

Pandemic vaccines

Evidence summary

This document summarises the evidence presented in:

Evidence and advice on candidate pandemic influenza vaccines for response to an influenza pandemic, Associate Professor Jodie McVernon, Vaccine and Immunisation Research Group, Murdoch Children's Research Institute, and Melbourne School of Population Health, The University of Melbourne.

The full literature review and other supporting documents are available on the Australian Government Department of Health and Ageing website at www.health.gov.au

Contents

Abbreviations and acronyms.....	4
1 Introduction.....	5
1.1 Types of influenza vaccines	5
1.2 Evaluation of influenza vaccines for immunogenicity and effectiveness	5
1.3 Achievable vaccine coverage during a pandemic.....	6
2 Administration of candidate pandemic vaccine	7
2.1 Introduction	7
2.2 Currently licensed candidate pandemic vaccines	7
2.3 Effectiveness of candidate pandemic vaccines.....	7
2.3.1 Reviews of H5N1 and H1N1 vaccine immunogenicity in humans	7
2.3.2 Efficacy of H5N1 vaccines in animal models.....	8
2.3.3 Immunogenicity of individual licensed prepandemic vaccines.....	8
2.4 Safety of candidate pandemic vaccines.....	10
2.4.1 Reviews of H5N1 vaccine safety in humans	10
2.4.2 Safety of individual licensed prepandemic vaccines	10
2.5 Additional safety data from clinical trials and studies of H1N1 monovalent pandemic vaccines.....	11
2.5.1 Adjuvant safety	11
2.5.2 Safety of adjuvanted vaccines in pregnancy	12
2.5.3 Paediatric immunogenicity and safety	12
2.5.4 Effect of dosing schedule on immunogenicity and safety	13
2.6 Stockpiling of candidate pandemic vaccines.....	13
2.6.1 Type of vaccine for stockpiling	13
2.6.2 Shelf life and presentation	13
2.7 Circumstances and target groups for administration of vaccine.....	13
2.8 Cost-effectiveness of vaccination.....	14
3 Administration of customised pandemic vaccine	15
3.1 Introduction	15
3.2 Cross-protection across influenza strains and subtypes	15
3.3 Circumstances and target groups for administration of vaccine.....	15
3.4 Cost-effectiveness of vaccination.....	15

4	Administration of seasonal influenza vaccine	16
4.1	Effect of seasonal influenza vaccine on effectiveness of pandemic vaccine.....	16
4.2	Effects of vaccination on subsequent seasonal epidemics.....	17
	References	18

Abbreviations and acronyms

EMA	European Medicines Agency
FDA	United States Food and Drug Administration
HA	haemagglutinin
HI	haemagglutination inhibition
NA	neuraminidase
TGA	Therapeutic Goods Administration
TIV	trivalent inactivated influenza vaccine

1 Introduction

The report '*Evidence and advice on Candidate pandemic influenza vaccines for response to an influenza pandemic*', reviews the current state of evidence regarding pre-pandemic candidate influenza vaccines, predominantly directed against H5N1 strains.

1.1 Types of influenza vaccines

Technologies for development of influenza vaccines are based on either live attenuated virus, inactivated whole virus, split virus (derived by disrupting whole virus particles with detergents) or viral subunits (prepared by enriching for the viral surface glycoproteins haemagglutinin—HA) and neuraminidase—NA).

Inactivated whole-virus preparations, which were first developed more than 60 years ago using egg-culture techniques, have the disadvantage of being highly reactogenic. Split-virus formulations are safer, but are less immunogenic, particularly in the case of novel (pandemic) strains against which the population is not primed.¹ The lower immunogenicity means that higher antigen doses are required, and this reduces the number of vaccine courses that can be delivered in the event of a pandemic.

Approaches to overcoming the problem of limited antigen supply during a pandemic response include using:

- adjuvants to increase the immune response, including adjuvants based on oil-in-water emulsions (e.g. MF59, AS03)²
- intradermal delivery of vaccine³
- cell-based, rather than egg-based, culture methods to increase antigen yield²
- recombinant antigen; an HA vaccine made from protein expressed by baculovirus vectors in insect cells has performed well in safety and effectiveness studies.⁴

Live attenuated and adjuvanted vaccines induce broader cross-protective immune responses than inactivated and unadjuvanted formulations.²

Because influenza vaccines provide only strain-specific protection, the antigenic composition of vaccines must be constantly updated to match that of the circulating influenza virus strain (either seasonal or pandemic).⁵

1.2 Evaluation of influenza vaccines for immunogenicity and effectiveness

The haemagglutination inhibition (HI) assay is the primary method used to assess the immunogenicity of influenza vaccines. The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) have set seroconversion and seroprotection thresholds for licensure of seasonal influenza vaccines.^{6,7} Compared with seasonally circulating H1N1 and H3N2 viruses, the HA of H5N1 influenza viruses has been shown to have low immunogenicity in humans, suggesting that these thresholds may not be appropriate for H5-containing vaccines.⁸ Alternative methods for evaluation of immunogenicity that are more sensitive have therefore been proposed, including virus neutralisation (sometimes known as microneutralisation) or serial radial haemolysis assays. All these assays are subject to between-laboratory variability.^{9,10}

