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2009 Pandemic Influenza A (H1N1) Vaccine

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Key Points

- The pH1N1 vaccines provide unexpectedly good immune responses.
- Oil-in-water emulsion adjuvants, such as AS03 and MF59, significantly increase immunogenicity of the inactivated split pH1N1 vaccine, allowing a reduction in the dose of hemagglutinin (HA) antigen needed to provide protection.
- Aluminum adjuvant-based pH1N1 vaccines had limited effects on immune response.
- Results from a limited number of published and unpublished studies suggest impressive estimates of pH1N1 vaccine effectiveness (VE).
- The overall safety of the pH1N1 vaccine has been confirmed.
- These findings support the use of either two doses of unadjuvanted pH1N1 vaccine containing 7.5 µg HA administered 21 days apart or one dose of AS03-adjuvanted pH1N1 vaccine containing 1.9 µg of HA to provide adequate protection in children less than 9 years of age.
- The inherent trade-off between community-level risk versus individual-level risk warrants recognition.

Background

Since the emergence and spread of the 2009 pandemic influenza A H1N1 virus (pH1N1) in March 2009, there has been substantial influenza activity worldwide (1). As of August 1, 2010, more than 214 countries and overseas territories reported laboratory-confirmed pH1N1 cases, including at least 18,449 deaths, to the World Health Organization (WHO) (2). Vaccines are expected to be the most effective public health mitigation and prevention strategy (3) against the anticipated circulation of the pH1N1 virus, and its expected seasonal influenza like behavior.

Regulatory authorities have already approved pH1N1 vaccines in a number of countries, including Canada, United States, United Kingdom, and Australia (Table 1) (5,6). In Canada, the pH1N1 vaccine comprised two components: a pH1N1 immunizing antigen (inactivated, split-virion) and an AS03 adjuvant (oil-in-water

emulsion) (7). The pH1N1 antigen was derived from the influenza A/California/7/2009 strain, which was officially recommended by WHO for the manufacture of pandemic influenza vaccines. An unadjuvanted pH1N1 vaccine was also authorized for use.

GlaxoSmithKline (GSK), given its longstanding contract with the Government of Canada to uphold vaccine production capacity to meet vaccine needs during a pandemic (8), produced both formulations of the pH1N1 vaccine. A small order of unadjuvanted pH1N1 vaccine was also obtained from Commonwealth Serum Laboratories (CSL) in Australia to allow timely access to pH1N1 vaccination for pregnant women. Preparations for production began when the WHO first identified the pandemic potential of the pH1N1 virus in late April 2009 (9). Shortly after, the A/California/7/2009 seed strain was made available to GSK in late May 2009. The production method for the pH1N1 vaccine was similar to that for seasonal influenza vaccine (10). First, the pH1N1 virus was injected into the fluid surrounding the embryo of fertilized hens' eggs (11,12). This facilitated infection of the egg so the pH1N1 virus could multiply. The pH1N1 virus was then harvested, purified, chemically-inactivated and used to produce the vaccine. Since the current pH1N1 strain had not been a component of previous seasonal influenza vaccines, clinical trials were initiated to confirm immunogenicity and vaccine safety. Approval for use of the AS03-adjuvanted pH1N1 vaccine was granted by Health Canada on October 21, 2009 (7), and the unadjuvanted pH1N1 vaccine was approved on November 12, 2009. The total production and testing

time took approximately five to six months (13).

Clinical studies indicated that oil-in-water emulsion adjuvants, such as AS03, dramatically enhanced the immune response of vaccine recipients, with the potential for cross-protective immunity against possible mutations of the virus (14,15). More importantly, oil-in-water emulsion adjuvants are "antigen-sparing" (i.e. less antigen required per dose compared to unadjuvanted vaccines to produce the same level of immune response) (16). The AS03 adjuvant improves antigen presentation to immune cells and also acts as a depot, with antigen being slowly released from the inoculation site. Clinical trials of the pre-pandemic H5N1 vaccine formulated with oil-in-water emulsion adjuvants showed an acceptable safety profile (17,18).

The purpose of this evidence review is to consolidate pH1N1 vaccine research (related to both adjuvanted and unadjuvanted formulations) published since the start of the pH1N1 pandemic and to contextualize the findings in a Canadian setting. Specifically, seven aspects will be discussed – efficacy, effectiveness, safety and side effects, recommended dosage, priority sequencing, impact of 2009-2010 seasonal influenza vaccine on pH1N1, and public perception of Canada's pH1N1 immunization campaign.

Efficacy

Immunogenicity to influenza vaccine is traditionally assessed using a hemagglutination inhibition (HI) test (19). The appropriate endpoints, as defined by international criteria, include the proportion of vaccine recipients with hemagglutination inhibition antibody titres of 1:40 or greater (seroprotection rate or SPR), the proportion of vaccinees that achieved seroconversion (pre-vaccination titre of 1:10 with a post vaccination titre of 1:40 or greater), or a minimum increase in antibody titre by a factor of 4 (seroconversion rate or SCR), and the fold-increase in geometric mean titres (GMTs) (seroconversion factor or SCF) (20). As per the U.S. Food and Drug Administration (FDA) guidelines, the recommended serum HI antibody response profile for pandemic vaccines in adults aged 65 years or younger should be a SPR ≥ 70% or SCR ≥40% or SCF > 2.5 (21).

Corresponding thresholds for those older than 65 years of age are 60%, 30%, and 2.0.

Using these definitions, recent human clinical trials of candidate pandemic vaccines have demonstrated high immunogenicity (Table 2) (22-24). Compared to previous pre-pandemic H5N1 vaccine prototypes, the pH1N1 vaccines provide unexpectedly good immune responses (5). In clinical trials, unadjuvanted pH1N1 vaccines elicited potentially sufficient antibodies in children and adolescents (9 to 17 years old), adults (18 to 60 years old), and older adults (>60 years old) within two weeks of administering a single dose (25). In contrast, data in children less than 9 years of age consistently indicate poor immunogenicity to a single dose of unadjuvanted pH1N1 vaccine.

Oil-in-water emulsion adjuvants, such as AS03 and MF59, significantly increase immunogenicity of the inactivated split pH1N1 vaccine, allowing a reduction in the dose of hemagglutinin (HA) antigen needed to provide protection (Table 2) (16). Thus, the use of oil-in-water emulsion adjuvants may induce a more rapid immune response at a lower HA dose than unadjuvanted pH1N1 vaccines. A single dose of AS03-adjuvanted pH1N1 vaccine provided sufficient immune response in healthy children and adults as defined by established regulatory criteria. In contrast, aluminum adjuvant-based pH1N1 vaccines had limited effects on immune response (26). This is consistent with previous H5N1 clinical studies using aluminum-based adjuvants (27,28).

