

Pandemic H1N1 2009 influenza

PANDEMIC H1N1 2009 INFLUENZA VACCINE FOR AUSTRALIANS: INFORMATION FOR IMMUNISATION PROVIDERS

Disease and epidemiology

- Pandemic H1N1 2009 (pH1N1) influenza is a novel strain of influenza A virus that is genetically distinct from previously circulating seasonal H1N1 viruses. Antibodies against seasonal H1N1 influenza do not provide protection against the pandemic strain.
- The first cases of pH1N1 influenza were identified in North America in April 2009. In June 2009, the World Health Organization declared a pandemic with countries around the world confirming infections with the novel H1N1 strain.
- An infection with pH1N1 influenza can be variable in severity from asymptomatic to severe clinical disease. The most common symptoms are similar to those of seasonal influenza, and include fever, cough, sore throat, rhinorrhoea, headache, chills, shortness of breath and myalgia.
- Evidence shows that hospitalisation rates from pH1N1 influenza were higher for younger age groups compared with rates of seasonal influenza.
- Higher rates of complications following pH1N1 infection were also observed among pregnant women, Aboriginal and Torres Strait Islander people, and obese patients.
- It is likely, but not certain, that pH1N1 will be the main influenza strain circulating throughout the 2010 influenza season in Australia.

Vaccines

- A monovalent vaccine against pH1N1 influenza (Panvax[®], CSL Limited) has been available in Australia for people aged 10 years or older since September 2009. In December 2009, the vaccine was also registered for children from 6 months to 9 years of age.
- The 2010 seasonal trivalent influenza vaccine contains the pH1N1 influenza strain (A/H1N1), as well as two additional strains (an A/H3N2 and a B strain).
- Both Panvax[®] and the 2010 seasonal influenza vaccine can be used to provide protection against pH1N1 influenza.
- Panvax[®] is available free to all Australians under a special government program. The seasonal 2010 influenza vaccine is only available free of charge for people with risk factors for severe influenza as funded by the National Immunisation Program.

Who should be vaccinated?

- Priority groups for vaccination against pH1N1 influenza include people with chronic medical conditions, the severely obese (BMI ≥ 35), pregnant women, Aboriginal and Torres Strait Islander people, and those who are more likely to transmit influenza to vulnerable people.
- Panvax[®] is recommended for any person ≥ 6 months of age who wishes to be protected against pH1N1 influenza, unless there is a contraindication.
- Panvax[®] is an inactivated split virion vaccine made in the same way as seasonal influenza vaccines. Because the vaccines are produced in the embryos of chicken's eggs, vaccination of people with previous severe allergies (anaphylaxis) to egg is not recommended.

Pandemic H1N1 2009 influenza disease

Infection with the novel pandemic H1N1 2009 (pH1N1) influenza A strain was first identified in the USA in April 2009.¹ This virus was then identified in clinical specimens obtained from March 2009 in various parts of Mexico. Within the following few months, this virus strain spread rapidly through North America, South America, Australia, Europe and Asia.² In June 2009, the World Health Organization declared a pandemic. At that time, 74 countries and territories around the world had reported confirmed cases of pH1N1 influenza.

The first case of pH1N1 influenza in Australia (that did not have a history of overseas travel) was identified on 16 May 2009. As of 19 February 2010, there were 37,636 confirmed cases of pH1N1 influenza notified in Australia in 2009.³

Clinical features

Pandemic H1N1 influenza illness has symptoms similar to seasonal influenza. These include fever, cough, sore throat, rhinorrhoea, headache, chills, shortness of breath and myalgia. Fever is the most common symptom reported in confirmed cases. However, in a small proportion of infections fever is absent.⁴⁻⁶ In comparison with seasonal influenza, gastrointestinal symptoms such as vomiting and diarrhoea appear to be more common, recorded in up to 39% of cases.^{5,6}

The complications from pH1N1 influenza infection appear to be similar to those from seasonal influenza, with some notable exceptions. Recognised complications include pulmonary (including asthma exacerbation), cardiac, exacerbation of pre-existing chronic medical conditions, and neurological sequelae.⁷ In comparison with seasonal influenza, the pandemic has been notable for:

- a higher rate and increased severity of complications among pregnant women and their offspring⁸⁻¹¹
- an increase in the number of and severity of illness in intensive care unit (ICU) admissions (particularly in younger aged persons)¹²
- an increase in the rate of severe disease among moderate to severely obese patients.¹¹⁻¹⁶

Diagnosis

Pandemic H1N1 is a novel strain of influenza A which is antigenically different to seasonal H1N1 strains. Rapid antigen tests specific for influenza A can be used to detect pH1N1; however, these tests are not able to differentiate pH1N1 from other influenza A subtypes (including H3 influenza A).^{17,18} Molecular diagnostic testing, such as polymerase chain reaction (PCR), is more sensitive, and

can differentiate pH1N1 virus from other seasonal influenza A viruses.^{19,20} Specimens identified as positive for influenza A by rapid antigen test can be confirmed and sub-typed by PCR-based methods.