Because of the high mortality associated with H5N1 infection of humans, clinical evidence of protection is difficult to establish; use of challenge models is ethically unacceptable.¹¹ An HI titre of 40 has been shown to correlate with 50% protection against experimental influenza infection in historical challenge studies with matched seasonal viruses.¹² However, it is not known whether this correlation also applies to the H5 HA, which is poorly immunogenic. It is also not known whether efficacy of an H5 vaccine can be extrapolated from data on the effectiveness of a similarly formulated unadjuvanted seasonal or pandemic (eg H1N1, H3N2) vaccine in clinical endpoint efficacy studies.¹³

Animal studies using mice (for safety and immunogenicity trials), followed by ferrets and/or nonhuman primates, are typically used before phase I human clinical trials.¹¹ Ferrets provide an excellent model because they are readily infected with human influenza strains and have a similar symptomatic course to that seen in humans.¹⁴

1.3 Achievable vaccine coverage during a pandemic

High levels of vaccine uptake in the event of a pandemic will require early distribution of vaccine and clear communication about the benefits of vaccination. Compliance with pre-pandemic or pandemic vaccine recommendations will be influenced both by perceptions of disease risk and vaccine effectiveness.^{15, 16} These perceptions may change, and compliance may decrease, during the course of a pandemic response.¹⁷

2 Administration of candidate pandemic vaccine

2.1 Introduction

Candidate pandemic vaccines are vaccines that are based on a viral strain that is thought to have ‘pandemic potential’, specifically the H5N1 (bird flu) strain. Vaccination with a pre-pandemic vaccine could be used to prime the population for an immune response against an emergent variant and to provide some cross-protection. Safety of the vaccine is essential for this phase.¹⁸

Because it is difficult to predict the strains that have pandemic potential, one strategy is development of broadly cross-protective vaccines that protect against both seasonal and pandemic strains through the use of adjuvants or novel delivery approaches.² These vaccines are likely to target B and T cell epitopes on the virus particle that are more highly conserved than the HA and NA proteins, and are therefore shared across strains and subtypes; however, such epitopes are likely to be less immunogenic and have not yet been identified.⁵

2.2 Currently licensed candidate pandemic vaccines

Nine H5N1 pre-pandemic vaccines are currently licensed by regulatory agencies in Australia, the United States, China and Europe. These comprise three inactivated whole-virus vaccines, five split-virus vaccines and one subunit vaccine.

Of the nine vaccines, five are licensed by the Therapeutic Goods Administration (TGA) in Australia (see below for details of studies on their effectiveness and safety):

- Celvapan (manufactured by Baxter)—inactivated whole virus
- Panvax (manufactured by CSL Ltd)—split virus
- Emerflu (manufactured by Sanofi Pasteur)—split virus
- Arepanrix, Pandemrix (manufactured by GlaxoSmithKline—GSK)—split virus
- Aflunov (manufactured by Novartis)—subunit.

2.3 Effectiveness of candidate pandemic vaccines

2.3.1 Reviews of H5N1 and H1N1 vaccine immunogenicity in humans

A multiple treatments meta-analysis of candidate H5N1 vaccines published in 2009,¹⁹ including clinical trial protocols (Level I evidence), studied whole and split-virus vaccines, both unadjuvanted and including adjuvants (alum, AS03, MF59); HA antigen doses ranged from 3.75 to 90 mcg. The study showed a clear dose–response relationship for unadjuvanted and alum-adjuvanted vaccines, but not for vaccines formulated with a non-alum adjuvant. Non-alum adjuvants markedly improved the antibody response at low antigen doses;¹⁹ this would reduce the amount of antigen required during a pandemic response. The optimal proposed formulation was a vaccine containing 6 mcg of antigen or less, and an oil-in-water adjuvant.¹⁹

A systematic review in 2010 examined the immunogenicity of five currently licensed H5N1 vaccines in healthy adults in phase II and III trials (Level I evidence).²⁰ This review also found that an optimal candidate was a low-dose (3.8 mcg) vaccine with an oil-in-water adjuvant, based on its antigen-sparing ability.

Two meta-analyses of H1N1 pandemic vaccines reached similar conclusions about the superior immunogenicity of oil-in-water adjuvanted vaccines. Doses of A(H1N1)pdm09 HA as low as 1.8 mcg were immunogenic in published trials.²¹

Only two direct comparisons of two manufacturers' H1N1 pandemic vaccines have been published.^{22, 23} They compared a 7.5 mcg whole-virus vaccine produced in Vero cells with a 3.75 mcg AS03-adjuvanted vaccine. Both studies showed that the adjuvanted product was more immunogenic (with implications for dose sparing) but also more reactogenic.²² In particular, the AS03-adjuvanted vaccine was significantly more immunogenic in children younger than 3 years of age, although associated with higher rates of severe adverse reactions.²³

2.3.2 Efficacy of H5N1 vaccines in animal models

Duration of protection provided by an H5N1 vaccine against a homologous strain has been examined in ferrets.²⁴ The study used one or two doses (3 weeks apart), with or without AS03 adjuvant. Two doses of adjuvanted vaccine provided greater protection than a single adjuvanted dose or two doses of unadjuvanted vaccine.²⁴ Vaccine-induced antibody had waned when animals were challenged after 16 weeks (compared with 4 weeks).²⁴ HI and microneutralisation titres correlated with the observed level of protection.²⁴

A study in ferrets assessing cross-clade protection found that an adjuvanted Clade 2.1 (Indonesia) H5N1 vaccine provided greater protection than an unadjuvanted vaccine against challenge with a Clade 1 (Vietnam) H5N1 virus.²⁵

2.3.3 Immunogenicity of individual licensed prepandemic vaccines

Findings from clinical trials and published reviews of the nine licensed prepandemic vaccines are summarised below.