There are limited data on efficacy in vulnerable groups, such as pregnant women, indigenous peoples, immunocompromised individuals, those who are morbidly obese, and those with underlying comorbidities. At present, unpublished Canadian results indicate adequate immunogenicity among Aboriginal persons and HIV-infected individuals who received the AS03-adjuvanted pH1N1 vaccine (Personal communication, David Scheifele, PHAC/CIHR Influenza Research Network (PCIRN). Additional studies focusing on these populations are needed in order to strengthen the evidence base for these priority groups.

A note of caution is warranted due to the lack of standardization of the hemagglutination inhibition and microneutralization assays. The variability of titre measurements makes it difficult to compare results between studies (29).

Effectiveness

Results from clinical trials do not necessarily translate to the same results in "real world" effectiveness studies. However, with the use of a specific pandemic vaccine against a pH1N1 strain that has not drifted, effectiveness estimates should be relatively high (5). The results of a series of observational studies evaluating the effectiveness of the pH1N1 vaccine are anticipated. Results from a limited number of published and unpublished studies suggest impressive estimates of pH1N1 vaccine effectiveness (VE) (Table 3).

A community-based, case-control study (N=91) in New Brunswick involved children younger than 10 years of age with influenza-like-illness who were tested for pH1N1 (30). All children were recruited 21 days after the pandemic vaccine campaign began to allow for the pH1N1 vaccine to have taken effect. None of the cases (i.e. children with laboratory-confirmed H1N1) were vaccinated, compared to 38% of the controls. In other words, a single dose of the 2009 pH1N1 vaccine (AS03-adjuvanted inactivated split virion 1.9 µg HA per dose) was 100% effective in protecting children younger than 10 years of age from laboratory-confirmed pH1N1. In contrast, seasonal influenza vaccines are generally only moderately effective in children; a Cochrane systematic review reported an estimated vaccine effectiveness of only 59% despite receiving two doses (31).

A German study (N=45,733) also using the AS03-adjuvanted pH1N1 vaccine found very high estimates of VE in adults (i.e. those over the age of 14 years) (32). Using the screening method for rapid assessment of vaccinated or unvaccinated pandemic influenza cases, VE was estimated using the formula VE = (PPV-PCV) / PPV(1-PCV) x 100%, where PPV is the proportion vaccinated in the population and PCV the proportion of vaccinated cases. They found pH1N1 VE was 96.8% in persons aged 14 to 59 years and 83.3% in persons 60 years or older. In the U.K., Simpson and colleagues conducted a retrospective cohort study (N=246,368) using linked health administrative datasets (33). They found the pH1N1 vaccine to be 100% effective for preventing influenza and pneumonia hospitalizations. In addition, a Canadian study (N=552) based on a sentinel physician surveillance system involving British Columbia, Alberta, Ontario, and Quebec found the pH1N1 vaccine to be 92% effective at preventing pH1N1 infection (34).

Modeling studies suggest VE is influenced by when vaccines becomes available and the timing of mass vaccination rollout in relation to the epidemic curve (35,36). In Ontario, the pH1N1 campaign reduced the number of new pH1N1 cases at

a reasonable cost, despite the fact that the mass campaign began after the first wave of the pandemic (37). Earlier implementation would have decreased the size of the pH1N1 epidemic curve even further.

Since the available studies of VE used observational study designs, residual confounding may have biased VE estimates (38,39). Further studies are needed to confirm the high VE estimates.

Safety & Adverse Events

Evaluating the pH1N1 vaccine safety profile was a high priority in all clinical trials conducted by manufacturers. The benefits of a vaccine must outweigh potential risks in order to obtain regulatory approval (8). Results from some of the major clinical trials done to date suggest a well-tolerated pH1N1 vaccine, with only mild or moderate reactions, such as local pain, swelling and redness, temporary fever, headache, or fatigue (25). Thus adverse events associated with the pH1N1 vaccine lay within the expected safety profile for common events with seasonal influenza vaccines (40).

Roman and colleagues found that adverse events occurred more commonly in adults aged 18 to 60 years vaccinated with the AS03-adjuvanted pH1N1 vaccine compared to those receiving the unadjuvanted pH1N1 vaccine (22). Similarly, Waddington and colleagues found the adjuvanted pH1N1 vaccine was more reactogenic compared to the whole virion vaccine in children aged 6 months to 13 years (23). Two doses of adjuvanted pH1N1 vaccine were also more reactogenic than one dose, especially for fever ≥38°C in children under 5 years of age (24). Nonetheless, the side effects were transient and mild-to-moderate in intensity.

The occurrence of rare sequelae is inevitable when a vaccine is administered on a massive scale (41). Adverse events that may be too rare to be detected even in large clinical trials can become apparent when entire populations are vaccinated. In addition, adverse events can be coincidental with the time of vaccine administration and not directly caused by the vaccine. For example, Black and colleagues predicted that 22 cases of Guillian-Barré syndrome (GBS) would develop subsequent to vaccinating 10 million individuals, even if the vaccine did not increase the risk of the syndrome (42). Therefore, knowledge of background rates of potential untoward conditions is important in the assessment of pH1N1 vaccine safety. In particular, the Vaccine Adverse Event Reporting System (VAERS) in the U.S. reported 0.8 excess GBS cases per one million persons vaccinated, which is similar to what is found in seasonal influenza vaccines (43). The number of observed GBS cases appeared to be lower than the number of expected GBS cases, suggesting an absence of a significant association (44). In Canada, there were 1.2 reported GBS cases per one million persons vaccinated (45).

Egg-allergic individuals are of particular concern due to the potential risk of exposure to residual egg proteins that may be present in the vaccine as a consequence of the manufacturing process. However, studies suggest that even in egg-allergic individuals with mild allergies, the pH1N1vaccine can be safely administered by following appropriate precautions (46,47).

In summary, the overall safety of the pH1N1 vaccine has been confirmed. Although a small number of GBS cases were reported during the vaccination campaigns that took place in the fall of 2009, it was lower than the number of coincident background cases (48). Studies anticipated over the next 12 months can be expected to generate additional data defining the pH1N1 vaccine safety profile in more detail.

