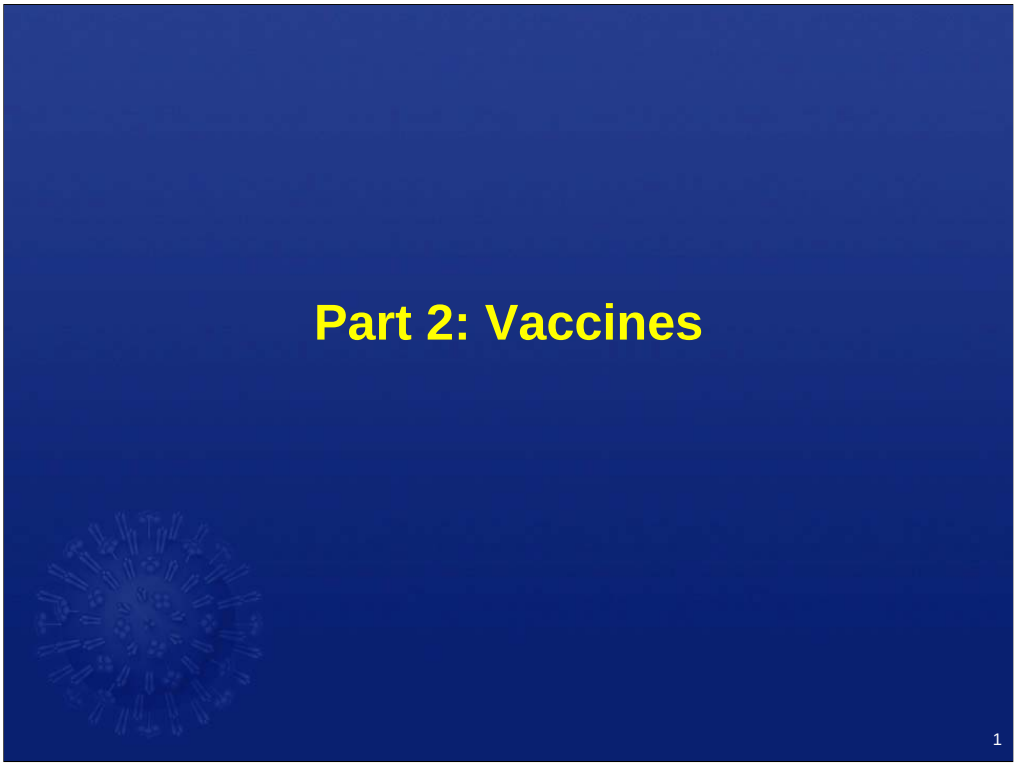
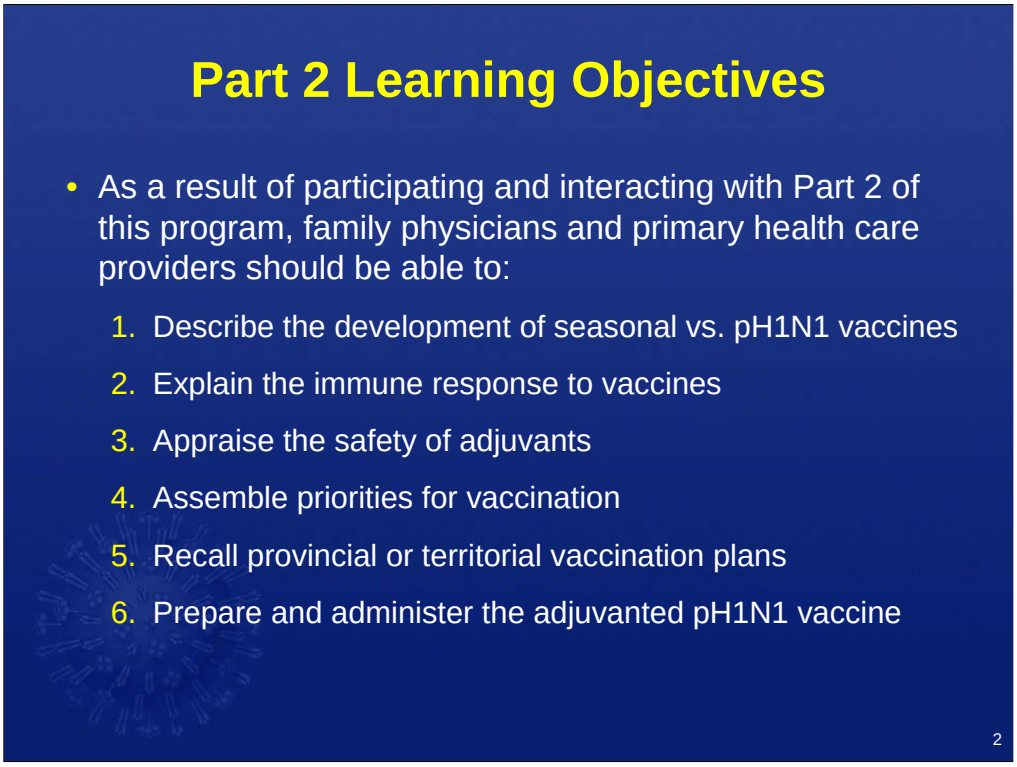
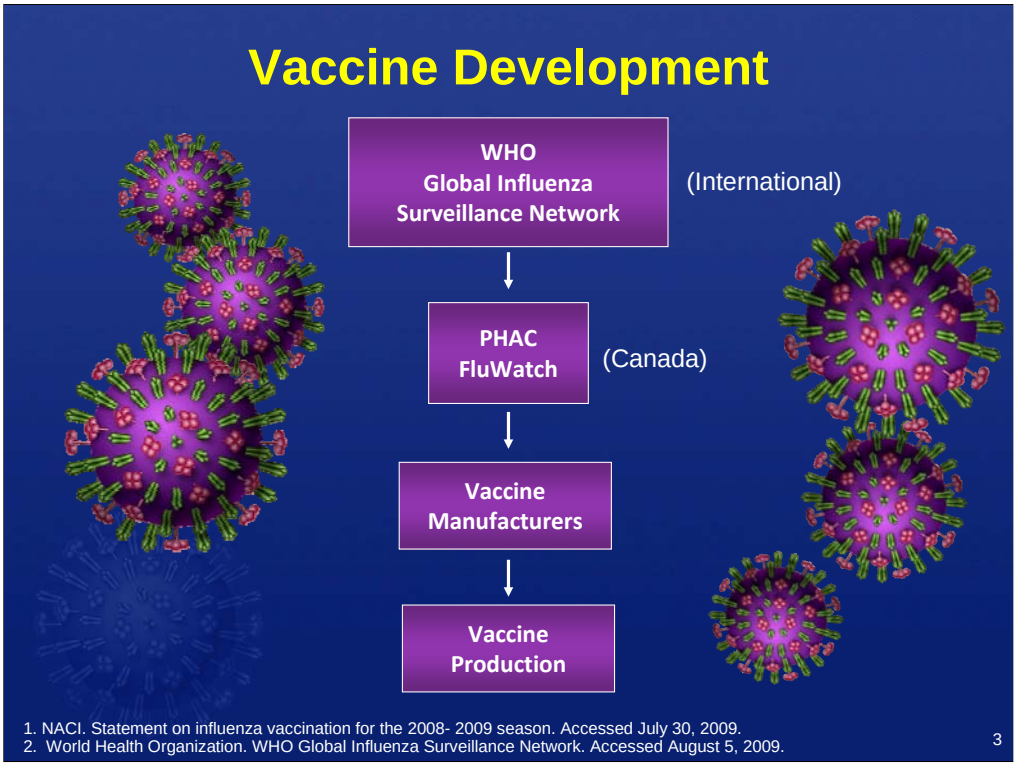


Part 2: Vaccines



As a result of participating and interacting with Part 2 of this program, family physicians and primary health care providers should be able to:

1. Describe the development of seasonal vs. pH1N1 vaccines
2. Explain the immune response to vaccines
3. Evaluate the safety of adjuvants
4. Assemble priorities for vaccination
5. Recall provincial or territorial vaccination plans
6. Prepare and administer the adjuvanted pH1N1 vaccine

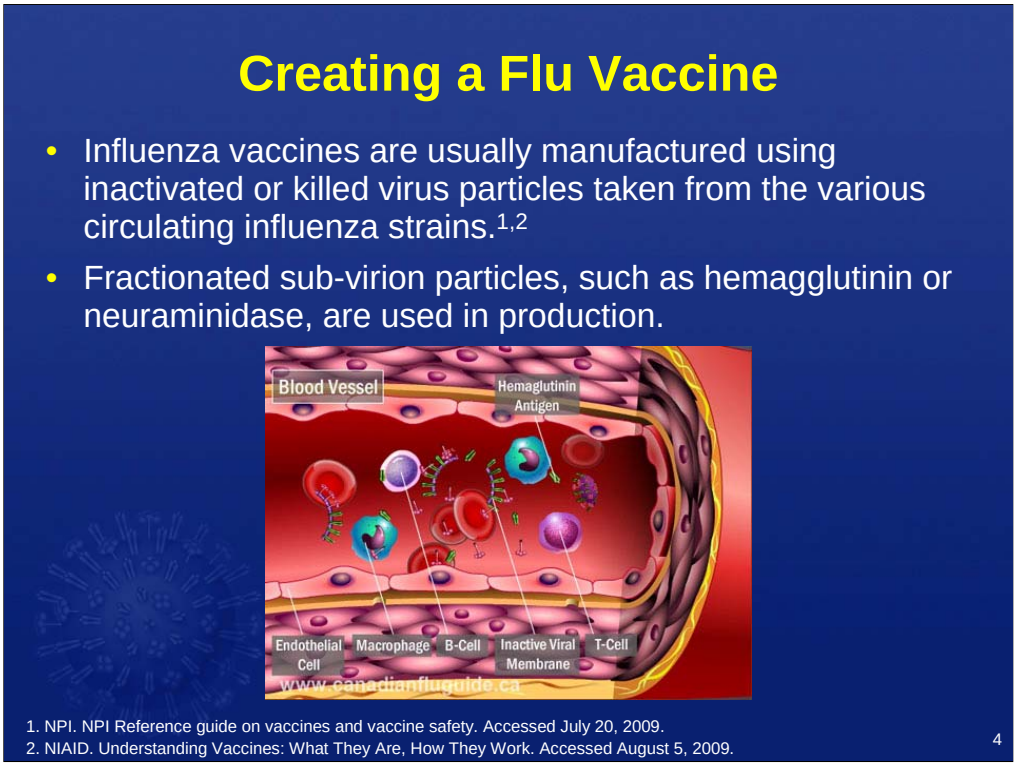


The World Health Organization (WHO) Global Influenza Surveillance Network consistently monitors the influenza strains circulating globally. Twice annually, the Network creates a list of influenza viruses that are most likely to be a public health concern in the upcoming year.[2(p1)] They release their recommendations to regulatory health bodies, including those in Canada. Furthermore, the Centre for Immunization and Respiratory Infectious Diseases, a division of the Public Health Agency of Canada (PHAC), collects national surveillance data through the FluWatch program.[1(p3)] Combining these surveillance data, PHAC makes a final decision on those strains that vaccine manufacturers should include in their seasonal vaccine preparations.