Inactivated whole-virus vaccines

Panflu (manufactured by Sinovac; licensed by the State Food and Drug Administration, China)—mostly Level II evidence:

- Two doses of 10 mcg each were required to meet EMA immunogenicity criteria for licensure.²⁶
- There was an obvious dose–response relationship.²⁶
- Immunogenicity was greater with a dosing interval of 28 days than 14 days.²⁶
- Responses were lower in children, with neither 15 mcg nor 30 mcg formulations achieving regulatory thresholds following two doses.²⁷
- The vaccine was based on a Clade I (Vietnam) strain, but provided reasonable cross-protection in adults against Clade 2.1 (Indonesia) and Clade 2.3 (Anhui) strains; cross-reactivity against a Clade 2.2 (Turkey) strain was poor.²⁸

- In healthy immunised adults, antibodies declined markedly over the 12 months following primary two-dose immunisation, but were readily boosted with administration of a third dose.²⁹

Fluval H5N1 (manufactured by Omniinvest; licensed by the HNIP, Hungary)—mostly Level IV evidence:

- In children,³⁰ adults³¹ and the elderly,^{32,33} immunogenicity developed following a single dose (containing 6 mcg of HA antigen³⁴).
- There was some degree of cross-reactivity against clades and subtypes.³⁵

Vepacel, Celvapan (manufactured by Baxter, licensed by the EMA and the TGA)—Level II evidence:

- Inclusion of alum adjuvant resulted in reduced immunogenicity of the 7.5 mcg and 15 mcg dose formulations, driving development of an unadjuvanted formulation.^{36,37}
- A dose–response relationship with regard to HA content was seen using unadjuvanted vaccines, including 30 mcg³⁶ and 45 mcg³⁷ of antigen.
- Unpublished trials data that were presented to the EMA for the purposes of licensure showed immunogenicity in the elderly, immunocompromised and chronically ill.³⁸
- A more recent vaccine based on a Clade 2.1 virus was more immunogenic than the Clade 1–based vaccine, achieving licensure criteria with unadjuvanted doses of only 3.75 mcg and 7.5 mcg.³⁹
- Priming with a Clade 1 vaccine led to some degree of cross-reactivity against Clade 2 viruses;^{36,40} the level of cross-protection against Clade 1 viruses was lower when a Clade 2 strain was used for priming.³⁹ In a mixed Clade 1/2 prime/boost regimen, high levels of antibody to both vaccine viruses were observed in adults administered a booster dose of vaccine up to 24 months after priming with a one or two dose primary series.⁴¹

Split-virus vaccines

Panvax (manufactured by CSL Ltd; licensed by the TGA)—Level II evidence:

- In adults, immunogenicity of two doses of a 7.5 mcg or 15 mcg preparation was greater in the presence of adjuvant than for unadjuvanted vaccine; however, even doses of 30 mcg and 45 mcg did not achieve licensure thresholds by HI assay.⁴²
- Immunogenicity was markedly better in children than adults following a two-dose schedule of 30 mcg and 45 mcg preparations; high levels of antibody persistence and cross-clade reactivity were observed 42 days following administration of the second vaccine dose.⁴³

Emerflu (manufactured by Sanofi Pasteur; licensed by the FDA)—Level II evidence:

- Both the adjuvanted and unadjuvanted formulation showed moderate immunogenicity in adults, increasing with HA antigen dose,⁴⁴ particularly for the unadjuvanted preparation.⁴⁵ However, neither the 30 mcg adjuvanted nor the 7.5 mcg unadjuvanted formulation met licensure criteria.⁴⁶
- In children, two full or half doses of either of these preparations produced levels of seroconversion required for licensure.⁴⁷
- Immunogenicity of unadjuvanted vaccine in adults was not enhanced by intradermal administration.^{48,49}

Arepanrix, Pandemrix (manufactured by GSK; licensed by the EMA but subsequently withdrawn, and by the TGA); Q-pan (manufactured by GSK; recently submitted for approval to the FDA)—Level II evidence:

- A dose–response relationship was observed for unadjuvanted formulations.⁵⁰
- An adjuvanted formulation was immunogenic at 3.75 mcg (with no increase in immunogenicity at higher doses⁵⁰), administered as two doses 21 days apart in healthy adults^{51, 52, 53, 54, 55, 56} and the elderly.^{57, 58} In children, immunogenicity sufficient for licensure occurred in healthy children following two injections of a half or full dose of this preparation.⁵⁹
- Cross-clade HI antibodies were demonstrated following two-dose priming with adjuvanted (but not unadjuvanted) Clade 1 or 2 vaccines^{51, 52, 54, 55, 56, 57, 60, 61} including in children.⁵⁹ Higher cross-reactivity was seen when the spacing of the primary course was increased (i.e. 21 days compared with 7 days).⁶²
- The response to a single dose in adults was insufficient to meet regulatory criteria, but robust booster responses to both priming and heterologous strains were elicited following either a homologous or heterologous booster dose administered 12 months later.⁶³