Recommended Dosage

Early reports indicated that immunogenicity was adequate in children/adolescents (9 to 17 years), adults (18 to 60 years), and older adults (>60 years) within two weeks of receiving a single dose of the pH1N1 vaccine (Table 2) (25). This was true with one dose of unadjuvanted split-virion vaccine containing 15 µg HA per dose, or oil-in-water adjuvanted vaccine containing 5.25 µg or 7.5 µg HA per dose. In particular, Plennevaux and colleagues found that 98% of healthy adults and 93% of healthy elderly persons elicited a protective influenza antibody response within three weeks after a single dose of unadjuvanted pH1N1 vaccine containing 15 µg of HA (49). Similarly, one dose of AS03-adjuvanted pH1N1 vaccine containing 5.25 µg of HA or one dose of MF59-adjuvanted pH1N1 vaccine containing 7.5 µg of HA resulted in seroconversion of 98% and 92% of healthy adults, respectively (22).

In comparison, immunogenicity data consistently demonstrated that two doses of unadjuvanted pH1N1 vaccine containing 7.5 µg HA per dose are necessary to provide protective antibody response in children under 9 years of age (25). Specifically, Liang and colleagues reported that only 76.7% of children aged 3 to12 years generated protective antibodies after a single dose (26). With a second dose, 97.7% of children were deemed protected. Conversely, Carmona and colleagues reported

Target Groups

At the beginning of the immunization campaign, the Public Health Agency of Canada recommended that the following groups and populations would benefit most from immunization:

- People under 65 with chronic health conditions
- Pregnant women
- Children 6 months to less than 5 years of age
- People living in remote and isolated settings or communities
- Health care workers involved in pandemic response or the delivery of essential health care services
- Household contacts and care providers of persons at high risk who cannot be immunized or may not respond to vaccines
- Populations otherwise identified as high risk

http://www.phac-aspc.gc.ca/alert-alerte/h1n1/faq/faq_rg_h1n1-fvv-eng.php#vs

that one dose of AS03-adjuvant pH1N1 vaccine containing 1.9 µg of HA provided a protective antibody response in 100% of children within 21 days of administration (24). As a result, these findings support the use of either two doses of unadjuvanted pH1N1 vaccine containing 7.5 µg HA administered 21 days apart or one dose of AS03-adjuvanted pH1N1 vaccine containing 1.9 µg of HA to provide adequate protection in children less than 9 years of age.

Waddington and colleagues found that when using the same dosage of HA, the addition of the AS03 adjuvant led to seroconversion of 99.3% of study participants, as compared to only 78.2% with the unadjuvanted pH1N1 vaccine (23). Furthermore, Roman and colleagues concluded that either an AS03-adjuvanted vaccine containing 5.25 µg HA or unadjuvanted vaccine containing 21 µg HA generated the same level of protective immunity, suggesting dose-sparing effects of AS03 (22). In contrast, evaluation of aluminum adjuvant-based pH1N1 vaccines showed they were less immunogenic than unadjuvanted vaccines (26,50).

Priority Sequencing

Since the production capacity of pandemic vaccines was insufficient to cover the entire population early during the second wave of the 2009 pandemic, setting priorities for administration of limited pandemic vaccine stock was an important aspect of pandemic planning (51). There were generally three strategies for prioritizing pH1N1 vaccination:

i) vaccinating school-aged children to reduce spread of influenza in the community (age-attack rate-based);

ii) vaccinating those with highest risk of severe disease to reduce morbidity and mortality (risk-based); and,

iii) vaccinating health care workers to ensure stability of health care infrastructure during a pandemic (52).

Children and adolescents play an important role in transmitting influenza. Loeb and colleagues conducted a cluster randomized trial in which children and adolescents in Hutterite communities were randomly assigned to receive seasonal influenza vaccination (53). They found that immunizing children and adolescents significantly reduced influenza morbidity in unimmunized residents of the community, which is consistent with findings from several observational studies (54,55). Mathematical modeling studies also suggest that vaccinating children would be the optimal vaccination strategy to slow disease spread (56,57,58). However, to induce indirect protection of the community by vaccinating children only, may be a risky strategy, as the number of hospitalizations and deaths can be reduced by directly vaccinating those at highest risk for severe outcomes along with health professionals who may come into contact with these individuals (51). Tuite and colleagues developed a model which suggested that vaccinating individuals most at risk of severe outcomes consistently decreased hospitalizations, intensive care unit admissions, and deaths (52).

Implementation of priority sequencing must be appropriately based on the timing and availability of the vaccine in relation to the pandemic evolution (Personal communication, Babak Pourbohloul, BC Centre for Disease Control). Directly vaccinating those most at risk for severe outcome is more effective than relying on indirect protection through herd immunity when there are high transmission rates, multiple entry points of the virus into a population, or delayed vaccination campaigns (59).

Although the Public Health Agency of Canada declared that there would

be an adequate supply of pH1N1 vaccines for every Canadian who needed or wanted to be vaccinated (60), it was logistically impossible to vaccinate the entire population simultaneously given supply and distribution constraints (61). Thus, vaccines were first given to certain groups and populations who would benefit the most from immunization (i.e., those with highest risk for severe outcomes). Specifically, persons under the age of 65 years with underlying chronic conditions, pregnant women, children aged 6 to 59 months, household contacts and caregivers of individuals who were at high risk and who could not be immunized (e.g. infants younger than 6 months of age), people living in remote and isolated settings or communities, and health care workers were targeted initially. Vaccination of individuals aged 65 or older was not made a priority due to the purported presence of pre-existing antibodies to pH1N1 from past exposure leading to anticipated reduced attack rates (7,62). Provinces and territories were expected to use these recommendations as guidelines and adapt based on local circumstances; thus, there was interprovincial variation in priority sequencing. Recommendations for pH1N1 vaccine target/priority groups developed in other countries, such as the U.S., the U.K. and Australia, were generally based on the same rationale (Table 4) (63,64).

The inherent trade-off between community-level risk *versus* individual-level risk warrants recognition. For example, priority sequencing that takes an age-attack rate approach may benefit the population but is not optimal for an individual. Children are responsible for most of the transmission; however, current recommendations fail to include school-aged children as a priority group since they are not at greatest risk of severe disease or complications for pH1N1. A potential obstacle is that the personal utility and incentive for vaccination is higher in the elderly as compared to children (65).