References:

1. NACI. Statement on influenza vaccination for the 2008- 2009 season. CCDR 2008;34 (ACS-3). http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/08vol34/acs-3/index-eng.php. Accessed July 30, 2009.

2. World Health Organization. WHO Global Influenza Surveillance Network. http://www.who.int/csr/disease/influenza/surveillance/en/. Accessed August 5, 2009.

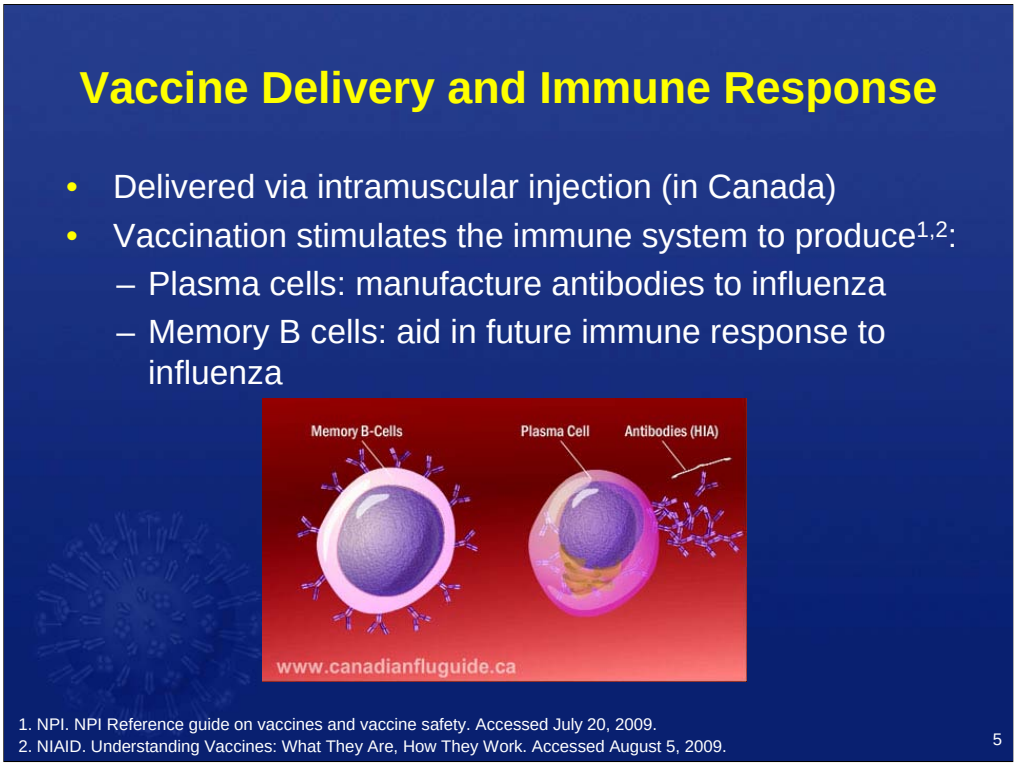


Creating a flu vaccine is a challenging and laborious process. Influenza vaccines are usually manufactured using inactivated or killed virus particles taken from the various circulating influenza strains.[1(p5),2(p3)] Fractionated sub-virion particles, such as hemagglutinin or neuraminidase, are used in production.

References:

1.National Partnership for Immunization (NPI). NPI Reference guide on vaccines and vaccine safety, Fourth Ed. 5-8; 2004. http://www2.cdc.gov/nip/isd/immtoolkit/content/products/NPIGuide.pdf. Accessed July 20, 2009.

2.National Institute of Allergy and Infectious Diseases (NIAID), U.S. Department of Health and H uman Services, National Institute of Health. Understanding Vaccines: What They Are, How They Work. NIH Publication No. 08-4219; January 2008. http://www3.niaid.nih.gov/topics/vaccines/PDF/undvacc.pdf. Accessed August 5, 2009.



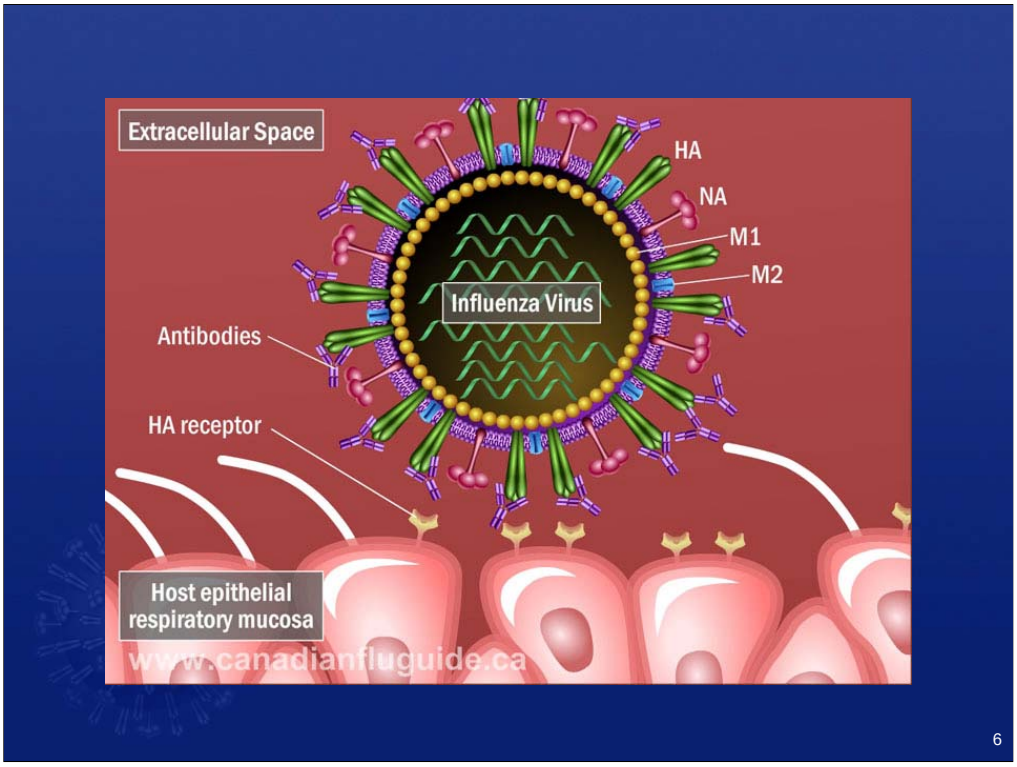
Influenza vaccines are administered a variety of ways including via syringe, patch or sprays. Currently in Canada, patch and spray delivery are investigational, and vaccines are only administered through an intramuscular injection.

Influenza vaccines are able to trigger an immune response by mimicking viral infection.[1(p5),2(p2)] As a result of vaccination, the immune system produces plasma cells that manufacture the hemagglutinin antibodies specific to the strain of influenza contained in the vaccine, and memory B cells to aid in future immune response when a person is exposed to viral contamination.

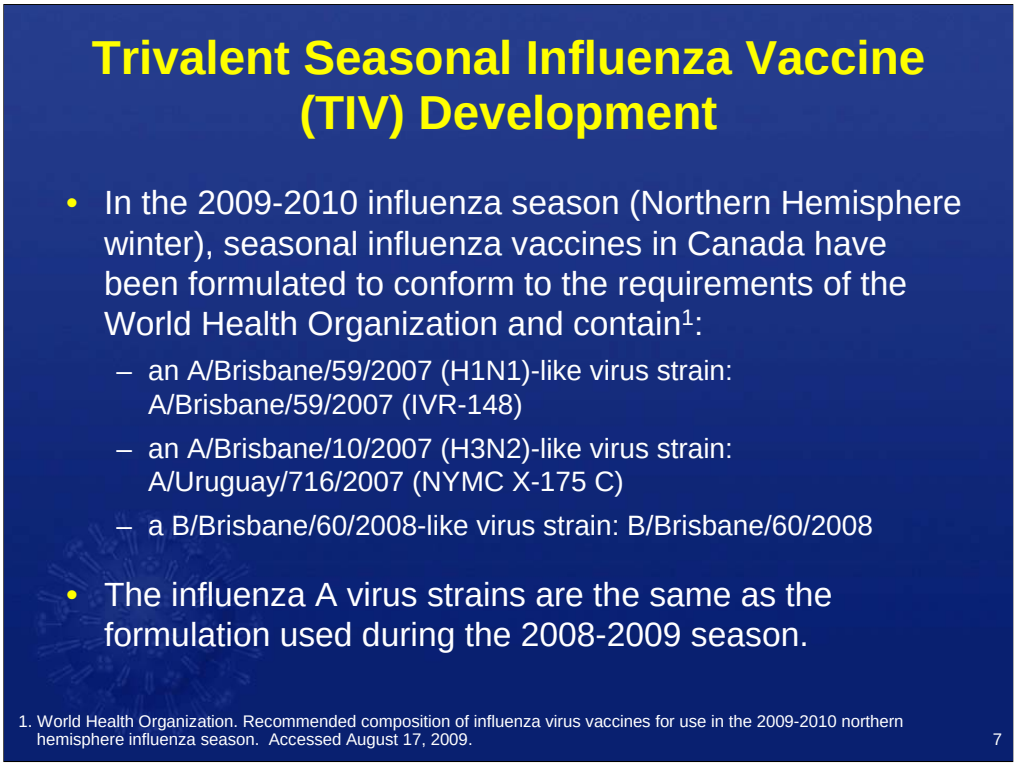
References:

1. National Partnership for Immunization (NPI). NPI Reference guide on vaccines and vaccine safety, Fourth Ed. 5-8; 2004. http://www2.cdc.gov/nip/isd/immtoolkit/content/products/NPIGuide.pdf. Accessed July 20, 2009.

2. National Institute of Allergy and Infectious Diseases (NIAID), US Department of Health and Human Services, National Institute of Health. Understanding Vaccines: What They Are, How They Work. NIH Publication No. 08-4219; January 2008. http://www3.niaid.nih.gov/topics/vaccines/PDF/undvacc.pdf Accessed August 5, 2009.