Subunit vaccines

Aflunov (manufactured by Novartis; licensed by the EMA and the TGA):

- Products adjuvanted using MF59 were more immunogenic than an AIOH-adjuvanted comparator.
- The 7.5 mcg and 15 mcg formulations showed similar immunogenicity in healthy adults and the elderly,^{64, 65} but smaller responses in children.⁶⁶
- The optimal spacing of doses in adults for the 7.5 mcg dose was at least 2 weeks.⁶⁷
- Prior⁶⁸ or concomitant⁶⁹ administration of seasonal influenza vaccine did not interfere with immunogenicity.
- Cross-reactivity between clades following primary administration of Clade 1 vaccines is modest.⁶⁵ It improves significantly with cross-clade boosting at either 6 months⁶⁴ or 18 months.⁷⁰

2.4 Safety of candidate pandemic vaccines

2.4.1 Reviews of H5N1 vaccine safety in humans

A multiple treatments meta-analysis of candidate H5N1 vaccines published in 2009¹⁹ found that adjuvant type was the primary determinant of reactogenicity, both local and systemic. The highest rates of adverse reactions were found with non-alum adjuvanted vaccines, followed by alum-adjuvanted vaccines. However, direct comparisons of published study findings are difficult because of inconsistent reporting of safety data.²¹

2.4.2 Safety of individual licensed prepandemic vaccines

Inactivated whole-virus vaccines

Panflu (Sinovac):

- The vaccine (which is alum adjuvanted) was associated with local and systemic adverse events in approximately 20–30% of trial participants.²⁷

Vepacel, Celvapan (Baxter):

- About 20–30% of adults experienced injection site reactions, and 20–45% reported systemic symptoms after either the first or the second dose.^{36, 39}
- There was no clear relationship between dose and symptoms.
- Adjuvanted formulations were usually, but not always, more reactogenic than the unadjuvanted product.³⁶
- Fewer reactions were observed in adults with a booster dose administered at 6, 12 or 24 months than with the first or second dose of the primary course.⁴¹

Split-virus vaccines

Panvax (CSL Ltd):

- Local adverse reactions to the alum-adjuvanted vaccine occurred at a high rate (80–90%) in both adults and children.^{42, 43} The unadjuvanted formulation had a reaction rate of 50–55% in adults.⁴² Headache was the most commonly reported systemic adverse event in adults.⁴² Systemic reactions were more common in children, affecting 60–100% of recipients after the first or second dose.⁴³

Emerflu (Sanofi Pasteur):

- The alum-adjuvanted vaccine (30 mcg dose) caused injection site pain in 50–75% of adults and systemic side effects in 30–65%.^{44, 45, 46, 49} Both local and systemic side effects occurred at lower rates in children.⁴⁷

Arepanrix, Pandemrix, Q-pan (GSK):

- The AS03-adjuvanted vaccine led to higher rates of local reactions (80–100%) than did the unadjuvanted formulation (20–40%);^{50, 51, 63} similar rates were observed in children.⁵⁹
- Systemic side effects (most commonly myalgia and fatigue) were reported by 50–70% of both adults^{50, 51, 63} and children.⁵⁹
- Symptoms rated as severe were more common following a booster dose than following the primary course in adults.⁶³

Subunit vaccines

Aflunov (Novartis):

- The MF59-adjuvanted vaccine was associated with injection site reactions in 40–70% of adults;^{64, 71} rates were similar in adolescents⁶⁶ but lower in the elderly^{65, 68} and in children.⁶⁶
- Approximately 15–40% of adults receiving the 7.5 mcg adjuvanted dose reported systemic reactions.^{64, 65, 68, 71}

2.5 Additional safety data from clinical trials and studies of H1N1 monovalent pandemic vaccines

2.5.1 Adjuvant safety

AS03 adjuvant (GSK)

GSK's AS03-adjuvanted H1N1 monovalent vaccine was widely distributed during the 2009 pandemic, on the basis of an acceptable safety profile in clinical trials⁷². A web-

based follow-up of Canadian healthcare workers who received the vaccine found that the vaccine had a similar safety profile to the 2010–11 seasonal vaccine (distributed the following year). A prospective observational study of individuals attending United Kingdom general practices during the 2009 pandemic found a reactogenicity profile of this vaccine similar to that expected from trials; however, children <5 years of age had higher rates of systemic adverse events than anticipated.⁷³

The United Kingdom study found significantly more first-onset convulsions than expected,⁷³ consistent with a Swedish self-controlled case series study.⁷⁴

A United Kingdom study found no increase in risk of development of Guillain–Barré syndrome,⁷⁵ whereas a Canadian study attributed approximately two additional cases of Guillain–Barré syndrome to every million doses of vaccine administered.⁷⁶