Impact of 2009-2010 Seasonal Influenza Vaccine on pH1N1

Several studies have examined the association between the receipt of seasonal influenza vaccine and pH1N1 immunogenicity and found a reduced protective immune response to the pH1N1 vaccine in children and adults who had received prior seasonal influenza vaccine. Nolan and colleagues found children who had prior exposure to the trivalent seasonal influenza vaccine showed decreased immune response to the pH1N1 vaccine (66). Post-pH1N1 HI titres for children who received the 2009 seasonal influenza vaccine was 151.1 (95% CI: 126.4, 183.0) compared to 215.4 (95% CI: 179.3, 258.8) in those who did not receive the seasonal influenza vaccine. Similarly, Roman and colleagues found adults who were previously vaccinated with seasonal influenza vaccine had lower GMTs when vaccinated with the AS03-adjuvanted pH1N1 vaccine (22). Specifically, the GMT 21 days after immunization with the adjuvanted pH1N1 was 446.3 (95% CI: 281.9, 706.8) in those who received seasonal influenza vaccination compared to a GMT of 626.4 (95% CI: 453.3, 865.6) in those who did not receive seasonal influenza vaccination.

Several Canadian epidemiologic studies determined that receipt of the 2009-2010 seasonal influenza vaccine was associated with increased risk of laboratory-confirmed pH1N1 illness (67). However, the presence of bias from residual confounding was not ruled out to explain this association. Studies conducted outside of Canada (i.e., U.S. and Mexico) show inconsistent results (68,69). Further studies are thus warranted to study this association in more detail.

> "Despite the best intentions, the Canadian pH1N1 immunization program failed in many aspects in the public's eye, especially in relation to public health communication and vaccine delivery."

Public Perception of Canada's pH1N1 Immunization Campaign

Despite the best intentions, the Canadian pH1N1 immunization program failed in many aspects in the public's eye, especially in relation to public health communication and vaccine delivery (61). Mixed messages regarding vaccine supply confused the general public. The Public Health Agency of Canada promised Canadians that anyone who wished to get vaccinated would be vaccinated. However, initial prioritization of those who had underlying comorbidites was the reality once pH1N1 vaccines started to be rolled out. Communication with Canadians regarding the safety of the adjuvanted pH1N1 vaccine had been unclear and inadequate. Most importantly, the limited capacity of the egg-based influenza vaccine manufacture technologies further hampered pH1N1 vaccination campaigns during the pandemic such that the pH1N1 vaccine was not available until the second wave was well underway in Canada (70).

Improving the current influenza vaccine production timeline is a global issue that requires urgent attention. While Canada has its own part to play in this systemic problem, there are also important lessons to be learned regarding its approach to the 2009 pH1N1 immunization campaign. Availability of two versions of the pH1N1 vaccine and differences in priority sequencing among provincial and local jurisdictions created unnecessary confusion in the general public. In order to successfully implement a vaccine program to mitigate the impact of a pandemic, a timely and efficacious vaccine needs to be complemented by uniform and consistent messaging among all levels of government. These factors are key to vaccine uptake and should be addressed to improve future pandemic preparedness efforts.

Table 1. Overview of Pandemic Influenza Vaccine Roll-out Worldwide

Country	Producer	Vaccine	Adjuvant	Vaccination Site	Hemagglutinin content	Number of doses
Canada	GSK	Arepanrix	AS03	Intramuscular injection	3.75 µg	All >10 years 1 x 0.5 mL
					1.87 µg	6 months to 9 years old 2 x 0.25 mL
		Monovalent Vaccine	None	Intramuscular injection	15 µg	Pregnant women 1 x 0.5 mL
	CSL Limited	Panvax	None	Intramuscular injection	15 µg	Pregnant women 1 x 0.5 mL
United States	CSL Limited	Monovalent Vaccine	None	Intramuscular injection	15 µg	All > 10 years old 1 x 0.5 mL 36 months to 9 years old 2 x 0.5 mL
					7.5 µg	6 months to 35 months 2 x 0.25 mL
	Novartis Vaccines and Diagnostics Limited	Monovalent Vaccine	None	Intramuscular injection	15 µg	All > 10 years old 1 x 0.5 mL 4 to 9 years old 2 x 0.5 mL
	Sanofi Pasteur, Inc.	Monovalent Vaccine	None	Intramuscular injection	15 µg	All >10 years old 1 x 0.5 mL 36 months to 9 years old 2 x 0.5 mL
					7.5 µg	6 months to 3 years old 2 x 0.25 mL
	MedImmune LLC	Monovalent Vaccine	None	Intranasal, administered as 0.1 mL per nostril	* 106.5-7.5 FFU live attenuated influenza virus	Children 2 – 9 years old 2 x 0.21 mL
						Children, adolescents, and adults 10 – 49 years old 1 x 0.21 mL
United Kingdom	Baxter	Celvapan	None	Intramuscular injection	7.5 µg	All > 6 months 2 x 0.5 mL
	GSK	Pandemrix	AS03	Intramuscular injection	3.75 µg	All >10 years old 2 x 0.5 mL
					1.87 µg	6 months to 9 years old 2 x 0.25 mL
Australia	CSL Limited	Panvax	None	Intramuscular injection	15 µg	All > 10 years old 1 x 0.5 mL
					15 µg	3 to < 10 years old 2 x 0.5 mL
					7.5 µg	6 months to < 3 years old 2 x 0.25 mL

Table 2. Summary of Human Clinical Trials of Pandemic H1N1 Influenza A 2009 Vaccines

