National Collaborating Centre for Infectious Diseases
Centre de collaboration nationale des maladies infectieuses

Purple Paper

Pandemic pH1N1 Weekly Literature Synthesis
(Weeks of December 13, 2009 – January 2, 2010)

pH1N1 Vaccine

Immune response after a single vaccination against 2009 influenza A H1N1 in USA: a preliminary report of two randomised controlled phase 2 trials.
Plennevaux E et al. *Lancet 2010; 375:41-48.*

Safety and immunogenicity of a 2009 pandemic influenza A H1N1 vaccine when administered alone or simultaneously with the seasonal influenza vaccine for the 2009-10 influenza season: a multicentre, randomised controlled trial.
Vajo Z et al. *Lancet 2010; 375:49-55.*

Safety and immunogenicity of 2009 pandemic influenza A H1N1 vaccines in China: a multicentre, double-blind, randomised, placebo-controlled trial.
Liang X-F et al. *Lancet 2010; 375:56-66.*

Immunogenicity and safety in adults of one dose of influenza A H1N1v 2009 vaccine formulated with and without AS03$_A$-adjuvant: preliminary report of an observer-blind, randomised trial.
Roman F et al. *Vaccine. Published online December 22, 2009.*

Immunogenicity of a monovalent 2009 influenza A(H1N1) vaccine in infants and children: a randomized trial.
Nolan T et al. *JAMA 2010; 303:37-46.*

Five clinical trials were published in recent weeks reporting the immunogenicity and safety profile of several monovalent pH1N1 vaccines administered to subjects of various age groups. All **clinical trials** were **double-blind** and **randomized**, but only two were **placebo-controlled**. All studies enrolled healthy subjects with no documented history of known or suspected pH1N1 infection.

The induced antibody titer against pH1N1 in vaccinees was determined by laboratory assays. Vaccine immunogenicity was in turn inferred by 4 standard antibody measures: geometric mean titer (GMT), geometric mean titer ratio (the ratio of GMT after and before vaccination), seroprotection rate (proportion of vaccinees with titers ≥ 1:40), and seroconversion rate (proportion of vaccinees with pre-vaccination titer < 1:10 and a post-vaccination titer ≥ 1:40, or a pre-vaccination titer ≥ 1:10 and ≥ 4-fold increase after vaccination).

Vaccine safety assessment was primarily based on adverse events reported by vaccinees that were then graded by investigators.

Vaccine formulation and dosage under investigation were different in each study; nevertheless, findings on immunogenicity and safety are in general agreement. Study vaccines included split-virion as well as whole-virion formulations. Antigen doses varied from 5 to 30 micrograms hemagglutinin. Some trials used unadjuvanted vaccines only, and trials using adjuvanted vaccines used aluminium phosphate, aluminium hydroxide, or AS03$_A$ oil-in-water adjuvant containing tocopherol.

The following are the result highlights:

1. In all studies, a single dose of pH1N1 vaccine elicited antibody protection in the majority of adult subjects.
2. Adults aged 18-60 years developed a higher antibody titer after one dose than elderly adults > 60 years of age and young children.
3. Findings on vaccine dosage requirement for children younger than 9 years were mixed. Of the three studies examining children as part of their cohorts, two studies showed that two doses of vaccine given 21 days apart would be needed to afford sufficient protection in young children. This is in contrast to the third study which showed that one dose of unadjuvanted split-virion pH1N1 vaccine containing 15 micrograms hemagglutinin was immunogenic in infants and children aged 6 months or older.
4. The pH1N1 vaccine could be safely administered with the seasonal influenza vaccine at the same time. Subjects who received simultaneous injections of the pH1N1 and seasonal influenza vaccines developed a strong antibody response

against pH1N1 comparable to the response in subjects who received the pH1N1 vaccine only.
5. Adverse events associated with the pH1N1 vaccine were generally mild and similar to adverse events related to seasonal influenza vaccines. The most common adverse event was pain at the injection site. Reported systemic reactions in adults included fatigue, headache, myalgia, malaise, and fever. Irritability, loss of appetite and fever were the most frequent systemic adverse events in infants and young children.