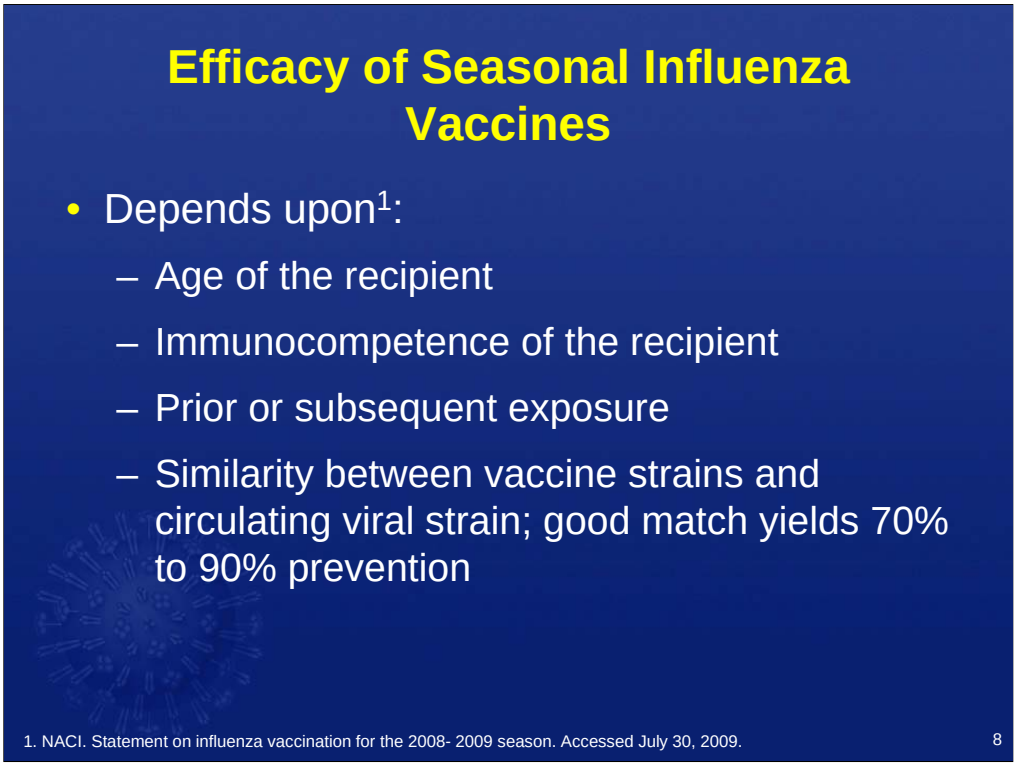
Hemagglutinin antibodies, produced by the individuals plasma cells, bind to host epithelial cells and block viral attachment of live influenza virus. As a result of vaccination, the immune system is able to recognize the virus and overall disease is either avoided or diminished in severity.



In the 2009-2010 influenza season (ie, the Northern Hemisphere winter), seasonal influenza vaccines in Canada contain the following formulation to conform to the requirements of the World Health Organization[1]: (1) an A/Brisbane/59/2007 (H1N1)-like virus strain: A/Brisbane/59/2007 (IVR-148), (2) an A/Brisbane/10/2007 (H3N2)-like virus strain: A/Uruguay/716/2007 (NYMC X-175 C), and (3) a B/Brisbane/60/2008-like virus strain: B/Brisbane/60/2008. These influenza A strains are the same as the formulation used during the 2008-2009 season.

Reference:

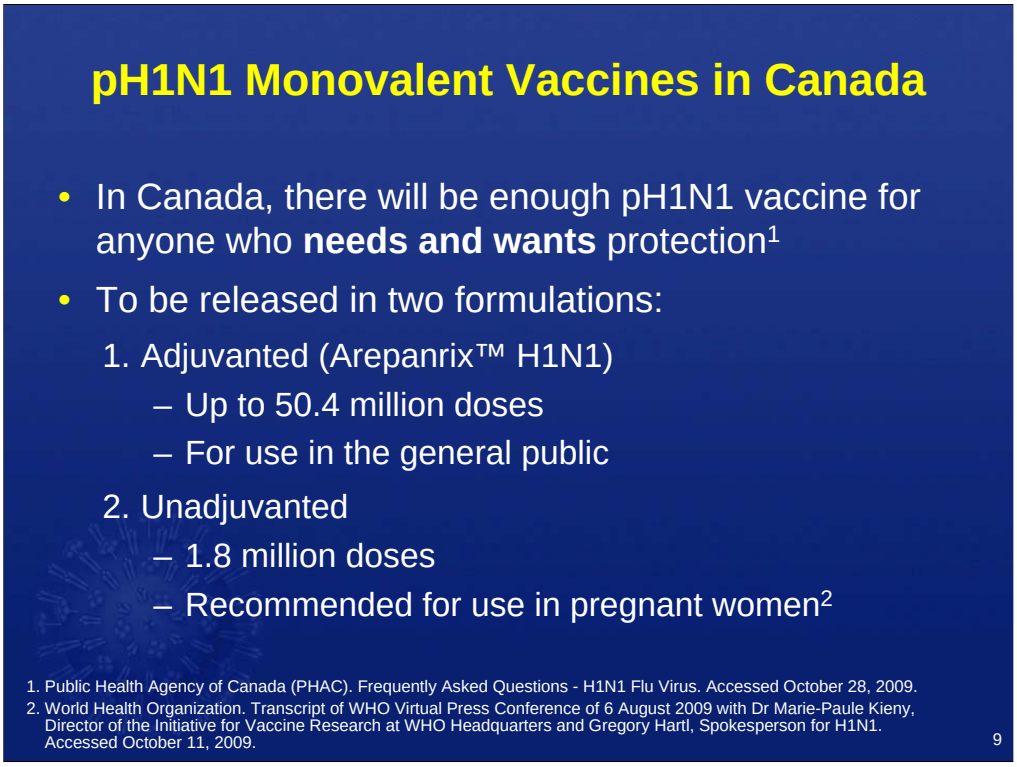
1. World Health Organization. Recommended composition of influenza virus vaccines for use in the 2009-2010 northern hemisphere influenza season; February 2009. http://www.who.int/csr/disease/influenza/recommendations2009_10north/en/index.html. Accessed August 17, 2009.



The antibody response, and thus the efficacy of an influenza vaccine, depends upon multiple factors. The efficacy of the seasonal vaccine is determined by the age of the recipient, immunocompetent state of an individual, and prior or subsequent exposure to the vaccine.[1(p18)] Moreover, if the correct viral strains are included in the seasonal vaccine, then the efficacy increases substantially: a good match can prevent illness in 70% to 90% of healthy individuals.

Reference:

1. NACI. Statement on influenza vaccination for the 2008- 2009 season. CCDR 2008;34 (ACS-3). http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/08vol34/acs-3/index-eng.php. Accessed July 30, 2009.

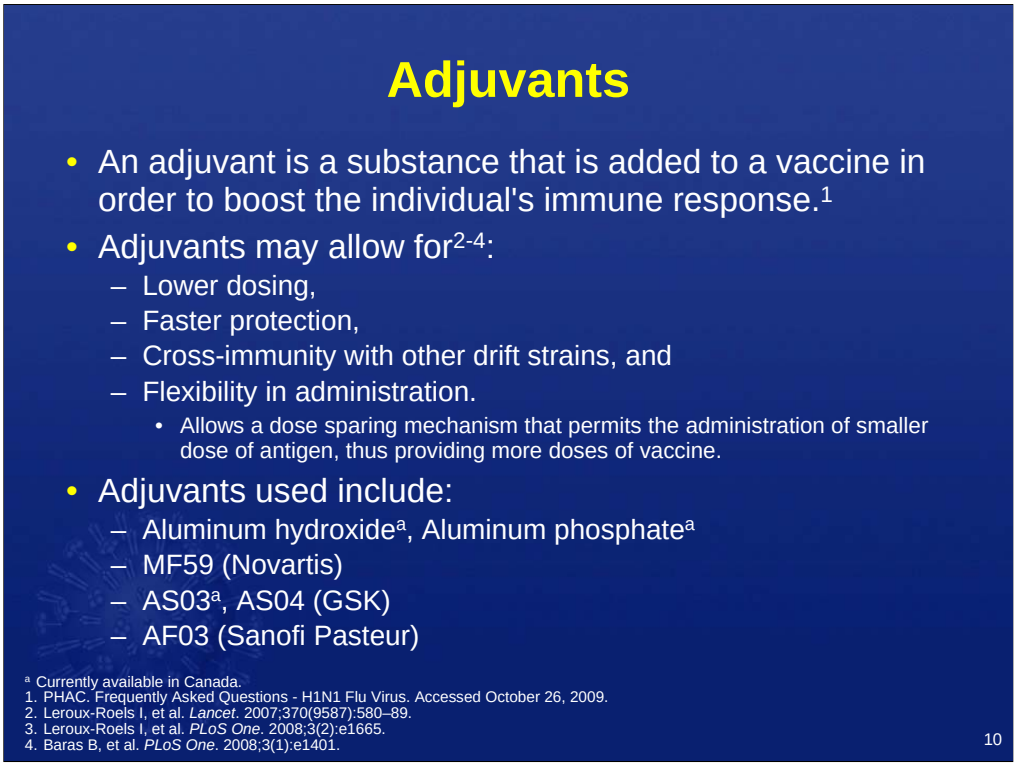


The Government of Canada has purchased enough pH1N1 vaccine for anyone who needs and wants protection. season.[1(p5)] The vaccine will be released in two formulation. Most of the vaccine will be purchased as an adjuvanted form, to be used in the general public.[1(p9)] Adjuvanted vaccines have favorable safety profiles but have not been tested on pregnant women. Therefore, the WHO's Strategic Advisory Group of Experts (SAGE) suggests that pregnant women receive the unadjuvanted vaccine.[2(p10)] As a result of the WHO recommendation the Government of Canada intends to purchase approximately 2 million doses of unadjuvanted vaccine for use in pregnant women.[1(p9)]

References:

1. Public Health Agency of Canada. Frequently Asked Questions - H1N1 Flu Virus; October 20, 2009. http://www.phac-aspc.gc.ca/alert-alerte/h1n1/faq_rg_h1n1-eng.php#av. Accessed October 28, 2009.

2. World Health Organization. Transcript of WHO Virtual Press Conference of 6 August 2009 with Dr Marie-Paule Kieny, Director of the Initiative for Vaccine Research at WHO Headquarters and Gregory Hartl, Spokesperson for H1N1. Available from: http://www.who.int/mediacentre/pandemic_h1n1_presstranscript_2009_08_06.pdf. Accessed October 11, 2009.



An adjuvant is a substance that is added to a vaccine in order to boost the immune response of an individual.[1]

Adjuvants may allow for lower dosing, faster protection, cross-immunity with other drift strains, and flexibility in terms of administration, allowing for a dose sparing mechanism that permits the administration of smaller doses of antigen that increases the number of available doses.[2-4]

Adjuvants are employed by many companies and used worldwide. Commonly utilized adjuvants include aluminum hydroxide, aluminum phosphate, MF59 (used by Novartis), ASO3 and ASO4 (used by GlaxoSmithKline) and AF03 (used by Sanofi Pasteur). Currently only aluminum hydroxide, aluminum phosphate and AS03 are available in Canada.