Type of Vaccine (strain)	Adjuvant	Dosage(s) (HA µg)	Study Population (N)	Vaccine Regimen	% Responders at Specific Titre (dose +/- adjuvant)		Results	Reference
Monovalent inactivated split-virion (A/ California/7/2009)	AS03	5.25, 21	Healthy adults 18-60 years old (130)	1 dose	HI ≥40: 98.2 (5.25+) 98.4 (21-)		Either 5.25 µg AS03 adjuvanted vaccine or 21 µg unadjuvanted vaccines were sufficient to generate protective antibody response, suggesting dose sparing effects of AS03.	Roman et al. (2010)(22)
Monovalent inactivated split-virion (A/ California/7/2009)	AS03	7.5	Children 6 months to ≤ 13 years old (937)	2 doses, 21 days apart	HI ≥32 after 1st dose: N/A N/A	HI ≥32 2nd dose: 99.3 (7.5+) 78.2 (7.5-)	Two doses of 7.5 µg adjuvanted vaccine were more immunogenic compared to unadjuvanted whole-virion vaccine, especially in children < 3 years old.	Waddington et al. (2010)(23)
Monovalent inactivated split-virion (A/ California/7/2009)	AS03	1.9, 3.75	Healthy children aged 6-35 months (157)	2 doses, 21 days apart	HI ≥40 after 1st dose: 100 (1.9+) 100 (3.75+)	HI ≥40 after 2nd dose: 100(1.9+) 100(3.75+)	One dose of 1.9 µg AS03 adjuvanted vaccine is highly immunogenic in children.	Carmona et al. (2010)(24)
Monovalent inactivated split-virion (A/ California/7/2009)	AS03	3.75	Canadian Aboriginals (138)	1 dose	HI ≥40: 99.3 (3.75+)		One dose of 3.75µg adjuvanted vaccine elicited protective antibody response in Canadians Aboriginals.	Personal communication, David Scheifele, PHAC/CIHR Influenza Research Network (PCIRN)
Monovalent inactivated split-virion (A/ California/7/2009)	AS03	3.75	HIV-infected individuals	2 doses, 21 days apart	HI ≥40 after 1st dose: 81 (3.75+)	HI ≥40 after 2nd dose: 94 (3.75+)	One dose of 3.75µg adjuvant vaccine was immunogenic but a 2nd dose significantly increased protection	Personal communication, Curtis Cooper &David Scheifele, PHAC/ CIHR Influenza Research Network (PCIRN)
Monovalent inactivated split-virion (A/ California/7/2009)	MF59	7.5, 15, 30	Adults 18-50 years old (176)	2 doses, 21 days apart	HI ≥40 after 1st dose: 92 (7.5+) 77 (15+) 72 (15-) 63 (30-)	HI ≥40 after 2nd dose: 100 (7.5+) 92 (15+) 79 (15-) 74 (30-)	One dose of 7.5 µg adjuvant vaccine was sufficient to generated protective antibody response. Adjuvanted vaccine was more immunogenic than unadjuvanted vaccine.	Clark et al. (2009)(71)
Monovalent inactivated split-virion (A/ California/7/2009)	Aluminum Hydroxide	7.5, 15, 30	Healthy individuals ≥ 3 years old (12691)	2 doses, 21 days apart	HI ≥40 after 1st dose: 69.5 (7.5+) 81.2 (15+) 86.8 (30+) 86.5 (7.5-) 89.7 (15-) 93.8 (30-)	HI ≥40 after 2nd dose: 89.6 (7.5+) 95.0 (15+) 98.6 (30+) 97.0 (7.5-) 98.1 (15-) 98.5 (30-)	One dose of 7.5 µg unadjuvanted vaccine generated protective antibody response in adolescents and adults. Two doses of 7.5µg unadjuvanted vaccine likely required to produce adequate immune response in children 3-12 years old. No adjuvant effect of aluminum hydroxide.	Liang et al. (2009)(26)

Type of Vaccine (strain)	Adjuvant	Dosage(s) (HA µg)	Study Population (N)	Vaccine Regimen	% Responders at Specific Titre (dose +/- adjuvant)		Results	Reference
Monovalent inactivated split-virion (A/ California/7/2009)	Aluminum phosphate	6	i) Healthy adults 18- ≤ 60 years old (203) ii) Healthy seniors > 60 years old (152)	1 dose	HI ≥40 after 1st dose: i) 74.3 (6+) ii) 61.3 (6+)		One dose of 6 µg adjuvanted vaccine was immunogenic in both adults and elderly age groups.	Vajo et al. (2010) (72)
Monovalent inactivated split-virion (A/ California/7/2009)	Aluminum	7.5, 15, 30	Individuals 3–77 years old (2200)	2 doses, 21 days apart	HI ≥40 after 1st dose: 61.2 (7.5+) 76.1 (15+) 85.5 (30+) 86.9 (15-) 89.1 (30-)	HI ≥40 after 2nd dose: 92.1 (7.5+) 94.7 (15+) 97.8 (30+) 97.1 (15-) 98.1 (30-)	One dose of 15 µg unadjuvanted vaccine generated protective antibody response in adolescents and adults. Two doses of 15µg unadjuvanted vaccine likely necessary to produce adequate immune response in children 3-12 years old and elderly above age 65. No adjuvant effect of aluminum hydroxide.	Zhu et al. (2009) (50)
Monovalent inactivated split-virion (A/ California/7/2009)	None	15, 30	Infants 6 months to ≤ 9 years old (370)	2 doses, 21 days apart	HI ≥40 after 1st dose: 92.5 (15-) 97.7 (30-)	HI ≥40 after 2nd dose: 100 (15-) 100 (15-)	One dose of 15 µg unadjuvanted vaccine was sufficient to produce protective immune response	Nolan et al. (2010)(66)
Monovalent inactivated split-virion (A/ California/7/2009)	None	7.5, 15, 30	i) Healthy children ≥ 6-35 months old (229) ii) Healthy children 3-9 years old (245) iii) Healthy adults 18-64 yrs old (497) iv) Healthy elderly ≥65 years old (352)	2 doses, 21 days apart	HI ≥40 after 1st dose: i) 45 (7.5-) 50 (15-) N/A (30-) ii) 69 (7.5-) 75 (15-) N/A (30-) iii) 95 (7.5-) 98 (15-) 100 (30-) iv) 94 (7.5-) 93 (15-) 95 (30-)	HI ≥40 after 2nd dose: N/A	One dose of 7.5 µg unadjuvanted vaccine was immunogenic in adults and the elderly. Two doses of 7.5 µg unadjuvanted vaccine likely required to protect children less than 9 years old.	Plennevaux et al. (2010)(49)
Monovalent inactivated split-virion (A/ California/7/2009)	None	30	Healthy children: i)1-2 years old ii)3-5 years old iii)6-9 years old	2 doses, 21 days apart	HI ≥40 after 1st dose: i) 36.2% ii) 52.5% iii) 56.7%	HI ≥40 after 2nd dose: i) 87.7% ii) 86.9% iii) 90.0%	Two doses of 30 µg unadjuvanted vaccine likely required to protect children less than 9 years old.	Lu et al. (2010) (73)
Monovalent inactivated split-virion (A/ California/7/2009)	None	15, 30	Healthy adults 18-64 years old (240)	2 doses, 21 days apart	HI ≥40 after 1st dose: 95 (15-) 89.1 (30-)	HI ≥40 after 2nd dose: 98.3 (15-) 96.5 (30-)	One dose of 15µg unadjuvanted vaccine was sufficient to protect adults.	Greenberg et al. (2009)(74)