The main unanticipated adverse event associated with receipt of the AS03-containing vaccine in 2009–10 was an abrupt increase in childhood narcolepsy. This was seen in Finland,⁷⁷ Denmark,⁷⁸ Sweden⁷⁸ and the United Kingdom.⁷⁹

MF59 adjuvant (Novartis)

A range of studies of the MF59 monovalent H1N1 vaccine during the 2009 pandemic^{80, 81, 82} found that most reported events were not serious and were anticipated from clinical trials,^{80, 82} and the safety profile of the vaccine was comparable to the similarly formulated Novartis seasonal vaccine product.⁸³ No reports of narcolepsy were found in the European pharmacovigilance database for this product.⁸⁴

2.5.2 Safety of adjuvanted vaccines in pregnancy

A Danish record linkage study compared pregnancy outcomes of 7,000 women who received AS03-adjuvanted pandemic H1N1 vaccine with the rest of the annual birth cohort, and observed neither adverse nor beneficial effects on a range of fetal outcomes.⁸⁵ This finding was despite the fact that maternal immunisation has been proposed as likely to benefit the newborn, based on active transfer of seroprotective levels of H1N1 antibody to infants born to women immunised from the second trimester of pregnancy until the week before delivery.⁸⁶

In a similar Taiwanese study, 1,275 women who received MF59-adjuvanted monovalent H1N1 vaccine during the 2009 pandemic showed an apparent reduction in the risk of spontaneous abortion following vaccine administration.⁸⁷ A study in the Netherlands, Italy and Argentina showed reduced rates of preterm delivery associated with maternal vaccination with an MF59-adjuvanted H1N1 vaccine.⁸⁸ The absence of reported benefit with the AS03 containing vaccine is an important negative, given our expectation of reduced infant risk as found in the study of the M59 vaccine.

2.5.3 Paediatric immunogenicity and safety

Only limited data are available regarding safety and immunogenicity in children of most candidate pandemic vaccines. Although the Sanofi Pasteur alum-adjuvanted product seems to be a promising candidate, with high immunogenicity and moderate reactogenicity in the paediatric age group, this observation was made on the basis of only a single trial.⁴⁷

2.5.4 Effect of dosing schedule on immunogenicity and safety

For most vaccines, the second dose of a priming course is less reactogenic than the initial dose. Side effects following a booster dose are more variable; they tend to be less frequent for some products (Celvapan [Baxter], Aflunov [Novartis]) and more frequent and/or severe for others (Pandemrix [GSK]).

2.6 Stockpiling of candidate pandemic vaccines

2.6.1 Type of vaccine for stockpiling

Review of the immunogenicity and safety profiles of currently licensed pre-pandemic vaccines indicates that no single product is likely to meet the range of population indications associated with a pandemic. As a result, a mixed stockpile would need to be purchased.

2.6.2 Shelf life and presentation

Shelf life of vaccines has implications for the cost of maintaining a viable vaccine supply in a stockpile. Candidate H5N1 pandemic vaccines currently listed on the Australian Register of Therapeutic Goods (ARTG) have different shelf lives: 1 year (Panvax® [CSL Ltd], Emerflu® [Sanofi]), 18 months (Arepanrix®[GSK]), 2 years (Celvapan® [Baxter]) and 3 years (Aflunov®[Novartis]).

Apart from Aflunov (Novartis), all of the licensed pre-pandemic candidate vaccines are presented as multidose vials (MDVs). MDVs have a number of advantages, including faster manufacture, reduced wastage from overfilling, lower packaging costs and lower requirements for refrigeration storage space.⁸⁹ There is a small risk of contamination associated with MDV use, and the safety and desirability of MDV presentations will need to be conveyed to providers and the public in the event of a pandemic.

2.7 Circumstances and target groups for administration of vaccine

The WHO Strategic Advisory Group of Experts on Immunization H5N1 working group on inter-pandemic vaccine use has divided the population into a number of groups, based on their risk of exposure.⁹⁰ Groups that are likely to benefit from vaccine administration during the first ('readiness') stages of a pandemic are:

- laboratory personnel working with H5N1 virus
- first response personnel investigating possible H5N1 outbreaks in animals or humans
- people who may come into contact with infected animals
- healthcare workers evaluating or managing suspected or confirmed H5N1 cases in designated referral facilities, or in primary care during early emergence of human cases.

Administration of a stockpiled pre-pandemic vaccine during the response phase of a pandemic would depend on impact levels, likely effectiveness, epidemiology and the timeframe for production of a strain-specific vaccine.

During the recovery phase, it is likely that strain-specific pandemic vaccines would be available.