Epidemiology of pandemic H1N1 2009 influenza in Australia

As of 19 February 2010, nearly 5,000 people have been reported as hospitalised in Australia with confirmed pH1N1 influenza. Of those hospitalised, 14% (681/4,992) have been admitted to an intensive care unit. There have been 191 deaths recorded among those with confirmed pH1N1 influenza.³ In most age groups, except for the elderly, the number of cases requiring hospitalisation for confirmed pH1N1 influenza in 2009 was higher than for seasonal influenza. In particular, a higher proportion of young adults infected with pH1N1 influenza developed severe illness that required ICU admission compared with seasonal influenza. These trends are consistent with those observed overseas.

Specific groups that are at higher risk of serious disease following pH1N1 influenza infection have been identified. Indigenous Australians are >6 times more likely to be hospitalised with pH1N1 influenza than non-Indigenous Australians.⁸ Pregnant women are also over-represented among the more severe cases; 32% of women aged 20–39 years who required hospitalisation for the disease were pregnant, and their risk of hospitalisation was estimated to be >5 times that of non-pregnant women of child-bearing age.⁸ Chronic lung disease was the most common co-morbidity among hospitalisations, ICU admissions and deaths associated with confirmed pandemic influenza.

It is important to note that a considerable proportion of patients with severe disease (45% of those hospitalised, 24% of those admitted to an ICU, and 34% of deaths) were not from a high-risk group (Indigenous, pregnant or presenting with at least one co-morbidity).³

Vaccination against pandemic H1N1 2009 influenza

For the 2010 influenza season, two influenza vaccine formulations are available: the pH1N1 influenza vaccine (Panvax[®]) and the 2010 seasonal trivalent influenza vaccine. While Panvax[®] only provides protection against pH1N1 influenza, the 2010 seasonal vaccine will provide protection against the pH1N1 strain as well as two additional influenza strains (A/H3 and B). Pandemic

H1N1 is likely to be the predominant influenza strain that will circulate in Australia in the 2010 influenza season.

Vaccination against pH1N1 influenza is recommended for all Australians ≥ 6 months of age who wish to be protected against it. People with medical conditions that increase their risk of severe influenza or complications should not delay receiving influenza immunisation. Information on both influenza vaccines available in 2010 is outlined below.

Panvax[®]

The pH1N1 influenza vaccine, Panvax[®] (CSL Limited, Parkville, Australia), is currently registered by the Therapeutic Goods Administration (TGA) in Australia. It has been registered for use in people 10 years of age or older since September 2009, and for children aged 6 months to 9 years since December 2009.

Panvax[®] is a monovalent inactivated split virion vaccine. The techniques used in manufacturing Panvax[®] are similar to the standard chicken egg-based culture techniques used for manufacturing the seasonal influenza vaccines.²¹ Each 0.5 mL dose contains 15 μg of the haemagglutinin antigen derived from the A/California/2009 (H1N1) virus, the pandemic strain. Panvax[®] does not contain any adjuvants, unlike some pH1N1 influenza vaccines registered overseas.

Immunogenicity

The results of two randomised clinical trials conducted in Australia that assessed the immunogenicity and safety of Panvax[®] have been published. The first study recruited adult subjects 18–64 years of age,²¹ whereas the second study assessed Panvax[®] in children aged 6 months to 9 years.²² Both trials assessed two dosages (15 μg and 30 μg) of hemagglutinin antigen in a two-dose immunisation regimen (administered 21 days apart). In both studies, a single 15 μg dose of Panvax[®] resulted in a robust antibody response as measured by multiple methods, including hemagglutination inhibition antibody titres (HI titre) to the H1N1 antigen. The percentage of study participants in these two studies with an HI titre equal to or greater than 1:40 (a commonly used indicator for seroprotection against influenza in clinical studies) are summarised in Table 1.

Data on duration of protection following Panvax[®] vaccination are not yet available. However, there is some evidence that suggests vaccination with seasonal influenza vaccine may continue to have a protective effect against non-drifted strains for up to three subsequent influenza seasons.²³ It is expected that the protection gained after receiving Panvax[®] from late 2009 onwards will extend throughout the 2010 influenza season.