Table 3. Summary of Recent pH1N1 Effectiveness Studies

Study Design	Location	Population (N)	Outcome Measure	Variables Adjusted For	Estimates of Vaccine Effectiveness	References
Case-control	New Brunswick	Children 6 months to 9 years old (91)	Laboratory-confirmed pH1N1	Age >35 months, First Nation status, receipt of seasonal vaccine, gender, and hospitalization	100%	Van Buynder et al.(2010)(30)
Case-control	British Columbia, Alberta, Ontario, Quebec	All patients from sentinel physician surveillance system (552)	Laboratory-confirmed pH1N1	Age, comorbidity, province, timeliness of specimen collection, and week of ILI onset	92%	Skowronski et al. (2010)(34)
Cohort	Scotland, United Kingdom	All patients from 41 general practices (246,368)	Pneumonia and influenza hospitalizations	Age, gender, deprivation, being in an at risk morbidity group	100%	Simpson et al.(2010)(33)
Post Marketing Surveillance (Screening Method)	Germany	Individuals 14 years or older (45,733)	Laboratory-confirmed pH1N1	None	Age 14-59 96.8% Over 60 83.3%	Wichmann et al.(2010)(32)

Table 4. Recommendations of Priority/ Target Groups for pH1N1 Vaccines

World Health Organization (Strategic Advisory Group of Experts on Immunization)	Canada (Public Health Agency of Canada)	United States (Centers for Disease Control and Prevention/Advisory Committee on Immunization Practices)-Plentiful Supply	United Kingdom (National Health Service)	Australia (Australian Government, Department of Health and Ageing)
Individuals aged >6 months with one of several chronic medical conditions	Persons with underlying chronic conditions under age of 65	Persons aged 25-64 years old with underlying chronic conditions	Persons aged 6 months to 65 years old with underlying chronic conditions	Children and adults with underlying chronic disease
Pregnant women	Pregnant women	Pregnant women	Pregnant women	Pregnant women
Healthy children	Children 6 months of age to under 5 years old	Children aged 6 months to 4 years old	Children aged 6 months to under 5 years old (December - March 2010)	Children in schools and institutions that are exclusively special needs based
Healthcare workers	Healthcare workers	Healthcare workers	Healthcare and Social workers	Healthcare and Social workers
Healthy adults (aged >15 to 65) and elderly (aged >65)	Household contacts and caregivers of individuals who are at high risk, and who cannot be immunized (persons living with infants less than 6 months of age or weakened immune system)	Persons who live with or provide care for infants aged less than 6 months	Household contacts of people with compromised immune system	Persons who live with or provide care for infants aged less than 6 months
	People living in remote and isolated settings or communities	Persons aged 6 months to 24 years old	Persons over age 65 years old with underlying chronic conditions	Indigenous people in remote and isolated settings or communities with vulnerable people
				Individuals with moderate to severe obesity (BMI >35)