The effort and opportunity costs to the healthcare sector of a large-scale vaccine program must be weighed up against the expected outcomes. These will depend on the severity of the disease and its transmissibility; for example, in a high severity – high transmissibility scenario, widespread distribution of a vaccine that provides even partial protection could benefit the population if delivery is early and wide enough to achieve herd immunity.^{91,92}

During the 2009 pandemic, WHO and other vaccine advisory bodies recommended prioritising healthcare workers and the vulnerable for vaccination.⁹³ Groups at highest risk are the priority for vaccine allocation,⁹⁴ and vaccination of key transmitting groups is likely to confer additional benefits on the most vulnerable.⁹⁵ Modelling studies suggest that potential benefits of targeting younger age groups with transmission-reducing strategies are only fully realised if implemented in the early stages of a pandemic, with achievable outcomes shifting to mitigation among high-risk individuals as the outbreak reaches its peak.^{96,97,98}

During a pandemic response, international and local evidence about the disease and the safety, immunogenicity and efficacy of available vaccines will need to be continually appraised.¹⁷

2.8 Cost-effectiveness of vaccination

An Australian evaluation found that distribution of a combined prepandemic vaccine and antiviral medicines was likely to be most cost-effective under some circumstances.⁹⁹ Cost-effectiveness of vaccination depends on the effectiveness of the vaccine (vaccination alone is preferable when vaccine efficacy is above 50%), transmissibility of the virus, disease severity, the timeliness of vaccination, and the ability to deliver vaccination at low cost through mass vaccination clinics.⁹⁹

The cost-effectiveness of national stockpiling of vaccine is related to the case-fatality rate in the pandemic and the effectiveness of the vaccine in preventing infection and death.¹⁰⁰

3 Administration of customised pandemic vaccine

3.1 Introduction

In the event of a pandemic, a customised influenza vaccine—with an antigenic composition matching that of the pandemic virus strain—would provide a greater level of protection than an unmatched prepandemic vaccine.

The need to develop and produce a matched vaccine, and to conduct clinical trials to ensure safety, immunogenicity and adequate dosing, will result in delays to vaccine delivery.¹⁰¹ It took 5 months for a matched strain-specific vaccine against the 2009 pandemic strain to be commercially available.¹⁰¹

WHO reviews available virus information obtained through the Global Influenza Surveillance and Response System to provide formal recommendations for the composition of vaccines against emerging viruses of pandemic potential. H5, H7 and H9 viruses of avian origin and H3N2 variant viruses of swine origin are currently considered strains of pandemic potential against which vaccine seed strains have been developed.^{102, 103, 104}

3.2 Cross-protection across influenza strains and subtypes

Current vaccine technologies do not provide cross-subtype protection. A match of either (or both) of the HA or NA antigens between the pandemic virus and the vaccine is therefore necessary to induce adequate immunity.

3.3 Circumstances and target groups for administration of vaccine

‘Administration of candidate pandemic vaccine’, above, discusses the priorities for delivery of vaccine during the phases of a pandemic response. Strain-specific pandemic vaccines are likely to be available during the recovery phase of a pandemic.

As with the prepandemic vaccine, the delivery of vaccine will need to be prioritised to make best use of the pandemic vaccine as it becomes available. Unlike prepandemic vaccine strategies, however, the delivery strategy may need to take into account existing levels of immunity. For example, if natural infection has already led to high levels of immunity in children, prioritising children for vaccination will have less impact on reducing disease spread.¹⁰⁵

3.4 Cost-effectiveness of vaccination

As for prepandemic vaccines, economic evaluations that have found matched pandemic vaccines to be cost-effective have assumed rapid delivery and high efficacy of the vaccine, and moderate to high rates of clinical disease caused by the pandemic virus strain.¹⁰⁶

4 Administration of seasonal influenza vaccine

4.1 Effect of seasonal influenza vaccine on effectiveness of pandemic vaccine

Use of stockpiled vaccines (including seasonal influenza vaccines) in target subpopulations may have positive or negative impacts on effectiveness and reactogenicity of a subsequently administered strain-specific vaccine. However, few H5N1 vaccine trial protocols have examined the effect of administration of seasonal vaccine on H5N1 vaccine responses or immunogenicity.

Studies of both AS03-adjuvanted and MF59-adjuvanted H5N1 vaccines have found that administration of seasonal vaccine did not induce an H5 antibody response^{59, 69} or affect the immunogenicity of the H5N1 formulation.⁶⁹ However, receipt of seasonal influenza vaccines in previous years has been reported to reduce the immunogenicity of some H5N1 candidate vaccines (including the CSL Ltd alum-adjuvanted H5N1 candidate vaccine⁴³).

A recent study has shown protection against lethal H5N1 challenge in ferrets primed with seasonal trivalent inactivated influenza vaccine (TIV).¹⁰⁷ This protection is attributable to the NA (neuraminidase) component of the vaccine,¹⁰⁷ renewing interest in the role of NA in cross-protection against novel strains.¹⁰⁸

Although a seasonal vaccine sharing at least the NA with the pandemic strain might provide some level of clinical cross-protection, evidence from clinical trials suggests that the subsequent immunogenicity of matched H5N1 strain-specific vaccines, particularly adjuvanted formulations, may be impaired among those previously immunised with TIV.