The table below summarizes the parameters of the five clinical trials.

NCCID Comments:
These five clinical trials have consistently shown that the pH1N1 vaccine is immunogenic and safe. Nonetheless several questions remain.

1. The influenza A pH1N1 virus is a novel virus to which the general population lacks pre-existing immunity [1,2]. Yet, one pH1N1 vaccine dose can induce protective immunity in most vaccinees, contrary to the predicted two doses. The majority of study participants in the five clinical trials did not demonstrate protective levels of antibody against pH1N1 before receiving the pH1N1 vaccine, hence precluding a possible immunity boosting effect of the vaccine. What is the explanation for the unexpectedly high efficacy of a single dose of the pH1N1 vaccine?
2. Do children require a second dose of the pH1N1 vaccine to achieve protective immunity?
3. Is the pH1N1 vaccine equally effective in populations with increased risk of serious sequelae (e.g. pregnant women, aboriginal populations, people who are immunocompromised or have underlying chronic conditions)?
4. What is the optimal dosage and formulation of the pH1N1 vaccine?
5. Is inclusion of an adjuvant worthwhile? Which adjuvant is the most appropriate?

Because clinical trials lack the capacity to detect rare adverse events, post-marketing surveillance is still crucial for the continuing monitoring of adverse effects. To date, surveillance data from Canada and other countries have in fact indicated that the pH1N1 vaccine is as safe as seasonal influenza vaccine.

In Canada, 25.143 million doses of three types of the pH1N1 vaccine had been distributed as of December 19, 2009 – adjuvanted and non-adjuvanted vaccines from GlaxoSmithKline, and non-adjuvanted vaccine from CSL Limited (Australia). According to the January 6, 2010 update of PHAC's *Vaccine Surveillance Report – Adverse Events following Immunization*, a total of 5,407 adverse events have been reported to PHAC since the beginning of the pH1N1 vaccine campaign through December 19, 2009 [3]. Analysis of the reported adverse events found that:

- The types and frequency of both serious and non-serious adverse events reported to date are consistent with those observed in clinical trials and other countries where adjuvanted and unadjuvanted vaccines are used.
- The most common reported adverse events were not serious and included injection site reactions, nausea, vomiting, dizziness, headache and fever.
- Of all reported adverse events, 182 cases met the criteria for a serious adverse event. These included 7 deaths (still under investigation), 10 cases of Guillain-Barré Syndrome (GBS; still under investigation) and 107 cases of anaphylaxis.
- The 10 reported cases of GBS were equivalent to an incidence rate of 0.4 per million doses of pH1N1 vaccine distributed. As the report notes, the risk of GBS from receiving an influenza vaccine is at most one extra case per million doses administered. Canadians are actually at a higher risk of developing GBS from influenza infection than from influenza vaccine. Furthermore, based on surveillance in Canada and other countries, GBS does not appear to be associated with receipt of the pH1N1 vaccine.
- The 107 reported cases of anaphylaxis were equivalent to an incidence rate of 0.43 per 100,000 doses of pH1N1 vaccine distributed. This is within the normal range observed after receiving any vaccine. Except for one anaphylaxis case that resulted in death, all other cases were treated and have recovered.

For the complete *Vaccine Surveillance Report*, visit http://www.phac-aspc.gc.ca/alert-alerte/h1n1/vacc/addeve-eng.php.

Similar findings are observed in the USA. According to the December 4, 2009 issue of CDC's *Morbidity and Mortality Weekly Report*, reports submitted between October 1 and November 24, 2009 through the US Vaccine Adverse Event Reporting System (VAERS) and electronic data in Vaccine Safety Datalink (VSD) indicated that the overall reported proportion and type of serious adverse events appear similar for both pH1N1 and seasonal influenza vaccines [4].