References

1. Centers for Disease Control and Prevention (CDC). Update: influenza activity - United States, August 30, 2009-March 27, 2010, and composition of the 2010-11 influenza vaccine. MMWR - Morbidity & Mortality Weekly Report 2010 Apr 16;59(14):423-430.
2. World Health Organization (WHO). Pandemic H1N1 (2009) - update 10. Available at: http://www.who.int/csr/don/2010_07_23a/en/index.html. Accessed July 20, 2010.
3. Ferguson N, Cummings D, Fraser C, Cajka J, Cooley P, Burke D. Strategies for mitigating an influenza pandemic. Nature 2006;442(7101):448-52.
4. CIDRAP (Centre for Disease Research and Policy) News. WHO says H1N1 pandemic is over. 2010; Available at: http://www.cidrap.umn.edu/cidrap/content/influenza/swineflu/news/aug1010who.html. Accessed August 20, 2010.
5. Johansen K, Nicoll A, Ciancio BC, Kramarz P. Pandemic influenza A(H1N1) 2009 vaccines in the European Union. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin 2009;14(41):19361.
6. World Health Organization (WHO). Pandemic influenza A (H1N1) 2009 virus vaccine - conclusions and recommendations from the October 2009 meeting of the immunization Strategic Advisory Group of Experts. Weekly Epidemiological Record 2009 Dec 4;84(49):505-508.
7. Public Health Agency of Canada (PHAC). Guidance Document on the Use of Pandemic Influenza A (H1N1) 2009 Inactivated Monovalent Vaccine. 2009; Available at: http://www.phac-aspc.gc.ca/alert-alerte/h1n1/vacc/monovacc/intro-eng.php#n1. Accessed July 20, 2010.
8. Public Health Agency of Canada (PHAC). Regulation of H1N1 flu vaccine. 2010; Available at: http://www.phac-aspc.gc.ca/alert-alerte/h1n1/faq/faq_rg_h1n1-fvv-eng.php#fq3. Accessed Oct 30, 2010.
9. GlaxoSmithKline. GlaxoSmithKline Inc. Appearance before the standing committee on health. 2009; Available at: http://www.gsk.ca/english/docs-pdf/PNL_Hearing_Remarks_Oct_26th_ENG.pdf. Accessed August 1, 2010.
10. World Health Organization (WHO). Process of Influenza Development and Production. Available at: http://www.who.int/csr/disease/avian_influenza/Fluvaccvirusselection.pdf. Accessed Aug 1, 2010.
11. GlaxoSmithKline. GSK's flu vaccine development process. Available at: http://www.gsk.com/media/flu/GSK-Flu-Vaccine-Production-Process.pdf. Accessed July 20, 2010.
12. GlaxoSmithKline. Backgrounder: Egg-based vs. cell-based influenza vaccine production. 2005; Available at: http://www.gsk.com/press_archive/press2005/flu_backgrounder.pdf. Accessed July 20, 2010.
13. Public Health Agency of Canada (PHAC). Vaccine Development Process - H1N1 Flu Virus. 2009; Available at: http://www.phac-aspc.gc.ca/alert-alerte/h1n1/h1n1bck-eng.php. Accessed July 20, 2010.
14. Baras B, Stittelaar K, Simon J, Thoolen R, Mossman S, Pistoor F, et al. Cross-protection against lethal H5N1 challenge in ferrets with an adjuvanted pandemic influenza vaccine. PLoS ONE 2008;3(e1401).
15. Leroux-Roels G. Prepandemic H5N1 influenza vaccine adjuvanted with AS03: a review of the pre-clinical and clinical data. Expert Opinion on Biological Therapy 2009 Aug;9(8):1057-1071.
16. Atmar RL, Keitel WA. Adjuvants for pandemic influenza vaccines. Current Topics in Microbiology & Immunology 2009;333:323-344.
17. Rumke H, Bayas J, de Juanes J, Caso C, Richardus JH, Campins M, et al. Safety and reactogenicity profile of an adjuvanted H5N1 pandemic candidate vaccine in adults within a phase III safety trial. Vaccine 2008;26(19):2378-2388.
18. Levie K, Leroux-Roels I, Hoppenbrouwers K, Kervyn A, Vandermeulen C, Forgus S, et al. An adjuvanted, low-dose, pandemic influenza A (H5N1) vaccine candidate is safe, immunogenic, and induces cross-reactive immune responses in healthy adults. Journal of Infectious Diseases 2008;198(9):642-649.
19. Keitel W, Atmar RL. Vaccines for Pandemic Influenza: Summary of Recent Clinical Trials. Current Topics in Microbiology and Immunology 2009;333:431-47.
20. Baylor NW, Houn F. Considerations for licensure of influenza vaccines with pandemic and prepandemic indications. Current Topics in Microbiology & Immunology 2009;333:453-470.
21. FDA. Guidance for Industry: Clinical data needed to support the licensure of pandemic influenza vaccines. 2007b.
22. Roman F, Vaman T, Gerlach B, Markendorf A, Gillard P, Devaster JM. Immunogenicity and safety in adults of one dose of influenza A H1N1v 2009 vaccine formulated with and without AS03A-adjuvant: preliminary report of an observer-blind, randomised trial. Vaccine 2010 Feb 17;28(7):1740-1745.
23. Waddington C, Walker W, Oeser C, Reiner A, John T, Wilkins S, et al. Safety and immunogenicity of AS03B adjuvanted split virion versus non-adjuvanted whole virion H1N1 influenza vaccine in UK children aged 6 months-12 years: open label, randomised, parallel group, multicentre study. BMJ 2010;340(c2649).
24. Carmona A, Omeñaca F, Tejedor JC, Merino JM, Vaman T, Dieussaert I, Gillard P, Arístegui J. Immunogenicity and safety of AS03-adjuvanted 2009 influenza H1N1 vaccine in children 6-35 months. vaccine 2010;28(36):5837-5844.
25. Girard MP ea. Report of the 6th meeting on the evaluation of pandemic influenza vaccines in clinical trials World Health Organization, Geneva, Switzerland, 17-18 February 2010. Vaccine 2010 Oct 4; 28(42):6811-20.
26. Liang XF, Wang HQ, Wang JZ, Fang HH, Wu J, Zhu FC, et al. Safety and immunogenicity of 2009 pandemic influenza A H1N1 vaccines in China: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2010 Jan 2;375(9708):56-66.
27. Bresson J, Perronne C, Launay O, et al. Safety and immunogenicity of an inactivated split-virion influenza A/Vietname/1194/2004 (H5N1) vaccine: phase I randomised trial. Lancet 2006;367:1657-64.
28. Ehrlich HJ, Muller M, Oh HM, et al. A clinical trial of a whole-virus H5N1 vaccine derived from cell culture. N Engl J Med 2008;358:2573-84.
29. Fiore AE, Neuzil KM. 2009 influenza A(H1N1) monovalent vaccines for children. JAMA 2010 Jan 6;303(1):73-74.
30. Van Buynder P, Dhaliwal J, Van Buynder J, Couturier C, Minvill-LeBlanc M, Garceau R, et al. Protective effect of single-dose adjuvanted pandemic influenza vaccine in children. Influenza and Other Respiratory Viruses 2010;4(4).
31. Smith S, Demicheli V, Di Pietrantonj C, Harnden A, Jefferson T, Matheson N, et al. Vaccines for preventing influenza in healthy children. Cochrane Database Syst Rev 2006;1(CD004879).
32. Wichmann O, Stocker P, Poggensee G, Altmann D, Walter D, Hellenbrand W, et al. Pandemic Influenza A (H1N1) 2009 breakthrough infections and estimates of vaccine effectiveness in Germany 2009-2010. Euro Surveill 2010;15(18):pii=19561.
33. Simpson C, Ritchie L, Robertson C, Sheikh A, McMenamin J. Vaccine effectiveness in pandemic influenza-primary care reporting (VIPER): an observational study to assess the effectiveness of pandemic influenza A (H1N1) vaccine. Health Technology Assessment 2010;14(34):313-346.
34. Skowronski D, Janjua N, De Serres G, et al. Effectiveness of AS03-adjuvanted pandemic H1N1 vaccine: case-control evaluation based on the sentinel surveillance system in Canada, fall 2009. British Medical Journal 2010 (in press).
35. Khazeni N, Hutton D, Garber A, et al. Effectiveness and Cost-Effectiveness of Vaccination Against Pandemic Influenza (H1N1) 2009. Ann Intern Med 2009;151:829-839.
36. Sypsa V, Pavlopoulou I, Hatzakis A. Use of an inactivated vaccine in mitigating pandemic influenza A(H1N1) spread: a modelling study to assess the impact of vaccination timing and prioritisation strategies. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin 2009;14(41):19356.
37. Sander B, Bauch C, Fisman D, et al. Is a mass immunization program for pandemic (H1N1) 2009 good value for money? Evidence from the Canadian Experience. Vaccine 2010;28(38):6210-20.
38. Fireman B, Lee J, Lewis N, Bembom O, van der LM, Baxter R. Influenza vaccination and mortality: differentiating vaccine effects from bias. American Journal of Epidemiology 2009;170(5):650-6.
39. Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. International Journal of Epidemiology 2006;35(2):337-44.
40. Pfeifer D, Alfonso C, Wood D. Defining the safety profile of pandemic influenza vaccines. Lancet 2010 Jan 2;375(9708):9-11.

