



NOVEMBER 5, 2009

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

Use of Panvax[®] H1N1 Vaccine (CSL Biotherapies Inc.) (Unadjuvanted)

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 unadjuvanted pandemic H1N1 vaccine for pregnant women. 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 Addendum provides guidance regarding the use of Panvax[®] H1N1 vaccine (CSL Biotherapies Inc.). It is supplementary to the *Guidance Document on the Use of Pandemic Influenza A (H1N1) 2009 Inactivated Monovalent Vaccine*¹ recently published by the Public Health Agency of Canada (PHAC). Please refer to that document for additional information on the epidemiology of pandemic H1N1 human influenza (pH1N1), general recommendations for the use of pH1N1 vaccines (including use in pregnant women) and adverse reactions to influenza vaccines.

Canada has authorized access to Panvax[®] H1N1 vaccine to ensure that pregnant women are able to receive an unadjuvanted vaccine on a timely basis. Panvax[®] has been approved for use in Australia and the United States.

PRODUCT DESCRIPTION

Panvax[®] H1N1 vaccine is produced by CSL Biotherapies Inc. It is a purified, inactivated, monovalent, split virus vaccine. Panvax[®] is prepared from influenza virus propagated in eggs. It does not contain an adjuvant.

Each 0.5 mL dose contains 15 ug haemagglutinin (HA) derived from A/California/7/2009 (H1N1)v., 50 µg of thimerosal and trace residual amounts of egg proteins, sodium taurodeoxycholate, neomycin, polymixin B sulphate, beta-propiolactone and sucrose.²

Panvax[®] H1N1 vaccine is manufactured by the same process as CSL's seasonal trivalent influenza vaccine, which is marketed as Fluvax[®] in Australia and Afluria[®] in the United States.

IMMUNOGENICITY AND EFFICACY

Data from a single phase II clinical trial of Panvax[®] H1N1 vaccine have recently been published.³ Results from trials in children and adults 65 years of age and over are not yet available.

Greenberg et al³ report preliminary findings from a randomized, observer-blind, parallel-group trial conducted at a single site in Adelaide, Australia. Healthy, non-pregnant adults (N=240), age 18-64 years, were randomized to receive a single dose of vaccine containing either 15 µg or 30µg of HA. Serum antibody response was assessed by haemagglutination inhibition (HI) and viral microneutralization (MN) assays.

Results for both antigen doses were similar. Post-vaccination titres of ≥1:40 on day 21 by HI assay were observed in 96.7% (95% CI: 91.7-98.7) of recipients of the 15 µg dose. A substantial rise in geometric mean titres (GMTs) was also observed following vaccination. However, age differences were noted whereby those ≥50 years achieved numerically lower (but not significant) factor increases in GMT compared to those <50 years. This age-related effect was reflected in all measures of immunogenicity.

Table 1: Immune response after one dose (15 µg) of Panvax[®], as measured on hemagglutination-inhibition assay (HI)* 2,3

Immunogenicity end point	18-49 yrs (N=58)	50-64 yrs (N=62)	All ages (N=120)
Subjects with HI titre ≥1:40 (95% CI)	100% (93.8-100)	93.5% (84.6-97.5)	96.7% (91.7-98.7)
Subjects with seroconversion or significant increase in titre (95% CI)	75.9% (63.5-85.0)	66.1% (53.7-76.7)	70.8% (62.2-78.2)
Geometric mean titre (GMT) (95% CI)	306.9 (228.2-412.7)	157.0 (120.8-204.2)	217.1 (177.1-266.1)
Factor increase in GMT (95% CI)	14.3 (9.4-22.0)	8.1 (5.4-12.2)	10.7 (8.0-14.3)

* The immunogenicity end points were the proportion of subjects who had an antibody titer of 1:40 or more, the proportion of subjects who had either seroconversion (a pre-vaccination titer of less than 1:10 with a post-vaccination HI antibody titer of 1:40 or more) or an increase by a factor of four or more in antibody titer, and the factor increase in the geometric mean titer.

RECOMMENDATIONS FOR USE OF INFLUENZA A (H1N1) 2009 VACCINE

Panvax[®] H1N1 vaccine is indicated for use in adults, adolescents and children 10 years of age and older. However, in Canada, the vaccine has been specially acquired to ensure access to unadjuvanted vaccine for pregnant women.

Use of unadjuvanted vaccine for pregnant women is the preferred option in Canada, given that there are more safety data on the use of unadjuvanted seasonal influenza

vaccines in pregnant women.^{1,4} While Panvax[®] H1N1 vaccine has not been specifically studied in pregnant women, there is a long history of the safe use of unadjuvanted influenza vaccine in pregnant women in Canada and elsewhere. For more information regarding the use of influenza vaccine during pregnancy please refer to the *Guidance Document on the Use of Pandemic Influenza A (H1N1) 2009 Inactivated Monovalent Vaccine*¹ and the *Recommendations for pH1N1 Vaccine in Pregnancy*.⁴

SCHEDULE AND DOSAGE

A single dose (0.5 mL) is recommended for adults, adolescents and children older than 10 years of age.

ROUTE OF ADMINISTRATION

Panvax[®] H1N1 vaccine should be administered by intramuscular injection. The deltoid muscle is the recommended site in adults.