Oseltamivir Treatment of Influenza in Infants

Oseltamivir for treatment of influenza in infants less than one year.
Siedler K et al. *Pediatr Infect Dis J. Published online December 23, 2009.*

Oseltamivir is widely approved for the treatment and prophylaxis of influenza in children ≥ 1 year of age. It has been shown that oseltamivir can shorten the duration of influenza illness, decrease viral shedding and reduce the incidence of acute otitis media in treated children. Despite its potential benefits, safety concerns preclude the use of oseltamivir in children aged < 1 year. To assess possible adverse effects of oseltamivir in infants, investigators of this **case series** study performed a **retrospective chart review** of children < 1 year who were admitted to a German teaching hospital, and whose parents had consented to off-label oseltamivir treatment of influenza upon a positive diagnosis over 5 consecutive influenza seasons (2003-2007).

Medical charts were identified for 157 infants. The mean age of admitted infants was 6.3 months. No infants had received the seasonal influenza vaccine, and most infants had been ill with fever for less than 24 hours at admission. Upon a positive influenza diagnosis, oseltamivir treatment was started within 48 hours of symptom onset. The dosage of oseltamivir was 2mg/kg of body weight twice daily for 5 days.

The mean temperature for all infants was 38.8°C upon admission. Other common symptoms included rhinitis, pharyngitis, cough, feeding difficulties, and otitis media. During oseltamivir treatment, 50% of infants developed additional gastrointestinal symptoms not observed at initial presentation. The most common were vomiting and diarrhea, but they were mild in intensity. The extent to which these symptoms were due to the influenza infection itself was unclear. Detection of rotavirus and Salmonella in 11 infants may partially explain these gastrointestinal symptoms. The presence of other infectious agents able to cause gastroenteritis was not ruled out. Fever resolved within 36 hours of commencement of oseltamivir treatment in 128 (82%) infants and within 48 hours in 136 (87%) infants.

NCCID Comments:
There are only a limited number of studies examining possible oseltamivir-associated side effects in infants [5,6,7]. This study corroborates the findings of these studies:

- Oseltamivir can shorten the duration of fever in infants < 1 year as a result of influenza.
- Oseltamivir appears to be safe for use in infants < 1 year.

Oseltamivir is licensed in Canada for the treatment and prophylaxis of seasonal influenza in children aged 1 year and over. The emergence of the 2009 H1N1 pandemic has led to the provisional approval of oseltamivir treatment and prophylaxis in children aged < 1 year with pH1N1 infection. PHAC has recently released an updated *Guidance for expanded use of oseltamivir (Tamiflu®) in children under one year of age in the context of pandemic (H1N1) 2009* on December 22, 2009 [8]. For a copy of the *Guidance* and recommended oseltamivir dosages, visit http://www.phac-aspc.gc.ca/alert-alerte/h1n1/guidance_lignesdirectrices/guidance-tamiflu-eng.php.

Similar action in expanding the use of oseltamivir in infants < 1 year with pH1N1 infection has also been taken by the US Food and Drug Administration and European Medicines Agency.

Summary of five double-blind, randomized clinical trials on immunogenicity and safety of the monovalent pH1N1 vaccine.

