not deviate from that seen in clinical trials; however, there is a particular reason to follow reports of allergic reactions.

11.4 MF59-adjuvanted influenza vaccines

Another oil-in-water adjuvant called MF59 is used in Fludac[®], 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, Fludac[®] 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.⁵⁴ In addition, a recent randomized trial of MF59-adjuvanted versus unadjuvanted influenza vaccines in 269 children 6-35 months of age²² found that the adjuvanted vaccine was well tolerated; it had a slightly higher local reactogenicity but similar systemic reactogenicity to the unadjuvanted vaccine.

11.5 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.⁵⁵ 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 1976.⁵⁶

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.⁵⁷ A variety of infectious agents, including influenza, have been associated with GBS.^{58,59} 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, $p = 0.02$),⁶⁰ 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.^{61,62}

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.⁶³ 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.⁶⁴ 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-market surveillance.

12.0 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 (see http://www.csaci.ca/include/files/CSACI_H1N1_Statement.pdf). Guidance will be updated as new information becomes available.

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.

13.0 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.

As with all injectable vaccines, appropriate medical treatment and supervision should always be available to manage the rare event of an anaphylactic reaction following administration of the vaccine.

14.0 SIMULTANEOUS ADMINISTRATION OF OTHER VACCINES

Administration of one dose of GSK pH1N1 vaccine at the same time (but in opposite arms) as the annual seasonal influenza vaccine Fluarix[®] induced a strong response in older adults to both vaccines.⁶⁵ In this European study involving 168 adults over age 60, 89.3% of subjects receiving both vaccines at the same time developed a response to the pH1N1 vaccine that was above the seroprotective level of 1:40. The immune responses for the seasonal vaccine exceeded the regulatory threshold for annual seasonal vaccine registration (69.0%, 78.6%, and 100% seroprotection for the H1N1, H3N2, and B components respectively). The tolerability of the vaccines was in line with that observed in H5N1 trials and the pandemic H1N1 trials to date. These results are consistent with an earlier study in which preliminary data on a small number of people who received an unadjuvanted pH1N1 vaccine at the same time as seasonal influenza vaccine suggested that simultaneous administration results in an acceptable immune response to the pH1N1 vaccine.¹⁷

Pandemic influenza vaccine may be administered concurrently (but in a different limb) with seasonal influenza vaccine and/or other vaccines. If not given concurrently, there is no minimum

interval required between pH1N1 and other 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.

15.0 STORAGE AND ADMINISTRATION

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

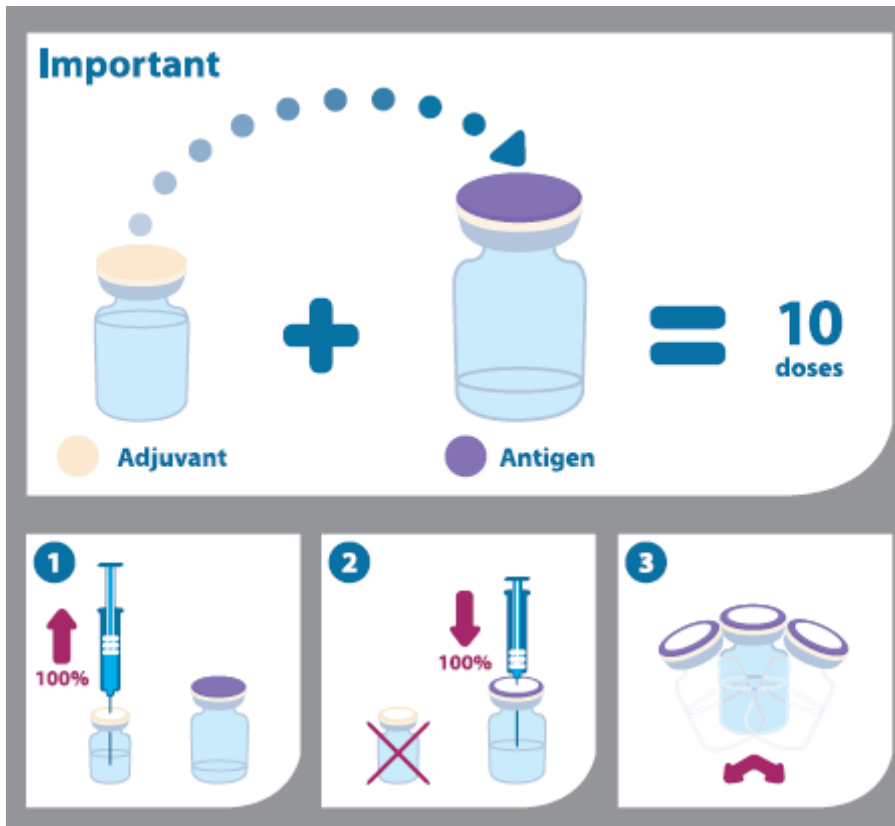
Arepanrix™ H1N1 consists of two containers: one multidose vial containing the antigen (suspension) and a second multidose vial containing the adjuvant (emulsion). The antigen suspension is a translucent to whitish opalescent suspension that may sediment slightly. The emulsion is a whitish homogeneous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



Influenza A (H1N1) 2009 Pandemic Monovalent Vaccine (Without Adjuvant) is supplied in a 10-dose multidose vial. The vaccine is a translucent to whitish opalescent suspension that may sediment slightly. It should be inspected visually for discoloration before administration and, if this exists, the vaccine should not be given. The multidose vial should be shaken vigorously before withdrawing a dose of vaccine. Proper aseptic technique should be used for each withdrawal of vaccine from the multidose vial, and the vial should be returned to recommended storage conditions. Once entered, the multidose vial should be discarded after 28 days.

16.0 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: 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.