ADVERSE REACTIONS

No deaths, serious adverse events, or adverse events of special interest resulting from administration of Panvax[®] H1N1 were reported by Greenberg et al in their trial of 240 healthy adults.³ Further data collection related to unsolicited adverse events is ongoing.

Local adverse events were reported among 46.3% (95% CI, 40.1-52.6) of subjects (94.6% graded as mild), the most common of which were injection-site tenderness (36.7%); pain (21.7%); redness (9.2%); induration (8.8%); and ecchymosis (5.0%).

Systemic adverse events reported among 45.0% (95% CI, 38.8-51.3) of subjects with 30.4% considered related to H1N1 vaccine. Headache (31.3%) followed by malaise (17.5%); myalgia (17.1%); nausea (7.1%); chills (6.7%); fever (3.8%) and vomiting (0.8%) were the most frequently reported.

Two reported adverse events were graded as severe: one with vaccine-related myalgia, malaise, nausea resolving after 5 days; one with non-vaccine-related nausea from day 6-10. Three subjects had an influenza-like illness (ILI) following vaccination, one of whom tested positive for pH1N1 on day 8 post-vaccination.

There are currently no published post-marketing data available for Panvax H1N1 vaccine. It is anticipated that the adverse events after vaccination will be similar to those spontaneously reported during post-approval use of CSL's seasonal influenza vaccine, Fluvax[®] / Afluria[®]. The seasonal vaccine is manufactured by CSL Biotherapies Inc. using the same process.

The following data reflect experience in children and adults with Fluvax[®]/Afluria[®], vaccine. Adverse event frequencies are defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10\ 000$ and $< 1/1000$) and very rare ($< 1/10\ 000$).). Most adverse events have been mild injection site or systemic reactions. Other reported adverse events include: transient thrombocytopenia (rare); allergic reactions including anaphylactic shock (rare);

neuralgia, paraesthesia and convulsions (rare); encephalitis, neuritis or neuropathy and Guillain-Barré syndrome (very rare); vasculitis with transient renal involvement (very rare); and pruritus, urticaria and rash (uncommon).^{2,5}

CONTRAINDICATIONS

Panvax[®] is contraindicated in individuals with known anaphylactic hypersensitivity to eggs or any other component of the vaccine including thimerosal, neomycin, or polymyxin B sulfate.

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 stopper used for Panvax[®] H1N1 vaccine is latex-free, latex allergy is not a contraindication to receipt of this vaccine.

PRECAUTIONS

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.

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 Guillain-Barré syndrome (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.

The immune response to Panvax[®] may be diminished among immunocompromised persons, including those receiving immunosuppressive therapy.

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

There are currently no data to assess the concomitant administration of Panvax[®] with other vaccines. If Panvax[®] H1N1 vaccine is to be given at the same time as another injectable vaccine (such as seasonal influenza vaccine), the vaccines should be administered at different injection sites. If not given concurrently, there is no minimum interval required between the two influenza vaccines.

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 ADMINISTRATION

Panvax[®] H1N1 vaccine should be stored, protected from light, at 2°C to 8°C and should not be frozen.

It is important that the contents of the container be shaken thoroughly immediately before use. The vaccine should appear as a clear to slightly opaque liquid with some sediment that re-suspends upon shaking.

Additional conditions for the use of multi-dose vials are:

- The Australian leaflet² (that accompanies the shipment) states that the vaccine should be used within 24 hours once the stopper has been pierced. A leaflet that has been approved in the U.S.⁵ (based primarily on the seasonal version of the CSL vaccine) states that the shelf life would be 28 days once the stopper has been pierced if stored under cold chain. Each jurisdiction is free to make its own decision about the use within the 28 day period.
- aseptic technique must be used to withdraw each dose, using a separate sterile needle and syringe
- following withdrawal of vaccine from the vial, the syringe must be used within the one vaccination session (up to a maximum time interval of 4 hours) and cannot be stored for use at a later date
- at the end of the 24 hour period, any remaining contents within the vials should be discarded in accordance with local requirements.

REFERENCES

¹ Public Health Agency of Canada. 2009. Guidance Document on the Use of Pandemic Influenza A (H1N1) 2009 Inactivated Monovalent Vaccine. Available at <http://www.phac-aspc.gc.ca/alert-alerte/h1n1/vacc/pdf/monovacc-guide-eng.pdf>. Accessed October 26, 2009.

² CSL Ltd. Panvax[®] H1N1 Vaccine [Product Information]. Melbourne, Australia: CSL Limited. 2009. Available from: <http://secure.healthlinks.net.au/content/csl/pi.cfm?product=csppanva10909>.

³ Greenberg ME, Lai MH, Hartel GF, et al. Response after one dose of a monovalent influenza A (H1N1) 2009 vaccine---preliminary report. N Engl J Med 2009 [E-pub]. Available at <http://content.nejm.org/cgi/reprint/NEJMoa0907413.pdf?resource-type=HWCIT>. Accessed October 7, 2009.

⁴ Public Health Agency of Canada, 2009. Recommendations for pH1N1 Vaccine in Pregnancy. Available at <http://www.phac-aspc.gc.ca/alert-alerte/h1n1/vacc/pregvacc-grossvacc-eng.php>. Accessed November 2, 2009.

⁵ CSL Biotherapies Inc. Influenza A (H1N1) 2009 Monovalent Vaccine. [Package Insert]. King of Prussia, PA: CSL Biotherapies Inc. 2009. Available from: <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM182401.pdf>.