Table 1. Percentage of study participants who developed an HI titre $\geq 1:40$ three weeks after each dose of Panvax[®]: summary of data from two independent randomised trials^{21,22}

Age group	Vaccine dosage (μg)	1st dose	2nd dose
		Subjects with HI titre $\geq 1:40$ % [95% CI]	Subjects with HI titre $\geq 1:40$ % [95% CI]
18–64 years	15	95.0 [89.4–98.1]	98.3 [94.0–99.8]
	30	89.1 [82.0–94.1]	96.5 [91.3–99.0]
3–9 years	15	92.9 [86.0–96.5]	100 [96.1–100]
	30	96.0 [90.1–98.4]	100 [96.2–100]
6–35 months*	15	92.1 [83.8–96.3]	100 [94.3–100]
	30	100 [95.0–100.0]	100 [94.7–100]

* At the time of preparation of this fact sheet, a clinical trial assessing the immunogenicity and safety of Panvax[®] in children aged 6–35 months using a dosage of 7.5 μg (the dosage recommended for children of this age) has been completed, but has not yet been published.

Vaccine safety

Safety data from the clinical trials of Panvax[®] and also from post-licensure surveillance of adverse events following immunisation with Panvax[®] suggest that the type and frequency of adverse events seen in adults and children are consistent with observations following seasonal influenza vaccination.^{21,22,24}

In adults, no serious adverse events were recorded in study participants. The most commonly reported adverse events were local injection site reactions, with 56.3% of subjects reporting at least one solicited local adverse event after the first or second vaccine dose.²¹ In addition, at least one systemic adverse event, such as headache, malaise and myalgia, was reported by 53.8% of subjects. The majority of adverse events were classed as mild. Some adverse events were more likely to occur in the participants who received the 30 µg dose than in those who received the 15 µg dose (the current recommended dose if aged ≥3 years).

The safety profile of Panvax[®] in children aged 6 months to 9 years was consistent with that observed in adults. Following the first vaccine dose, 57.5% of participants reported an adverse event.²² Pain at the injection site was the most commonly reported event. Common systemic adverse events included fever and irritability. Higher proportions of participants reporting fever were observed in the 30 µg group (41%) than in the 15 µg group (23.9%).

Dosage and administration

Panvax[®] is administered intramuscularly. The required dosage varies for different age groups as outlined in Table 2.

Table 2. Recommended doses of Panvax[®]

Age group	Doses	Quantity of each dose
Adults and children ≥10 years of age	1	0.5 mL (15 µg)
Children 3–9 years of age	2*	0.5 mL (15 µg)
Children 6–35 months of age	2*	0.25 mL (7.5 µg)

*Each dose to be administered 28 days apart.

Co-administration of Panvax[®] with other vaccines

There are no clinical trial data available specifically addressing the co-administration of Panvax[®] with other

vaccines. However, randomised clinical trials and observational studies on the co-administration of seasonal influenza vaccine with other vaccines have not identified any increased risk of adverse event or any significant reduction in immunogenicity.²⁵⁻²⁷ Based on this evidence, no specific safety concerns are expected following co-administration of Panvax[®] with other vaccines.

If Panvax[®] is to be given at the same time as another injectable vaccine, the two vaccines should be administered at different injection sites.

Interchangeability of Panvax[®] with other pandemic influenza vaccine formulations in children who require two doses

Currently Panvax[®] is the only pH1N1 influenza vaccine formulation licensed in Australia; however, there are different pH1N1 influenza vaccine formulations available overseas. Where feasible, the same formulation of vaccine should be used where a two-dose schedule is required. It is not advisable to routinely use different formulations for children who require two doses, as there are no data on safety or immunogenicity of mixed schedules, particularly the mixing of a non-adjuvanted with an adjuvanted vaccine or a live attenuated with an inactivated vaccine in the schedule.

Nevertheless, if a child has had a non-adjuvanted vaccine from another manufacturer, a second dose in Australia of Panvax[®] would be anticipated to provide a good boost response (and vice versa). If the first dose has been with an adjuvanted or live attenuated vaccine, a potential second dose with Panvax[®] should, on first principles, give a good boost response and a satisfactory protective response is likely.