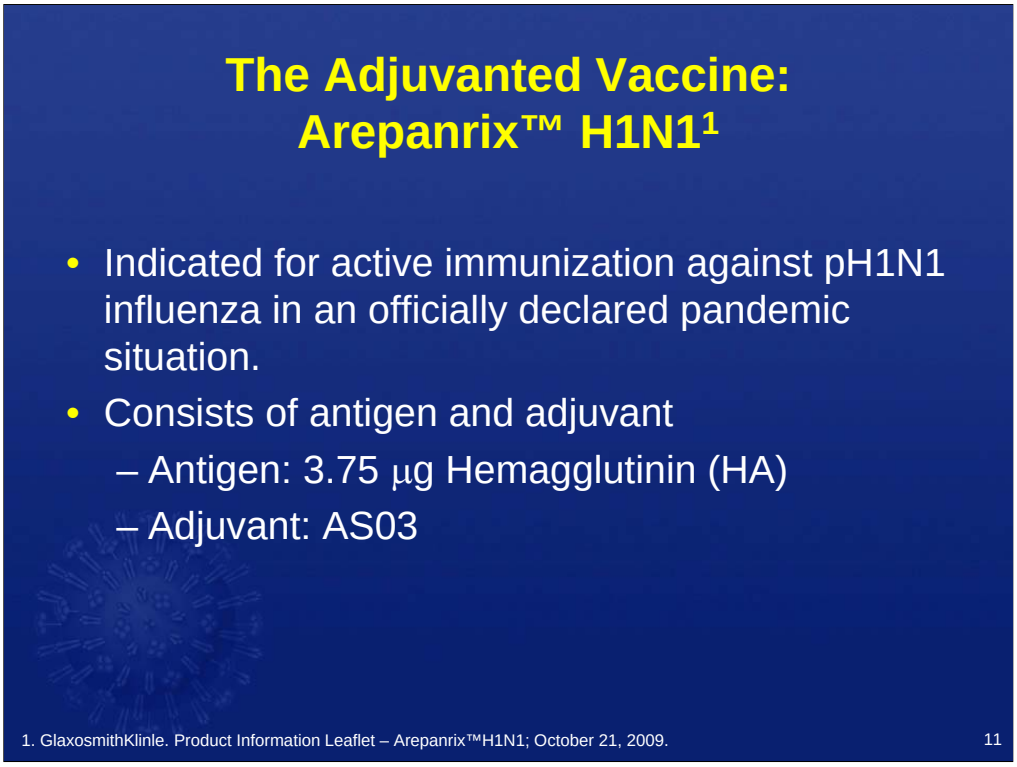
References:

1. Public Health Agency of Canada. Frequently Asked Questions - H1N1 Flu Virus; October 20, 2009. http://www.phac-aspc.gc.ca/alert-alerte/h1n1/faq_rg_h1n1-eng.php. Accessed October 26, 2009.

2. Leroux-Roels I, Borkowski A, Vanwolleghem T, et al. Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial. *Lancet*. 2007;370(9587):580–89.

3. Leroux-Roels I, Bernhard R, Gérard P, Darmé M, Hanon E, Leroux-Roels G. Broad Clade 2 Cross-Reactive Immunity Induced by an Adjuvant systemed Clade 1 rH5N1 Pandemic Influenza Vaccine. *PLoS One*. 2008;3(2):e1665.

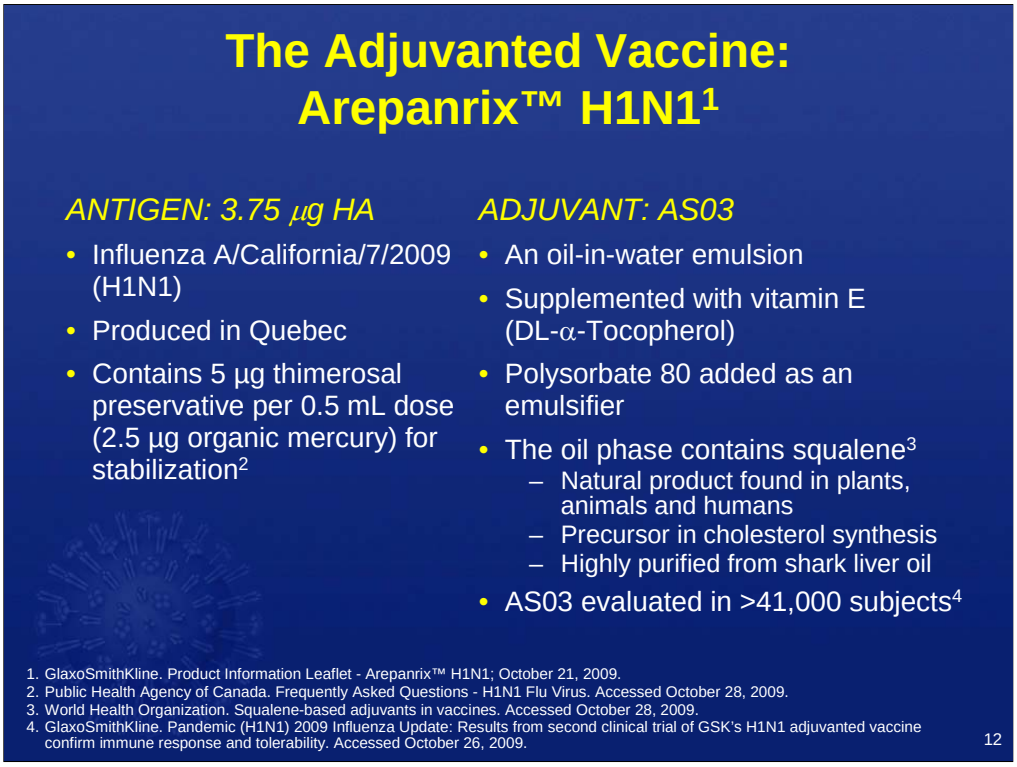
4. Baras B, Stittelaar KJ, Simon JH, et al. Cross-protection against lethal H5N1 challenge in ferrets with an adjuvanted pandemic influenza vaccine. *PLoS One*. 2008;3(1):e1401.



The adjuvanted Arepanrix H1N1 is indicated for active immunization against pH1N1 influenza in an officially declared pandemic situation.[1(p5)] The vaccine consists of 3.75 μg hemagglutini antigen and the AS03 adjuvant system.[1(p4)]

Reference:

1. GlaxoSmithKline. Product Information Leaflet - Arepanrix™ H1N1; October 21, 2009. Available at: http://www.gsk.ca/english/docs-pdf/Arepanrix_PIL_CAPA01v01.pdf



The antigen is a monovalent, inactivated, split-virion, influenza A/California/7/2009 (H1N1) virus produced in Quebec.[1(p4)] A thimerosol preservative (5 μg per 0.5 mL dose) containing 2.5 μg organic mercury is also included for stabilization.[1(p4),2(p12)] The AS03 adjuvant is a tocopherol oil-in-water based emulsion supplemented with vitamin E.[1(p4)] The adjuvant also contains polysorbate 80 as an emulsifier and squalene[1(p4)] – a natural product found in plants, animals and humans that is a precursor in cholesterol synthesis.[3] For vaccine production squalene is highly purified from shark liver oil.[3] AS03 has been evaluated in more than 41,000 individuals participating in influenza vaccination programs.[4]

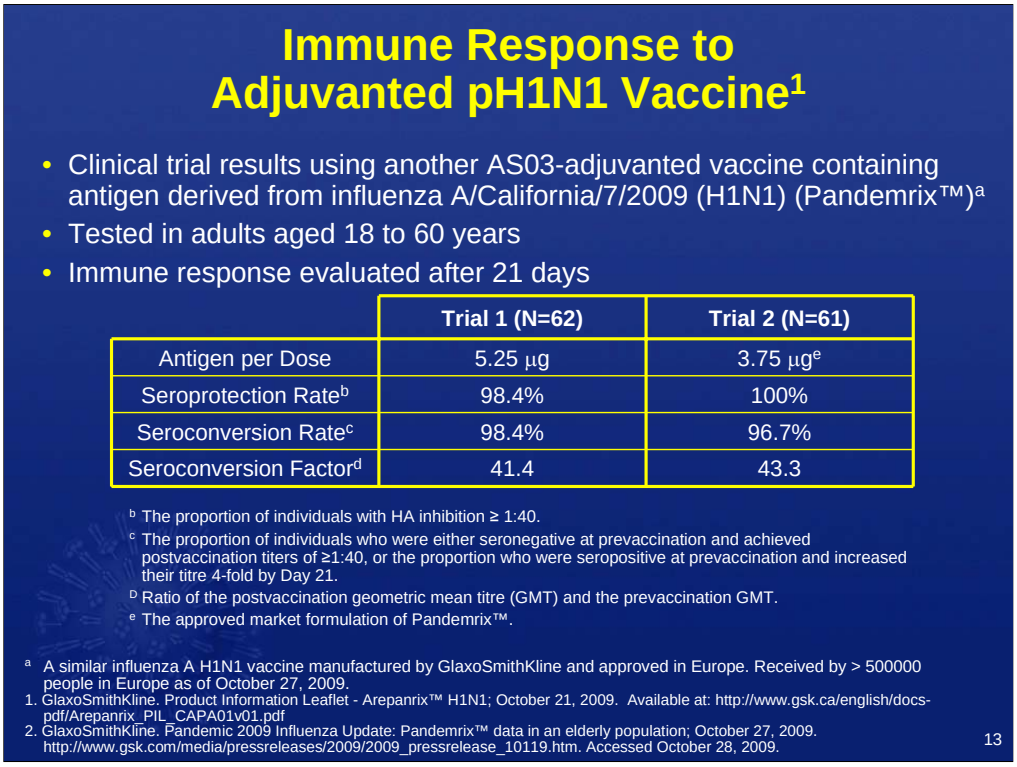
References:

1. GlaxoSmithKline. Product Information Leaflet - Arepanrix™ H1N1; October 21, 2009. Available at: http://www.gsk.ca/english/docs-pdf/Arepanrix_PIL_CAPA01v01.pdf

2. Public Health Agency of Canada. Frequently Asked Questions - H1N1 Flu Virus; October 20, 2009. http://www.phac-aspc.gc.ca/alert-alerte/h1n1/faq_rg_h1n1-eng.php#vac. Accessed October 28, 2009.

3. World Health Organization. Squalene-based adjuvants in vaccines; July 21, 2006. http://www.who.int/vaccine_safety/topics/adjuvants/squalene/questions_and_answers/en/index.html. Accessed October 28, 2009.

4. GlaxoSmithKline. Pandemic (H1N1) 2009 Influenza Update: Results from second clinical trial of GSK's H1N1 adjuvanted vaccine confirm immune response and tolerability; October 16, 2009. http://www.gsk.com/media/pressreleases/2009/2009_pressrelease_10111.htm. Accessed October 26, 2009.