Sera from adults immunised in seasonal vaccine trials showed a two-fold increase in antibodies cross-reactive to the novel H1N1 strain in the 2009 pandemic;^{109, 110} no such increase occurred in children.^{109, 111} Prior administration or coadministration of an unadjuvanted TIV to vaccine-naïve adults suppressed immune responses to both unadjuvanted and AS03-adjuvanted influenza A(H1N1)pdm09 monovalent vaccines.¹¹²

During the 2009 pandemic, conflicting reports were received about the risk of infection with the novel H1N1 strain among individuals who had previously received seasonal influenza vaccines. Some studies reported a modest degree of clinical cross-protection^{110, 113}—up to 34% efficacy¹¹⁴—whereas others observed no effect^{115, 116} or even an increase in disease risk.^{117, 118} Infection with seasonal influenza leads to development of immune responses to unrelated influenza viruses, presumably reflecting broadly cross-protective antibody and cellular responses.^{5, 119} Strain-specific vaccines do not induce these cross-reactive responses; they also block the acquisition of natural immunity that would result from influenza infection.¹¹⁹ This has led to suggestions that routine annual immunisation may confer an overall disadvantage during pandemic events, particularly among immunologically naïve children.¹²⁰

4.2 Effects of vaccination on subsequent seasonal epidemics

Since levels of protective antibodies decline over a period of months, the timing of vaccine delivery during a pandemic may have implications for protection against influenza in subsequent seasons.¹²¹ Where vaccines are not available in time to constrain a first epidemic wave, delayed administration may confer greater benefits during subsequent seasons.

References

1. Hampson AW. Vaccines for pandemic influenza. The history of our current vaccines, their limitations and the requirements to deal with a pandemic threat. *Annals of the Academy of Medicine, Singapore* 2008;37(6):510–517.
2. Rappuoli R, Del Giudice G, Nabel GJ, Osterhaus AD, Robinson R, Salisbury D, et al. Public health. Rethinking influenza. *Science* 2009;326(5949):50.
3. Watanabe Y, Ibrahim MS, Suzuki Y, Ikuta K. The changing nature of avian influenza A virus (H5N1). *Trends in Microbiology* 2012;20(1):11–20.
4. Treanor JJ, El Sahly H, King J, Graham I, Izikson R, Kohberger R, et al. Protective efficacy of a trivalent recombinant hemagglutinin protein vaccine (FluBlok®) against influenza in healthy adults: a randomized, placebo-controlled trial. *Vaccine* 2011;29(44):7733–7739.
5. Brown LE, Kelso A. Prospects for an influenza vaccine that induces cross-protective cytotoxic T lymphocytes. *Immunology and Cell Biology* 2009;87(4):300–308.
6. Committee for Proprietary Medicinal Products. Note for guidance on harmonisation of requirements for influenza vaccines. In: London: European Agency for the Evaluation of Medicinal Products; 1997.
7. US Center for Biologics Evaluation and Research. Guidance for industry: clinical data needed to support the licensure of pandemic influenza vaccines. Silver Spring, Maryland; 2007.
8. Girard MP, Katz J, Pervikov Y, Palkonyay L, Kieny MP. 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;28(42):6811–6820.
9. Wood JM, Gaines-Das RE, Taylor J, Chakraverty P. Comparison of influenza serological techniques by international collaborative study. *Vaccine* 1994;12(2):167–174.
10. Haaheim LR, Katz JM. Immune correlates of protection against influenza: challenges for licensure of seasonal and pandemic influenza vaccines, Miami, FL, USA, March 1–3, 2010. *Influenza and Other Respiratory Viruses* 2011;5(4):288–295.
11. Bodewes R, Rimmelzwaan GF, Osterhaus ADME. Animal models for the preclinical evaluation of candidate influenza vaccines. *Expert Review of Vaccines* 2010;9(1):59–72.
12. Potter CW, Oxford JS. Determinants of immunity to influenza infection in man. *British Medical Bulletin* 1979;35(1):69–75.
13. US Center for Biologics Evaluation and Review. Summary minute, Vaccines and Related Biological Products Advisory Committee, 14–15 November 2012. Silver Spring, Maryland; 2012.
14. van der Laan JW, Herberts C, Lambkin-Williams R, Boyers A, Mann AJ, Oxford J. Animal models in influenza vaccine testing. *Expert Review of Vaccines* 2008;7(6):783–793.
15. Seale H, McLaws ML, Heywood AE, Ward KF, Lowbridge CP, Van D, et al. The community's attitude towards swine flu and pandemic influenza. *Medical Journal of Australia* 2009;191(5):267–269.
16. Seale H, Heywood AE, McLaws ML, Ward KF, Lowbridge CP, Van D, et al. Why do I need it? I am not at risk! Public perceptions towards the pandemic (H1N1) 2009 vaccine. *BMC Infectious Diseases* 2010;10:99.
17. Ibuka Y, Chapman GB, Meyers LA, Li M, Galvani AP. The dynamics of risk perceptions and precautionary behavior in response to 2009 (H1N1) pandemic influenza. *BMC Infectious Diseases* 2010;10:296.
18. Evans D, Cauchemez S, Hayden FG. ‘Prepandemic’ immunization for novel influenza viruses, ‘swine flu’ vaccine, Guillain–Barré syndrome, and the detection of rare severe adverse events. *The Journal of Infectious Diseases* 2009;200(3):321–328.
19. Manzoli L, Salanti G, De Vito C, Boccia A, Ioannidis JP, Villari P. Immunogenicity and adverse events of avian influenza A H5N1 vaccine in healthy adults: multiple-treatments meta-analysis. *Lancet Infect Dis* 2009;9(8):482–492.
20. Prieto-Lara E, Llanos-Méndez A. Safety and immunogenicity of prepandemic H5N1 influenza vaccines: a systematic review of the literature. *Vaccine* 2010;28(26):4328–4334.