Priority groups for vaccination with Panvax[®]

Any Australian who wants to be protected against pH1N1 influenza is able to receive Panvax[®] free of charge from their immunisation provider. It is particularly important that individuals who are at high risk of complications following infection with pH1N1 influenza be vaccinated as soon as possible. These at-risk groups include:

- people with chronic medical conditions, including:
 - cardiac disease
 - chronic respiratory disease (including asthma and COPD)
 - diabetes mellitus

- chronic metabolic disease
- chronic renal disease
- haemoglobinopathies
- impaired immunity from disease or treatment (including cancers, HIV/AIDS infection, transplant recipients)
- chronic neurological conditions
- severe obesity (BMI ≥ 35)
- pregnant women
- Aboriginal and Torres Strait Islander people
- those with increased risk of transmitting infection to people vulnerable to severe influenza, including:
 - health care workers or those who come in contact with at risk persons
 - people living in remote and isolated communities with vulnerable people
 - parents and guardians of infants up to 6 months old
 - children in special schools.

2010 seasonal trivalent influenza vaccine

Pandemic influenza A/H1N1 strain has been included in the 2010 seasonal influenza vaccine along with two other influenza strains (A/H3 and B). The seasonal influenza vaccine is funded under the National Immunisation Program (NIP) for people with risk factors as outlined in the *Immunise Australia Fact sheet for immunisation providers: influenza vaccination 2010*, available at:

[http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/IMM123-cnt/\\$File/imm123-fs-2010.pdf](http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/IMM123-cnt/$File/imm123-fs-2010.pdf)

From 2010, the seasonal influenza vaccine will also be available under the NIP for all children and adults aged from 6 months with specified medical conditions that increase their risks of severe influenza or complications.

People who are not eligible for free seasonal influenza vaccine under the NIP who want to be protected against influenza in 2010 may choose to:

- a) receive the free pH1N1 influenza vaccine Panvax[®], which is currently available, to obtain protection against pH1N1 influenza
- b) receive the seasonal influenza vaccine through private means to obtain protection against pH1N1 influenza as well as two additional subtype strains of influenza (A/H3 and B).

Recommended use of Panvax[®] and the 2010 seasonal trivalent influenza vaccine

a) Children ≥ 6 months and < 10 years of age

A summary of the dose recommendations by the Australian Technical Advisory Group on Immunisation (ATAGI) for pH1N1 and seasonal 2010 influenza vaccination for children between 6 months and 10 years of age can be found at:

<http://www.healthemergency.gov.au/internet/healthemergency/publishing.nsf/Content/national-vaccination-program#atagi>

An overview of these recommendations is listed below.

1. For children aged ≥ 6 months to < 10 years who plan to receive seasonal influenza vaccine in 2010:
 - a. If the child has received two or more doses of seasonal influenza vaccine in previous years, the recommendations are
 - one dose of 2010 seasonal vaccine as soon as practicable (consistent with the current advice on the use of seasonal influenza vaccine)
 - one dose of Panvax[®] ≥ 28 days after the 2010 seasonal vaccine is advisable if the child is immunocompromised because of a medical disease or medical treatment.
 - b. If the child has never received, or only received one dose of, seasonal influenza vaccine in previous years, the recommendation is
 - two doses of 2010 seasonal influenza vaccine, separated by at least 1 month, ≥ 28 days.
2. For children aged ≥ 6 months to < 10 years who are not planning to receive the 2010 seasonal influenza vaccine but desiring to achieve immune protection against pH1N1 influenza, the recommendation is
 - two doses of Panvax[®], ≥ 28 days apart.

b) People ≥ 10 years of age

Adults and children ≥ 10 years of age require one dose of pH1N1-containing vaccine. If a person has already received a single dose of Panvax[®] no additional vaccine is required for protection against pH1N1 influenza. It is expected that protection from a single Panvax[®] vaccination will persist well past the 2010 influenza season.

If a person has previously received Panvax[®] and wants to receive the 2010 seasonal vaccine for protection against the additional influenza strains, it is safe to do so. There are no time restrictions regarding the dose interval between vaccination with Panvax[®] and the

2010 seasonal influenza vaccine. If these two vaccines are given at least a month apart, an immunological boosting effect against pH1N1 influenza may occur, although this is not considered necessary.

Special issues relevant to Panvax®

Use of multi-dose vials

The majority of Panvax® doses are supplied by the manufacturer in multi-dose vials. The *Guideline for the administration of pandemic (H1N1) influenza vaccine from multi-dose vials (MDV)* has been issued by the Australian Government Department of Health and Ageing in conjunction with The Royal Australasian College of General Practitioners. The guideline is available at:

<http://www.healthemergency.gov.au/internet/healthemergency/publishing.nsf/Content/national-vaccination-program#atagi>

Thiomersal in the multi-dose formulation of Panvax®

The multi-dose vial formulation of Panvax® contains a very small quantity of thiomersal. Thiomersal is a mercury-containing organic compound, which is included as a preservative in vaccines presented in multi-dose vials to retard bacterial and fungal growth and to prevent vial contamination.²⁸ Single dose preparations of Panvax® do not require the use of preservatives and hence do not contain thiomersal. Influenza vaccines containing thiomersal are safe in infants, children, adolescents and adults (including pregnant women). This is based on consistent safety data from several laboratory and clinical studies and the conclusions of independent systematic reviews. Advice from ATAGI on this matter, *ATAGI advice regarding the use of influenza vaccines containing thiomersal*, is available at:

<http://www.healthemergency.gov.au/internet/healthemergency/publishing.nsf/Content/national-vaccination-program#atagi>

Is it safe to give Panvax® to pregnant women?