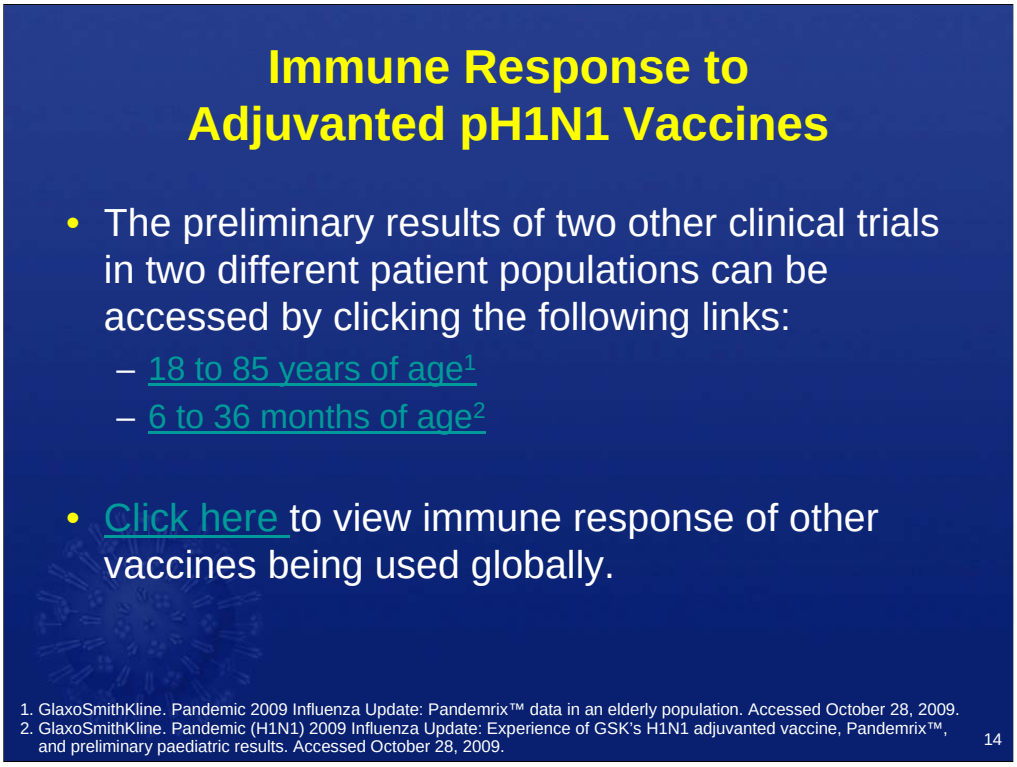
Dosing of the adjuvanted vaccine has been determined following clinical trials of another AS03-adjuvanted vaccine containing antigen derived from influenza A/California/7/2009 (H1N1) (Pandemrix™).[1] The trials were initiated in adults aged 18 to 60 years and immune response was measured 21 days following vaccination. Results were recorded as seroprotection and seroconversion rates. Seroprotection was defined as the proportion of individuals with hemagglutinin (HA) inhibition ≥ 1:40. Seroprotection measured the proportion of individuals who were either seronegative at prevaccination and achieved postvaccination titers of ≥1:40, or the proportion who were seropositive at prevaccination and increased their titre 4-fold by Day 21.

Trials were initiated with doses of either 5.25 μg (N=62) or 3.75 μg (N=61) of antigen. Seroprotection and seroconversion rates were over 96%, with seroprotection being observed in 100% of all subjects after a single 3.75 μg dose. These data indicate that a single dose of the adjuvanted vaccine is likely to provide protection in healthy adults.

References:

1. GlaxoSmithKline. Product Information Leaflet - Arepanrix™ H1N1; October 21, 2009. Available at: http://www.gsk.ca/english/docs-pdf/Arepanrix_PIL_CAPA01v01.pdf

2. GlaxoSmithKline. Pandemic 2009 Influenza Update: Pandemrix™ data in an elderly population; October 27, 2009. http://www.gsk.com/media/pressreleases/2009/2009_pressrelease_10119.htm. Accessed October 28, 2009.

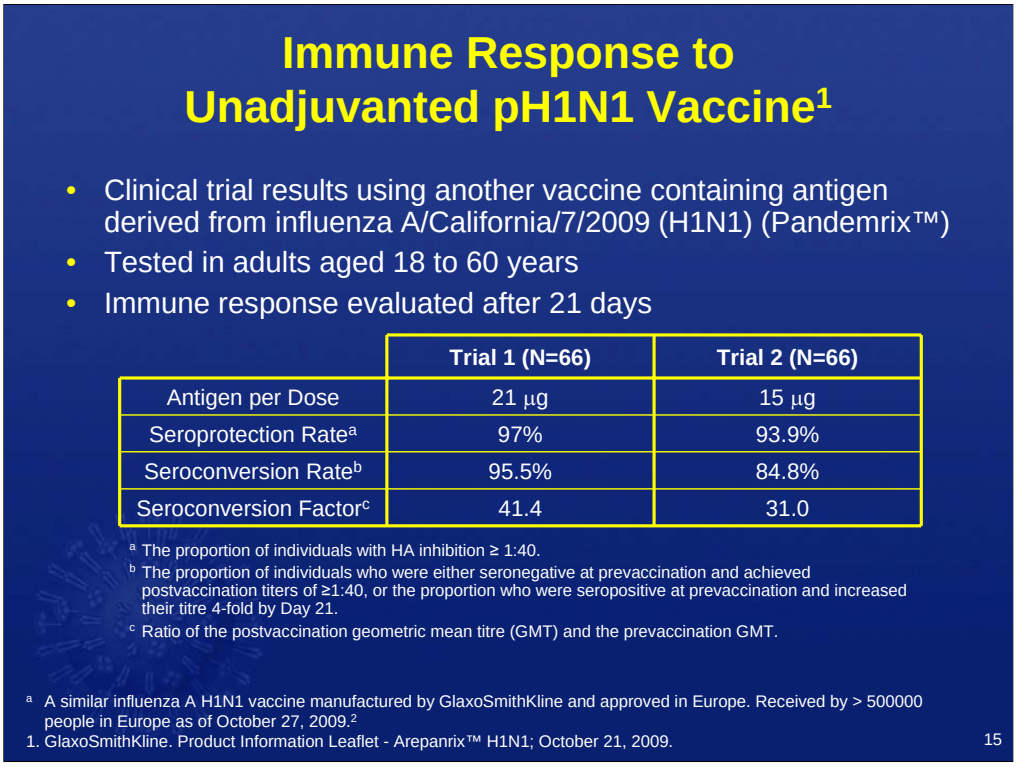


The preliminary results of two other Pandemrix™ clinical trials have been reported. Studies were conducted in subjects 18 to 85 years of age and in pediatric patients aged 6 to 36 months.[1,2] Multiple other studies have been carried out with vaccines produced by other manufacturers and distributed to other global markets. This information can be found in the Appendix of this slide deck.

References:

1. GlaxoSmithKline. Pandemic 2009 Influenza Update: Pandemrix™ data in an elderly population; October 27, 2009. http://www.gsk.com/media/pressreleases/2009/2009_pressrelease_10119.htm. Accessed October 28, 2009.

2. GlaxoSmithKline. Pandemic (H1N1) 2009 Influenza Update: Experience of GSK's H1N1 adjuvanted vaccine, Pandemrix™, and preliminary paediatric results; October 23, 2009. http://www.gsk.com/media/pressreleases/2009/2009_pressrelease_10116.htm. Accessed October 28, 2009.

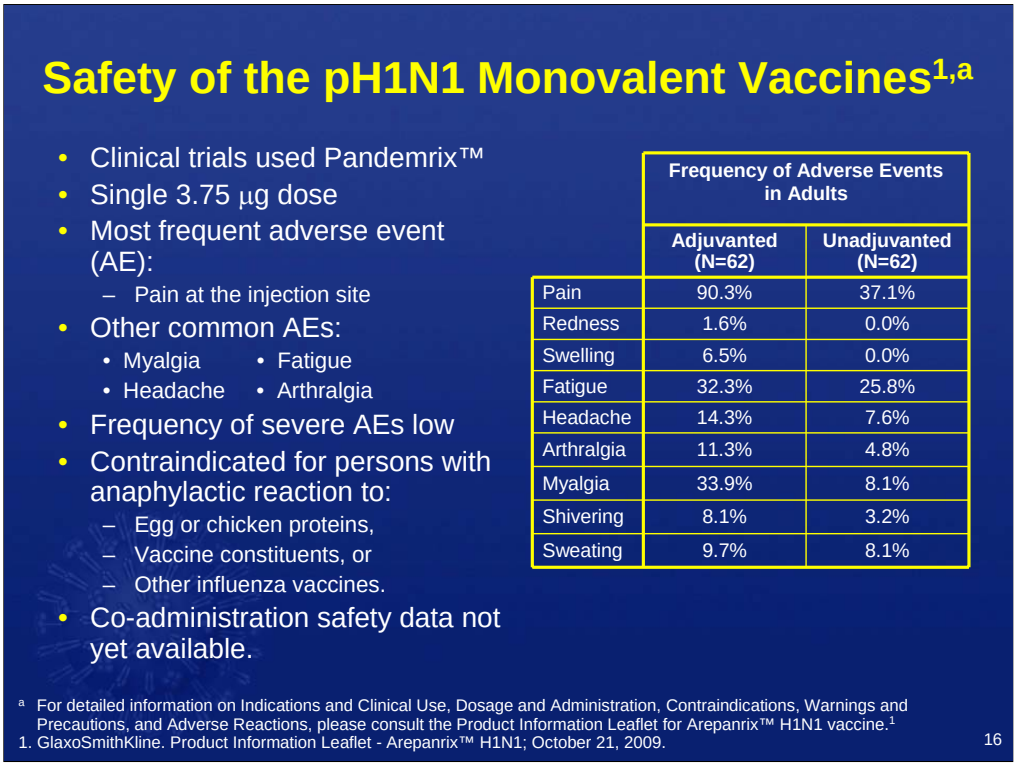


Dosing of the unadjuvanted vaccine has also been determined following clinical trials of Pandemrix™.[1] The trials were also tested in healthy adults and measured immune response 21 days following vaccination. Seroprotection and seroconversion rates were recorded.

These trials were initiated with doses of either 21 μg (N=66) or 15 μg (N=66) of antigen. Seroprotection and seroconversion rates were not as high as the adjuvanted vaccine, yet seroprotection was over 93% for both doses of the vaccine. Based on these data over 96%, with seroprotection being observed in 100% of all subjects after a single 3.75 μg dose. These data indicate that a single dose of the unadjuvanted vaccine is likely sufficient for protection in healthy adults, eg, pregnant women with no other medical conditions.