Study Country	Pharmaceutical Company	pH1N1 Vaccine Type	Participant Age Groups	Placebo-Controlled	pH1N1 Vaccine Dosage (µg HA) and Formulation for Each Study Group	pH1N1 Vaccine Adjuvant Composition	Number of pH1N1 Vaccine Doses Required to Induce Protective Immunity
USA	sanofi pasteur	inactivated, split-virion	6-35 months	Yes	7.5µg / 15µg	-	2
			3-9 years	Yes	7.5µg / 15µg	-	2
			18-64 years	Yes	7.5µg / 15µg / 30µg	-	1
			≥ 65 years	Yes	7.5µg / 15µg / 30µg	-	1
Hungary	Omninvest	inactivated, whole-virion	18-60 years	No	6µg	aluminium phosphate gel	1
					6µg + adjuvanted seasonal influenza vaccine	aluminium phosphate gel	1
			> 60 years	No	6µg	aluminium phosphate gel	1
					6µg + adjuvanted seasonal influenza vaccine	aluminium phosphate gel	1
China	10 Chinese manufacturers	inactivated, split-virion	3 - <12 years	Yes	7.5µg / 15µg / 30µg	-	2
					15µg / 30µg + adjuvant	aluminium hydroxide	2
			12 - <18 years	Yes	7.5µg / 15µg / 30µg	-	1
					7.5µg / 15µg / 30µg + adjuvant	aluminium hydroxide	1
			18-60 years	Yes	7.5µg / 15µg / 30µg	-	1
					7.5µg / 15µg / 30µg + adjuvant	aluminium hydroxide	1
			> 60 years	Yes	7.5µg / 15µg / 30µg	-	1
					7.5µg / 15µg / 30µg + adjuvant	aluminium hydroxide	1
		inactivated, whole-virion	18-60 years	Yes	5µg / 10µg + adjuvant	aluminium hydroxide	1
			> 60 years	Yes	10µg + adjuvant	aluminium hydroxide	1
Germany	GlaxoSmithKline	inactivated, split-virion	18-60 years	No	21µg	-	1
					5.25µg + adjuvant	oil-in-water emulsion containing DL-α-tocopherol, squalene, polysorbate	1
Australia	CSL Limited	inactivated, split virion	6 mo - <3 years	No	15µg	-	1
					30µg	-	1
			3 - <9 years	No	15µg	-	1
					30µg	-	1

Notable Publications

Effectiveness and cost-effectiveness of vaccination against pandemic influenza (H1N1) 2009.
Khazeni N et al. *Ann Intern Med 2009; 151:829-839.*

Severe 2009 H1N1 influenza in pregnant and postpartum women in California.
Louie JK et al. *N Engl J Med. Published online December 23, 2009.*

Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina.
Libster R et al. *N Engl J Med. Published online December 23, 2009.*

Outbreak of 2009 pandemic influenza (H1N1) at a New York City school.
Lessier J et al. *N Engl J Med 2009; 361:2628-2636.*

Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States.
Cauchemes S et al. *N Engl J Med 2009; 361:2619-2627.*

Mortality from pandemic A/H1N1 2009 influenza in England : public health surveillance study.
Donaldson LI et al. *BMJ. 2009 Dec 10; 339:b5213. doi: 10.1136/bmj.b5213.*

The Spanish influenza pandemic seen through the BMJ's eyes : observations and unanswered questions.
Jefferson T, Ferroni E. *BMJ. 2009 Dec 16; 339:b5313. doi: 10.1136/bmj.b5313.*

Cellular immune responses to recurring influenza strains have limited boosting ability and limited cross reactivity to other strains.
Keynan Y et al. *Clin Microbiol Infect. Published online on December 23, 2009.*

Anti N1 cross-protecting antibodies against H5N1 detected in H1N1 infected people.
Frobert E et al. *Curr Microbiol. Published online December 25, 2009.*

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[4] CDC. Safety of influenza A (H1N1) 2009 monovalent vaccines – United States, October 1-November 24, 2009. *MMWR 2009 Dec 4; 58(Early Release):1-6.*

[5] Okamoto S et al. Experience with oseltamivir for infants younger than 1 year old in Japan. *Pediatr Infect Dis J 2005; 24:575-576.*

[6] Tamura D et al. Oseltamivir phosphate in infants under 1 year of age with influenza infection. *Pediatr Int. 2005; 47:484-484.*

[7] Kimberlin DW et al. Safety of oseltamivir compared with the adamantanes in children less than 12 months of age. *Pediatr Infect Dis J. Published online November 25, 2009.*

[8] PHAC. Guidance for expanded use of oseltamivir (Tamiflu®) in children under one year of age in the context of pandemic (H1N1) 2009. Available online: http://www.phac-aspc.gc.ca/alert-alerte/h1n1/guidance_lignesdirectrices/guidance-tamiflu-eng.php.

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