Based on the morbidity resulting from pH1N1 influenza virus infection in pregnant women in Australia and worldwide, it is recommended that pregnant women receive the pH1N1 influenza vaccine as a matter of priority. Vaccination of pregnant women may also benefit their newborn infants who are not eligible for vaccination until ≥ 6 months of age.

Safety data on inactivated non-adjuvanted seasonal influenza vaccine administered to pregnant women are increasing. No increase in risks of teratogenicity or

fetal or neonatal adverse events has been reported.²⁹

Administration of seasonal influenza vaccine to pregnant women is recommended in the USA and also Australia.³⁰ The available passive surveillance safety data have not raised any concerns.³¹ ATAGI considers that it is safe for women to receive the seasonal influenza vaccine in pregnancy, and considers it appropriate to infer from the safety information of seasonal influenza vaccine that the pH1N1 influenza vaccine is safe for use in any stage of pregnancy. Specific immunogenicity and safety data on the use of pH1N1 influenza vaccine in pregnancy should soon become available.

Use of Panvax® in people with impaired immunity

There is no specific immunogenicity or safety data available on the use of Panvax® in people with impaired immunity. However, because Panvax® is an inactivated vaccine, there are no specific safety concerns. The immune response to Panvax® in people with impaired immunity may be less than that expected in healthy individuals. Clinical trials on the use of a pH1N1 influenza vaccine in HIV-infected pregnant women, and another in HIV-infected children and youth, are underway in the USA.³²

Influenza, influenza vaccines and Guillain-Barré syndrome (GBS)

An increased risk of Guillain-Barré syndrome, a demyelinating polyneuropathy, of approximately 9 extra cases per every million vaccinees occurred in the USA in 1976, in people immunised with the A/New Jersey/76 influenza ('swine flu') vaccine.³³⁻³⁵ That vaccine was provided to over 40 million people in anticipation of a pandemic which did not occur.³³ However, the consensus of studies conducted since 1976 is that there is no excess risk of GBS associated with subsequent seasonal influenza vaccines. Some studies have suggested a possible protective effect of influenza vaccination against GBS, based on the prevention of influenza infection, which is a recognised but relatively uncommon antecedent of GBS.

The document *ATAGI advice regarding influenza, influenza vaccines and Guillain-Barré Syndrome* is available at:

<http://www.healthemergency.gov.au/internet/healthemergency/publishing.nsf/Content/national-vaccination-program#atagi>

The risk of Guillain-Barré Syndrome is not expected to increase after receipt of the pH1N1 influenza vaccine. Nevertheless, to provide confirmation and reassurance

of the safety of the pH1N1 influenza vaccine, and to aid in the surveillance of any adverse events, it is essential that immunisation providers notify the TGA of patients with symptoms suggestive of GBS following vaccination. Information on notifying the TGA is given below (see *Safety monitoring*).

Contraindications and precautions

Due to the similarity in the manufacture of monovalent Panvax[®] and the trivalent seasonal influenza vaccines, their contradictions and safety precautions are similar and listed below.

- Panvax[®] is contraindicated in anyone who has experienced anaphylaxis following a previous dose of any influenza vaccine, or who has experienced anaphylaxis following any vaccine component, including the antibiotics neomycin or polymyxin.
- The vaccine should not be used in anyone who has experienced anaphylaxis to eggs or chicken protein.
- The immunological response may be diminished if the patient is immunocompromised due to disease or immunosuppressant treatment.

Safety monitoring

In Australia, serious or unusual adverse events following immunisation are notifiable. The TGA is monitoring all adverse reactions following vaccination with Panvax[®]. The current post-licensure surveillance data suggests that the profile of reported events following administration of Panvax[®] is similar to those observed following seasonal influenza vaccination.²⁴ Health professionals are encouraged to report adverse reactions by calling 18 02 007 or using an online reporting form found at:

<http://www.tga.gov.au/problem/panvaxh1n1.htm>

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