<u>Reference:</u>

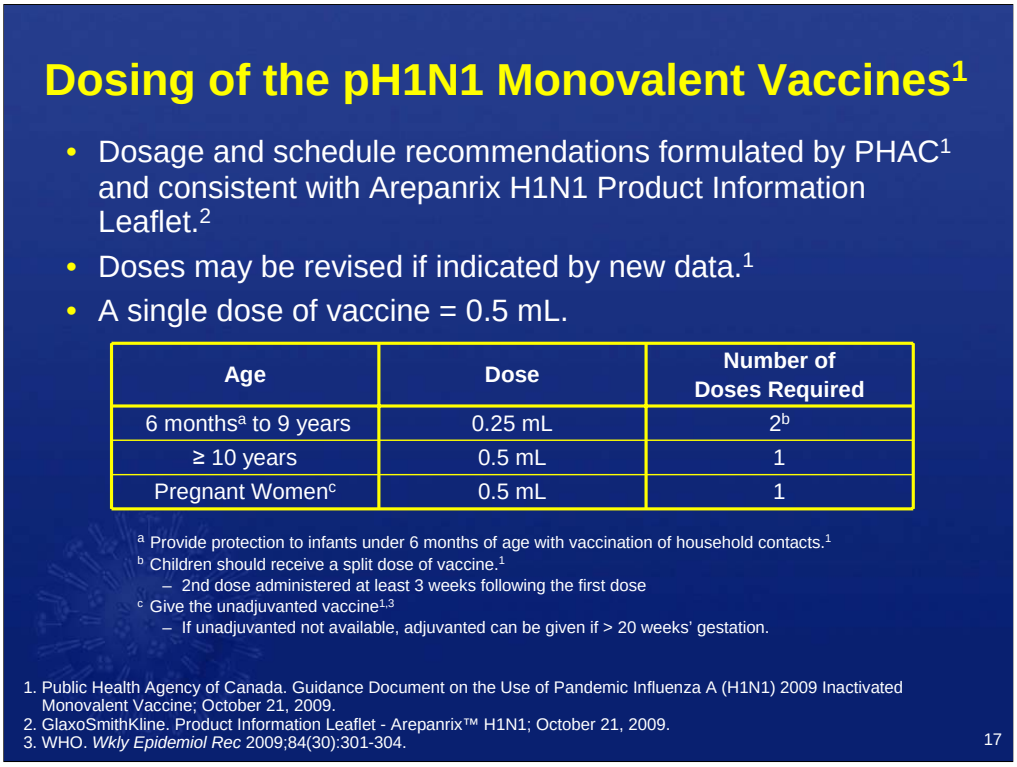
1. GlaxoSmithKline. Product Information Leaflet - Arepanrix™ H1N1; October 21, 2009. Available at: http://www.gsk.ca/english/docs-pdf/Arepanrix_PIL_CAPA01v01.pdf



Safety of the vaccines was tested in clinical trials using another vaccine that contains antigen derived from influenza A/California/7/2009 (H1N1) (Pandemrix™).[1] These data report the side effects in adults given a single 3.75 μg dose. The most frequents adverse event was pain at the injection site, while other very common adverse events included myalgia, fatigue, headache and arthralgia. In the two studies conducted the frequency of "related" Grade 3 symptoms was low and did not exceed 1.6%. It should be noted that the vaccine should not be given to persons with allergies to egg or chicken proteins, the vaccine components, or other influenza vaccines; as the pH1N1 vaccine may cause an allergic reaction in these individuals. Signs of an allergic response may include an itchy skin rash, shortness of breath and a swelling of the face or tongue.

Reference:

1. GlaxoSmithKline. Product Information Leaflet - Arepanrix™ H1N1; October 21, 2009. Available at: http://www.gsk.ca/english/docs-pdf/Arepanrix_PIL_CAPA01v01.pdf



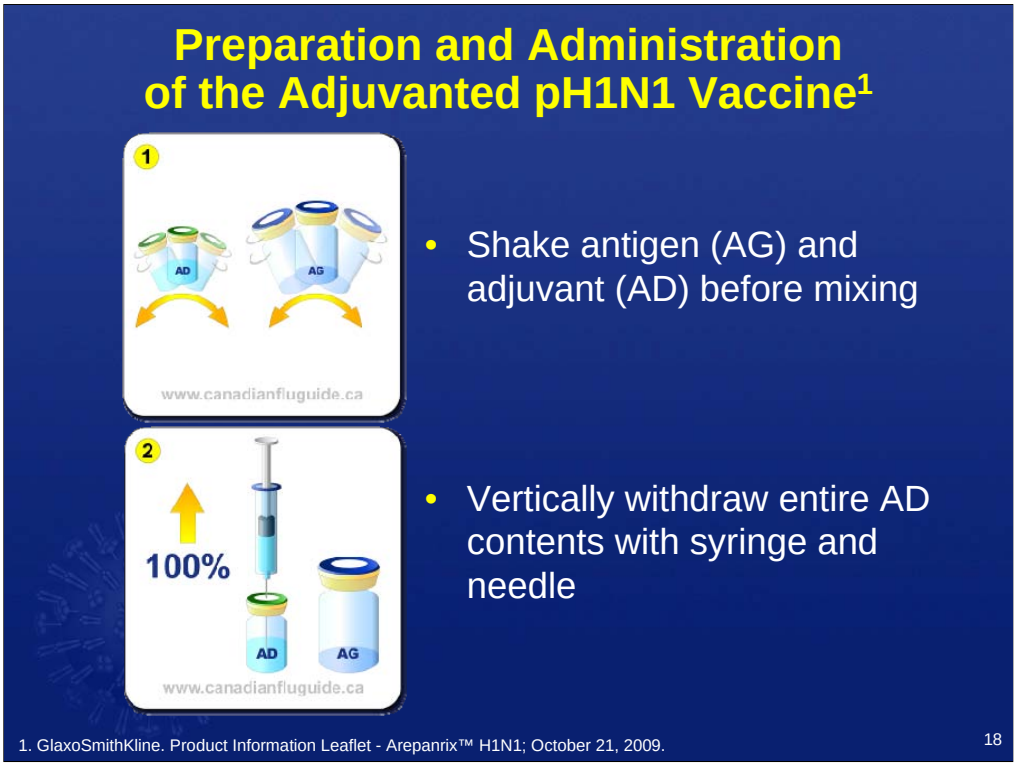
From clinical trial data the Public Health Agency of Canada has developed dosage and schedule recommendations[1] for delivery of the pH1N1 vaccine that are consistent with the Arepanrix™ H1N1 Product Information Leaflet.[2] A single 0.5 mL dose of the adjuvanted vaccine can be given to healthy adults.[1] This dosing also applies to children ten years of age or older. Children between six months and nine years of age should receive a split dose of vaccine (0.25 mL/dose), with the second dose administered at least three weeks following the first dose.[1] Infants under six months of age should not be vaccinated, but protection may be provided through vaccination of household contacts.[1] Pregnant women should receive the unadjuvanted vaccine given the limited availability of safety data in this population.[1] However, if unadjuvanted vaccine is not available then adjuvanted vaccine can be given to women with gestation periods > 20 weeks.[1,3]

References:

1. Public Health Agency of Canada. Guidance Document on the Use of Pandemic Influenza A (H1N1) 2009 Inactivated Monovalent Vaccine; October 21, 2009. Available at: http://www.phac-aspc.gc.ca/alert-alerte/h1n1/vacc/pdf/monovacc-guide-eng.pdf.

2. GlaxoSmithKline. Product Information Leaflet - Arepanrix™ H1N1; October 21, 2009. Available at: http://www.gsk.ca/english/docs-pdf/Arepanrix_PIL_CAPA01v01.pdf

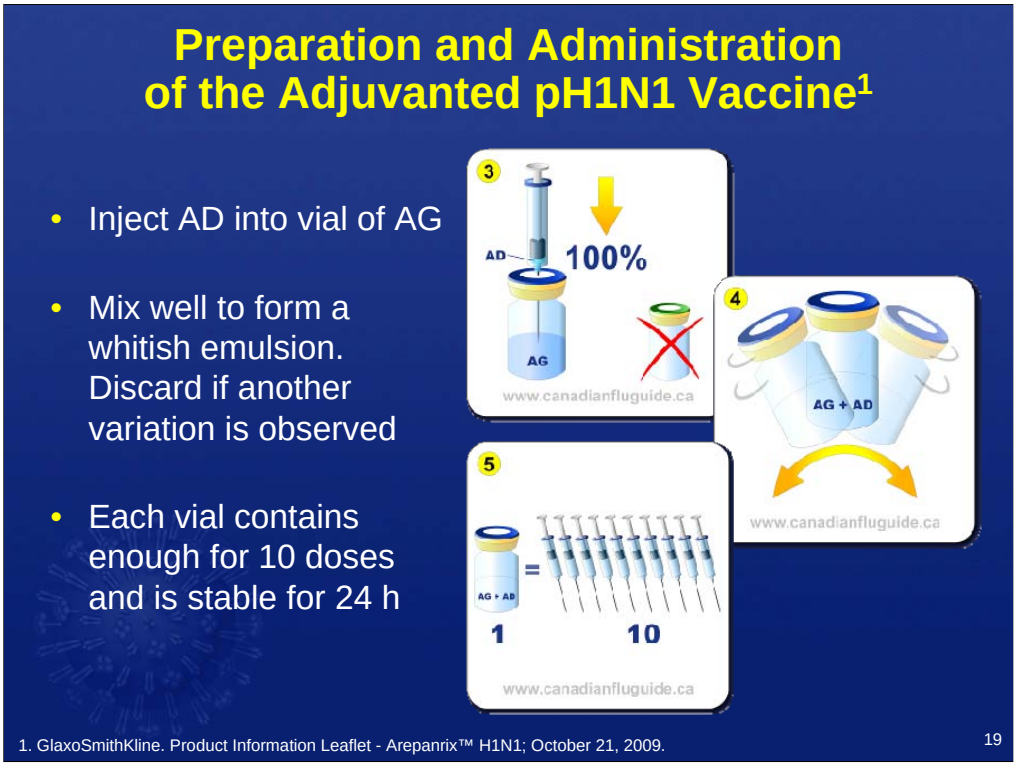
3. World Health Organization. Strategic Advisory Group of Experts on Immunization – report of the extraordinary meeting on the influenza A(H1N1) 2009 pandemic; July 7, 2009. *Wkly Epidemiol Rec* 2009;84(30):301-304. Available at: http://www.who.int/wer/2009/wer8430.pdf.



Arepanrix H1N1 is supplied as one multi-dose vial containing the antigen (AG) and a second multi-dose vial containing the adjuvant (AD).[1] The preparation of the vaccine requires several steps. First remove the vaccine components from storage at 2°C to 8°C and bring to room temperature. Inspect the vials for foreign particulate matter or an unusual appearance, and then mix the antigen and adjuvant components thoroughly. Vertically withdraw the entire contents from the adjuvant vial.

Reference:

1. GlaxoSmithKline. Product Information Leaflet - Arepanrix™ H1N1; October 21, 2009. Available at: http://www.gsk.ca/english/docs-pdf/Arepanrix_PIL_CAPA01v01.pdf



Inject the adjuvant emulsion into the vial containing antigen and mix thoroughly to form a whitish emulsion.[1] Discard the vaccine if another variation is observed. This vaccine mixture is stable for 24 hours at room temperature and contains enough vaccine for 10 doses.