41. World Health Organization (WHO). Safety of pandemic vaccines: Pandemic (H1N1) 2009 briefing note 16. 2009; Available at: http://www.who.int/csr/disease/swineflu/notes/briefing_20091119/en/index.html. Accessed July 26, 2010.
42. Black S, Eskola J, Siegrist CA, Halsey N, Macdonald N, Law B, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. Lancet 2009 Dec 19;374(9707):2115-2122.
43. Centers for Disease Control and Prevention (CDC). Preliminary Results: Surveillance for Guillain-Barré Syndrome After Receipt of Influenza A (H1N1) 2009 Monovalent Vaccine ---United States, 2009-2010. MMWR 2010;59(Early Release):1-5.
44. Centers for Disease Control and Prevention (CDC). Safety of Influenza A (H1N1) 2009 Monovalent Vaccines - United States, October 1-November 24, 2009. MMWR - Morbidity & Mortality Weekly Report 2009 Dec 11; 58(48): 1351-1356..
45. Public Health Agency of Canada (PHAC). Vaccine Surveillance Report - Adverse Events following Immunization. 2010; Available at: http://www.phac-aspc.gc.ca/alert-alerte/h1n1/vacc/addeve-eng.php. Accessed Oct 30, 2010.
46. Nasser S, Brathwaite N, BSACI Standards of Care Committee. Swine flu vaccination in patients with egg allergy. Clin Exp Allergy ;39(9):1288-90.
47. Gagnon R, Primeau MN, Des Roches A, Lemire C, Kagan R, Carr S, Ouakki M, Benoît M, De Serres G, PHAC-CIHR Influenza Research Network (PCIRN). Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. J Allergy Clin Immunol 2010;126(2):317-323.
48. Huang WT, Chuang JH, Kuo SH. Monitoring the safety of pandemic H1N1 vaccine. Lancet 2010 Apr 3;375(9721):1164.
49. Plennevaux E, Sheldon E, Blatter M, Reeves-Hoche MK, Denis M. Immune response after a single vaccination against 2009 influenza A H1N1 in USA: a preliminary report of two randomised controlled phase 2 trials. Lancet 2010 Jan 2;375(9708):41-48.
50. Zhu FC, Wang H, Fang HH, Yang JG, Lin XJ, Liang XF, et al. A novel influenza A (H1N1) vaccine in various age groups. N Engl J Med. 2009 Dec 17;361(25):2414-2423.
51. Schwartz B, Orenstein WA. Prioritization of pandemic influenza vaccine: rationale and strategy for decision making. Current Topics in Microbiology & Immunology 2009;333:495-507.
52. Tuite A, Fisman D, Kwong J, Greer A. Optimal pandemic influenza vaccine allocation strategies for the canadian population. PLoS One 2010;5(5):e10520. doi:10.1371/journal.pone.0010520.
53. Loeb M, Russel M, Moss L, et al. Effects of Influenza Vaccination in Children on Infection Rates in Hutterite Communities: A Randomized Trial. JAMA 2010;303(10):943-950.
54. Piedra P, Gaglani M, Kozinetz C, Herschler G, Fewlass C, Harvey D, et al. Herd immunity in adults against influenza-related illnesses with use of trivalent-live attenuated influenza vaccine (CAIV-T) in children. Vaccine 2005;23(23):1540-8.
55. Ghendon Y, Kaira A, Elshina G. The effect of mass influenza immunization in children on morbidity of the unvaccinated elderly. Epidemiology and Infection 2006;134(1):71-8.
56. Medlock J, Galvani AP. Optimizing influenza vaccine distribution. Science 2009 Sep 25;325(5948):1705-1708.
57. Germann T, Kadau K, Longini IJ, Macken C. Mitigation strategies for pandemic influenza in the United States. Proc Natl Acad Sci USA 2006;103:5935-5640.
58. Weycker D, Edelsberg J, Halloran M, Longini I, Nizam A, Ciuryla V, et al. Population-wide benefits of routine vaccination of children against influenza. Vaccine 2005;23(10):1284-93.
59. Bansal S, Pourbohloul B, Meyers L. A Comparative Analysis of Influenza Vaccination Programs. PLoS Med 2006;3(10):e387. doi:10.1371/journal.pmed.0030387.
60. Public Health Agency of Canada (PHAC). H1N1 Flu Virus Vaccine. 2009; Available at: http://www.phac-aspc.gc.ca/alert-alerte/h1n1/faq/faq_rg_h1n1-fvv-eng.php. Accessed August 1, 2010.
61. Low D, McGeer A. Pandemic (H1N1) 2009: assessing the response. CMAJ 2010. doi: 10.1503/cmaj.100900
62. Hancock K, Veguilla V, Lu X, Zhong W, Butler EN, Sun H, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. N.Engl.J.Med. 2009 Nov 12;361(20):1945-1952.
63. Centers for Disease Control and Prevention (CDC). Update: swine influenza A (H1N1) infections--California and Texas, April 2009. MMWR - Morbidity & Mortality Weekly Report 2009 May 1;58(16):435-437.
64. Chlibek R, Anca I, Andre F, et al. Central European Vaccination Advisory Group (CEVAG) guidance statement on recommendations for 2009 pandemic influenza A(H1N1) vaccination. Vaccine 2010;28(22):3758-66.
65. Galvani A, Reluga T, Chapman G. Long-standing influenza vaccination policy is in accord with individual self-interest but not with utilitarian optimum. PNAS 2007;104(13):5692-5697.
66. Nolan T, McVernon J, Skeljo M, Richmond P, Wadia U, Lambert S, et al. Immunogenicity of a monovalent 2009 influenza A(H1N1) vaccine in infants and children: a randomized trial. JAMA 2010 Jan 6;303(1):37-46.
67. Skowronski DM, De Serres G, Crowcroft NS, Janjua NZ, Boulianne N, et al. Association between the 2008–09 Seasonal Influenza Vaccine and Pandemic H1N1 Illness during Spring–Summer 2009: Four Observational Studies from Canada. PLoS Med 2010;7(4):e1000258. doi:10.1371/journal.pmed.1000258.
68. Kelly H, Grant K. Interim analysis of pandemic influenza (H1N1) 2009 in Australia: surveillance trends, age of infection and effectiveness of seasonal vaccination. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin 2009 Aug 6;14(31).
69. Iuliano AD, Reed C, Guh A, Desai M, Dee DL, Kutty P, et al. Notes from the field: outbreak of 2009 pandemic influenza A (H1N1) virus at a large public university in Delaware, April-May 2009. Clinical Infectious Diseases 2009 Dec 15;49(12):1811-1820.
70. Public Health Agency of Canada (PHAC). Summary of FluWatch findings for the week ending January 16, 2010. Ottawa (ON): The Agency; 2010. Available at: www.phac-aspc.gc.ca/fluwatch/09-10/w02_10/index-end.php. Accessed Oct 26, 2010.
71. Clark TW, Pareek M, Hoschler K, Dillon H, Nicholson KG, Groth N, et al. Trial of 2009 influenza A (H1N1) monovalent MF59-adjuvanted vaccine. N Engl J Med. 2009 Dec 17;361(25):2424-2435.
72. Vajo Z, Tamas F, Sinka L, Jankovics I. 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. Lancet 2010 Jan 2;375(9708):49-55.
73. Lu CY, Shao PL, Chang LY, Huang YC, Chiu CH, Hsieh YC, Lin TY, Huang LM. Immunogenicity and safety of a monovalent vaccine for the 2009 pandemic influenza virus A (H1N1) in children and adolescents. Vaccine 2010;28(36):5864-5870.
74. Greenberg ME, Lai MH, Hartel GF, Wichems CH, Gittleson C, Bennet J, et al. Response to a monovalent 2009 influenza A (H1N1) vaccine. N Engl J Med. 2009 Dec 17;361(25):2405-2413.

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