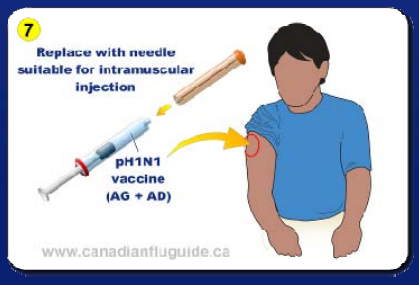
Reference:

1. GlaxoSmithKline. Product Information Leaflet - Arepanrix™ H1N1; October 21, 2009. Available at: http://www.gsk.ca/english/docs-pdf/Arepanrix_PIL_CAPA01v01.pdf

Injection of the Adjuvanted pH1N1 Vaccine[1]

- Mix thoroughly before each injection
- Withdraw 0.5 mL dose

- Replace needle with one suitable for intramuscular injection
- Proceed with intramuscular injection



1. GlaxoSmithKline. Product Information Leaflet - Arepanrix™ H1N1; October 21, 2009.

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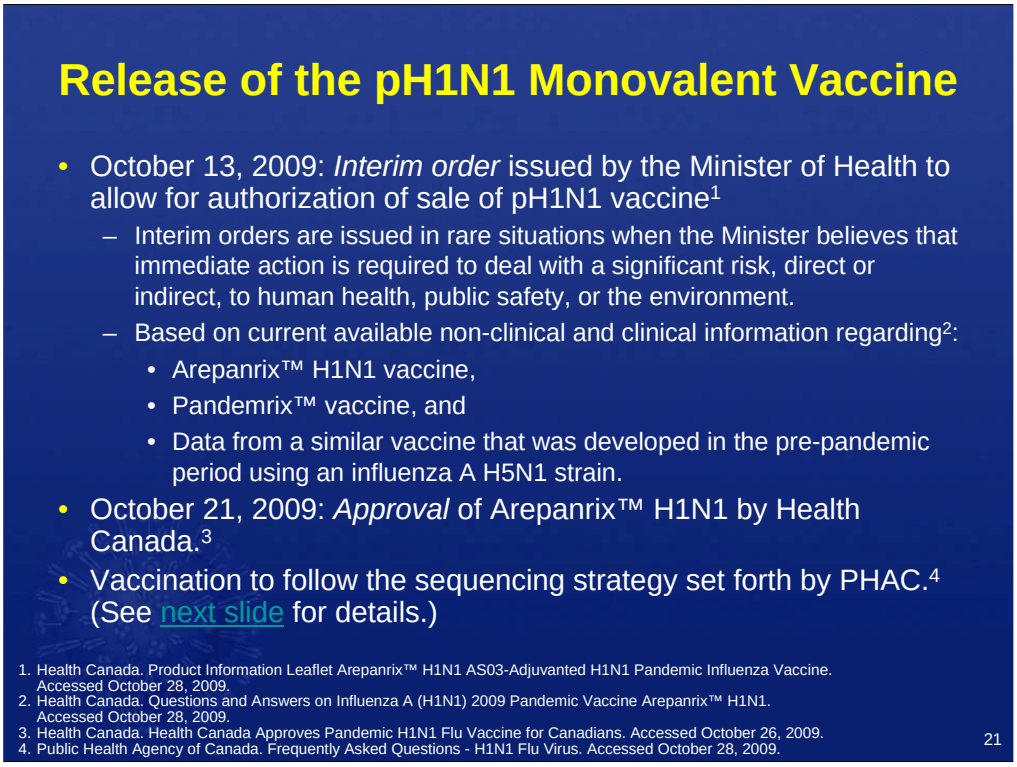
Before each injection, mix the emulsion thoroughly and then withdraw a 0.5 mL dose with a 1 mL syringe and 20G needle.[1] Next, replace the needle with a 25G needle before intramuscular injection.

Reference:

1. GlaxoSmithKline. Product Information Leaflet - Arepanrix™ H1N1; October 21, 2009. Available at: http://www.gsk.ca/english/docs-pdf/Arepanrix_PIL_CAPA01v01.pdf



On October 13, 2009, and interim order was issued by the Minister of Health to allow for authorization of sale of pH1N1 vaccine.[1] Interim orders are issued in rare situations when the Minister believes that immediate action is required to deal with a significant risk, direct or indirect, to human health, public safety, or the environment. The authorization was made based upon the currently available non-clinical and clinical information regarding the Arepanrix™ H1N1 vaccine, the Pandemrix™ vaccine, and other safety data from a similar vaccine that was developed in the pre-pandemic period using an influenza A H5N1 strain.[2]

On October 21, 2009, Health Canada approved the Arepanrix™ H1N1 vaccine.[3] Vaccination delivery will follow the sequencing strategy set forth by PHAC.[4]

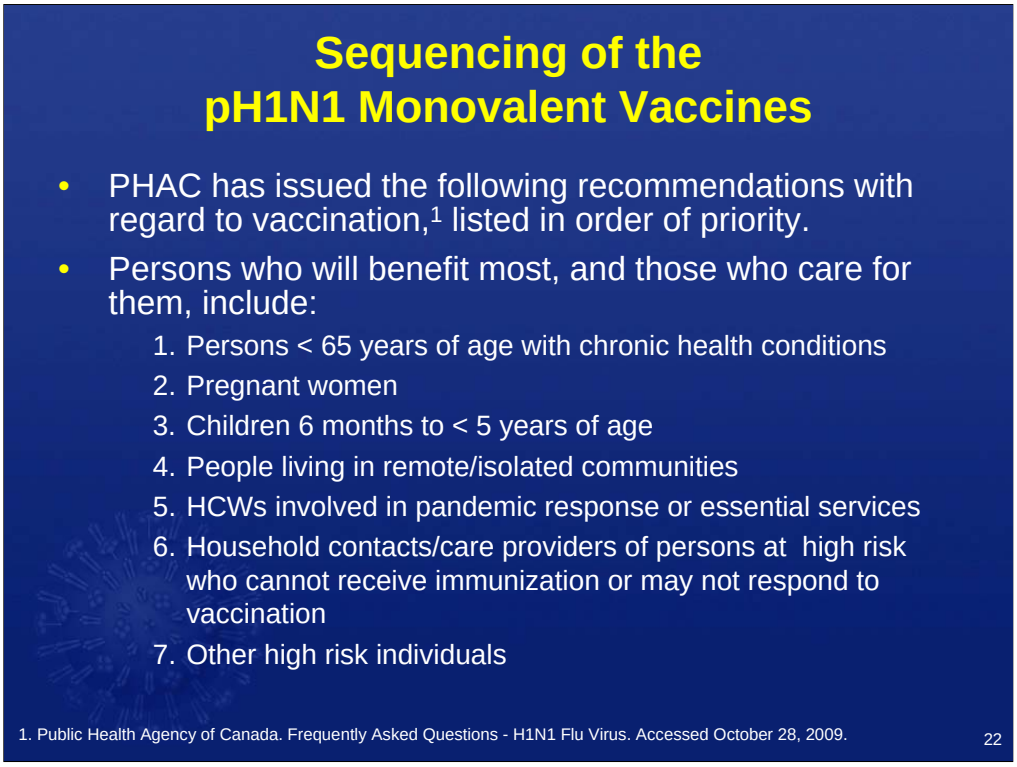
References:

1. Health Canada. Product Information Leaflet Arepanrix™ H1N1 AS03-Adjuvanted H1N1 Pandemic Influenza Vaccine; October 21, 2009. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/legislation/interimorders-arretesurgence/prodinfo-vaccin-eng.php. Accessed October 28, 2009.

2. Health Canada. Questions and Answers on Influenza A (H1N1) 2009 Pandemic Vaccine Arepanrix™ H1N1; October 21, 2009. http://www.hc-sc.gc.ca/dhp-mps/prodpharma/legislation/interimorders-arretesurgence/faq-vaccin-eng.php. Accessed October 28, 2009.

3. Health Canada. Health Canada Approves Pandemic H1N1 Flu Vaccine for Canadians; October 21, 2009. http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/_2009/2009_171-eng.php. Accessed October 26, 2009.

4. Public Health Agency of Canada. Frequently Asked Questions - H1N1 Flu Virus; October 20, 2009. http://www.phac-aspc.gc.ca/alert-alerte/h1n1/faq_rg_h1n1-eng.php#vac. Accessed October 28, 2009.

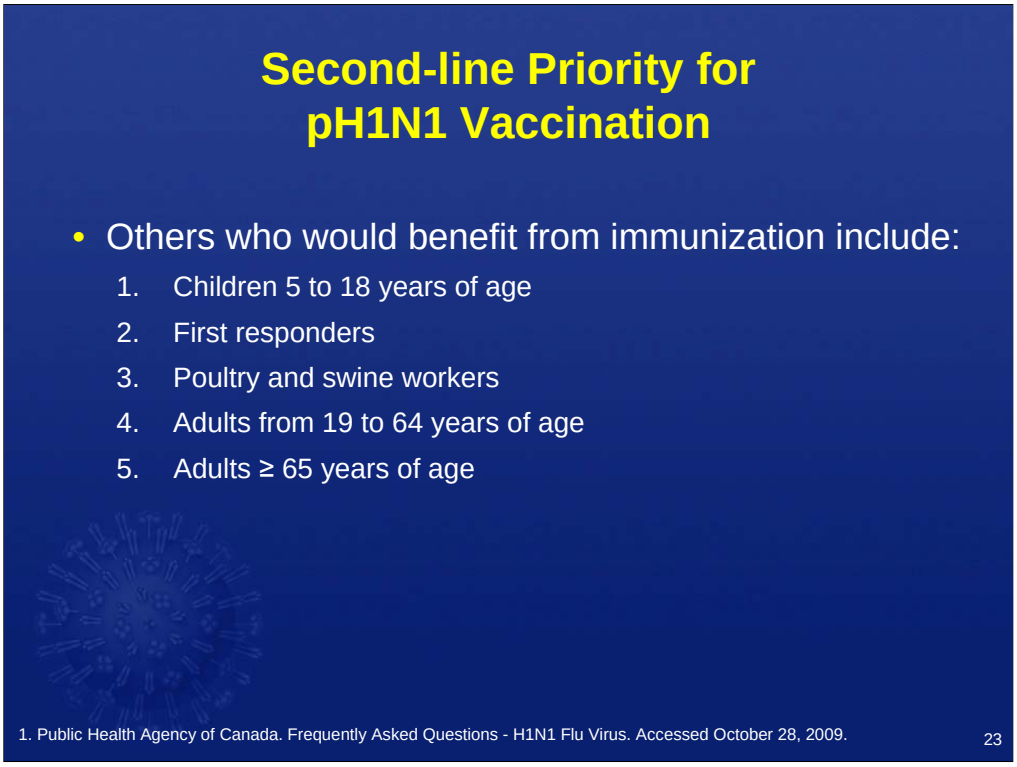


PHAC has issued the following recommendations with regard to vaccination,[1(p5)] listed in order of priority. Those persons who will benefit most from vaccination, or from vaccination of persons who care for them, should be vaccinated first. This group includes:

1. Persons < 65 years of age with chronic health conditions,
2. Pregnant women,
3. Children 6 months to < 5 years of age,
4. People living in remote or isolated communities,
5. Health care workers (HCWs) involved in pandemic response or providing essential services,
6. Household contacts or care providers of persons at high risk who cannot receive immunization or may not respond to vaccination, and
7. Other high risk individuals.

Reference:

1. Public Health Agency of Canada. Frequently Asked Questions - H1N1 Flu Virus; October 20, 2009. http://www.phac-aspc.gc.ca/alert-alerte/h1n1/faq_rg_h1n1-eng.php#vac. Accessed October 28, 2009.



Should remaining vaccines supplies exist following immunization of all high risk individuals listed on the previous slide, then the following additional groups should be considered for vaccination, as they may also benefit from immunization[1(p5)]:
1. Children 5 to 18 years of age,
2. First responders,
3. Poultry and swine workers,
4. Adults from 19 to 64 years of age, and
5. Adults ≥ 65 years of age.

Reference:

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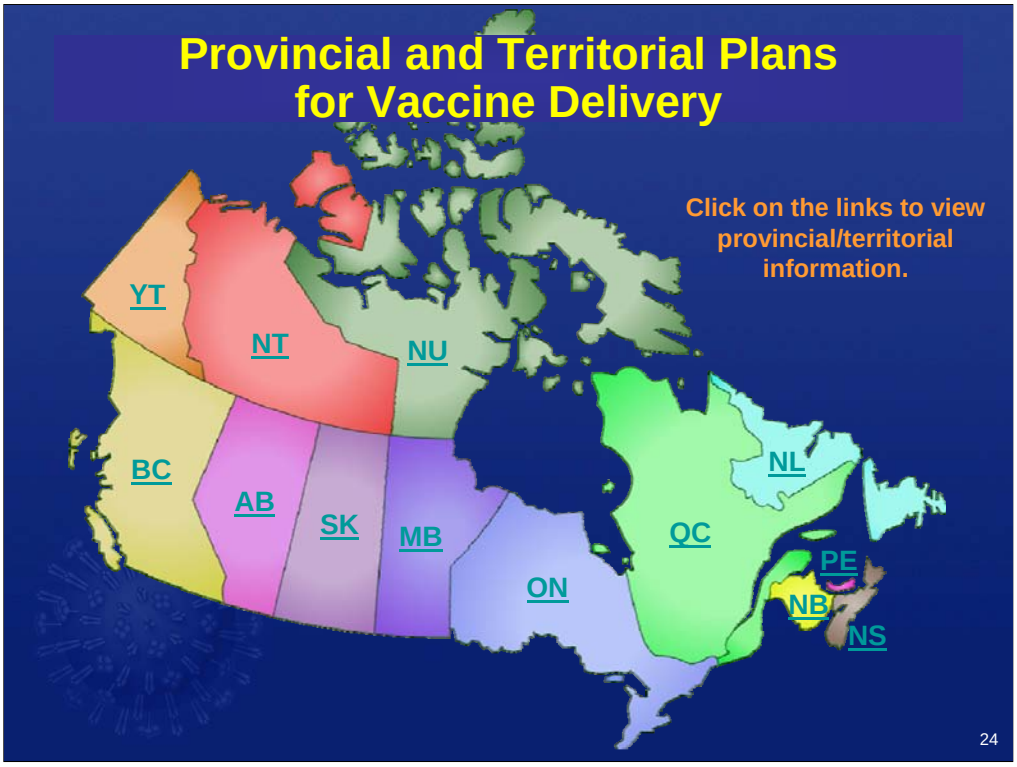

Each province or territory has established their own plans for influenza vaccination this season. Several jurisdictions indicate that the seasonal influenza vaccine will be offered in October to persons > 65 years of age and residents of long-term care facilities, followed by the pH1N1 vaccine to all persons when it becomes available.[1,2,4-11] Alberta, and Newfoundland and Labrador will also provide the seasonal flu vaccine to additional residents at high risk of influenza-related complications.[7,9] Quebec has chosen to reverse the vaccination order, first providing the pH1N1 vaccine when it becomes available and then the seasonal flu vaccine in January 2009.[3] New Brunswick plans to offer both the seasonal and pH1N1 vaccines to all of its residents,[13] while Nunavut will supply the pH1N1 vaccine.[12]

References on the next page.

References: Vaccination Plan

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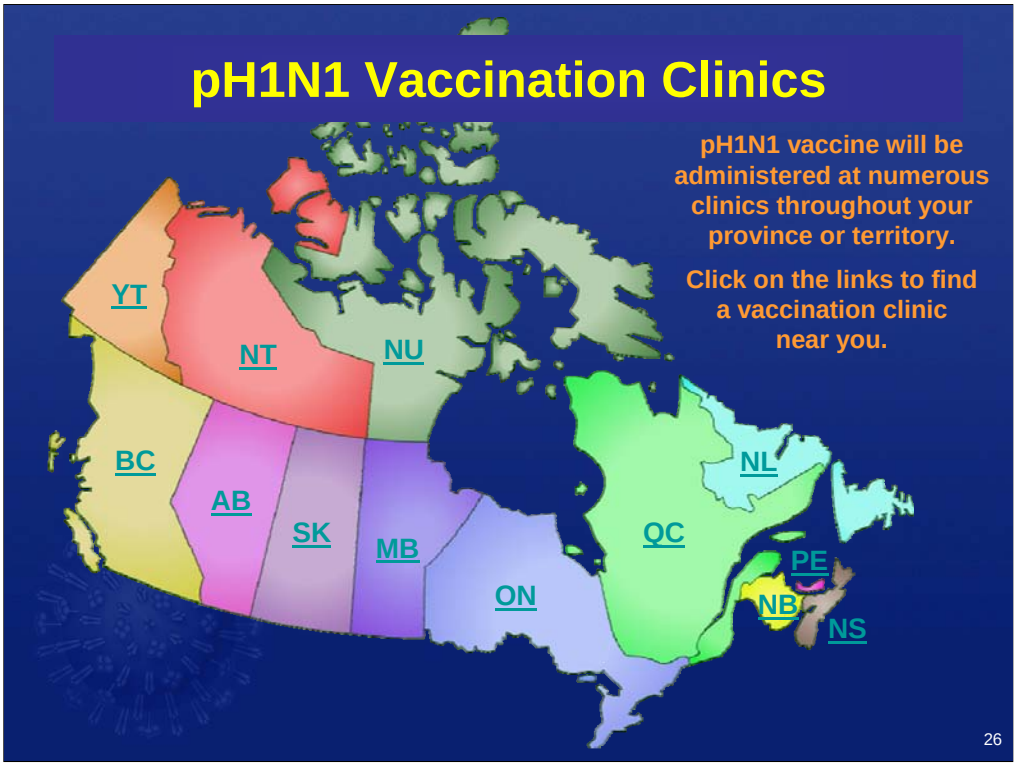

pH1N1 vaccine will be administered at various regional health clinics in your province or territory based on the sequencing guidelines set forth by PHAC. The links on this slide will direct you to information on where you can find your local vaccination clinic.

References on the next slide.

References: Vaccination Clinics

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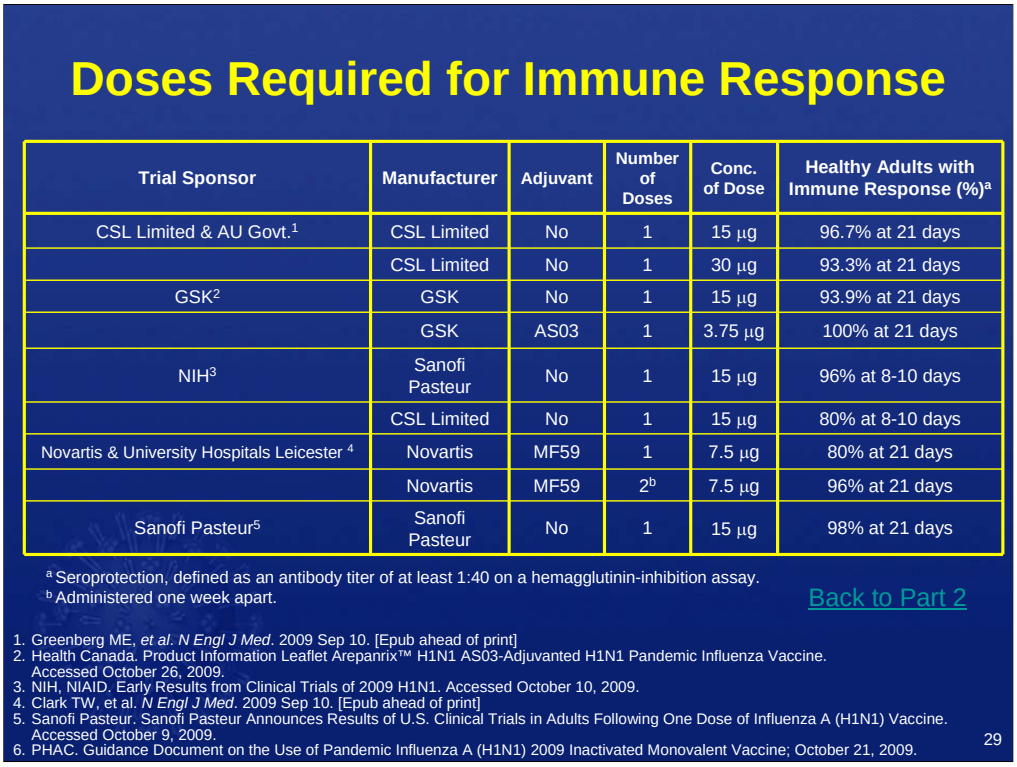
Appendix



Several clinical trials have been initiated in the last few months to test the safety, efficacy and required doses of the pH1N1 vaccine.[1-5] Data shown here report immunogenicity as the percentage of subjects with antibody titers of at least 1:40 on a hemagglutination-inhibition assay. These results suggest that a single 15 μg dose of unadjuvanted vaccine will provide seroprotection against pH1N1 in at least 93.9% of vaccinated subjects after 21 days.[1,2,5] Testing with adjuvanted vaccines shows that reduced antigen concentrations (3.75 to 7.5 μg) may provide seroprotection in a single dose,[2,4] yet one study indicates that the percentage of subjects with an immune response after 21 days is elevated with two doses administered one week apart.[4] In Canada, current guidelines suggest that for adults, a single dose of adjuvanted vaccine containing 3.75 μg of antigen should be given.[6]

References:

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