21. Manzoli L, Ioannidis JP, Flacco ME, De Vito C, Villari P. Effectiveness and harms of seasonal and pandemic influenza vaccines in children, adults and elderly: a critical review and re-analysis of 15 meta-analyses. *Human Vaccines & Immunotherapeutics* 2012;8(7):851–862.
22. Nicholson KG, Abrams KR, Batham S, Clark TW, Hoschler K, Lim WS, et al. Immunogenicity and safety of a two-dose schedule of whole-virion and AS03A-adjuvanted 2009 influenza A (H1N1) vaccines: a randomised, multicentre, age-stratified, head-to-head trial. *Lancet Infect Dis* 2011;11(2):91–101.
23. Waddington CS, Walker WT, 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: British Medical Journal* 2010;340:c2649.
24. Baras B, Stittelaar KJ, Kuiken T, Jacob V, Bernhard R, Giannini S, et al. Longevity of the protective immune response induced after vaccination with one or two doses of AS03A-adjuvanted split H5N1 vaccine in ferrets. *Vaccine* 2011;29(11):2092–2099.
25. Vela EM, Buccellato MA, Tordoff K, Stark G, Bigger JE. Efficacy of a heterologous vaccine and adjuvant in ferrets challenged with influenza virus H5N1. *Influenza and Other Respiratory Viruses* 2012;6(5):328–340.
26. Qiu YZ, Yin WD. Safety and immunogenicity of Sinovac's prototype pandemic influenza H5N1 vaccines: a review on clinical trials. *Influenza and Other Respiratory Viruses* 2008;2(6):237–242.
27. Wu J, Liu SZ, Dong SS, Dong XP, Zhang WL, Lu M, et al. Safety and immunogenicity of adjuvanted inactivated split-virion and whole-virion influenza A (H5N1) vaccines in children: a phase I-II randomized trial. *Vaccine* 2010;28(38):6221–6227.
28. Wu J, Fang HH, Chen JT, Zhou JC, Feng ZJ, Li CG, et al. Immunogenicity, safety, and cross-reactivity of an inactivated, adjuvanted, prototype pandemic influenza (H5N1) vaccine: a phase II, double-blind, randomized trial. *Clinical Infectious Diseases* 2009;48(8):1087–1095.
29. Lin JT, Li CG, Wang X, Su N, Liu Y, Qiu YZ, et al. Antibody persistence after 2-dose priming and booster response to a third dose of an inactivated, adjuvanted, whole-virion H5N1 vaccine. *The Journal of Infectious Diseases* 2009;199(2):184–187.
30. Vajo Z, Kosa L, Szilvasy I, Pauliny Z, Bartha K, Visontay I, et al. Safety and immunogenicity of a pre-pandemic influenza A (H5N1) vaccine in children. *Pediatric Infectious Disease Journal* 2008;27(12):1052–1056.
31. Vajo Z, Kosa L, Visontay I, Jankovics M, Jankovics I. Inactivated whole virus influenza A (H5N1) vaccine. *Emerging Infectious Diseases* 2007;13(5):807–808.
32. Vajo Z, Wood J, Kosa L, Szilvasy I, Paragh G, Pauliny Z, et al. A single-dose influenza A (H5N1) vaccine safe and immunogenic in adult and elderly patients: an approach to pandemic vaccine development. *Journal of Virology* 2010;84(3):1237–1242.
33. 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. *The Lancet* 2010;375(9708):49–55.
34. Vajo Z. Influenza A (H5N1) pandemic prototype vaccine Fluval. *Expert Review of Vaccines* 2009;8(5):619–624.
35. Fazekas G, Martosne-Mendi R, Jankovics I, Szilvasy I, Vajo Z. Cross-reactive immunity to clade 2 strains of influenza virus A subtype H5N1 induced in adults and elderly patients by Fluval, a prototype pandemic influenza virus vaccine derived by reverse genetics, formulated with a phosphate adjuvant, and directed to clade 1 strains. *Clinical and Vaccine Immunology* 2009;16(4):437–443.
36. Ehrlich HJ, Muller M, Oh HM, Tambyah PA, Joukhadar C, Montomoli E, et al. A clinical trial of a whole-virus H5N1 vaccine derived from cell culture. *New England Journal of Medicine* 2008;358(24):2573–2584.
37. Keitel WA, Dekker CL, Mink C, Campbell JD, Edwards KM, Patel SM, et al. Safety and immunogenicity of inactivated, Vero cell culture-derived whole virus influenza A/H5N1 vaccine given alone or with aluminum hydroxide adjuvant in healthy adults. *Vaccine* 2009;27(47):6642–6648.
38. Plosker GL. A/H5N1 pre-pandemic influenza vaccine (whole virion, vero cell-derived, inactivated) [Vepacel®]. *Drugs* 2012;72(11):1543–1557.

39. Tambyah PA, Wilder-Smith A, Pavlova BG, Barrett PN, Oh HM, Hui DS, et al. Safety and immunogenicity of two different doses of a Vero cell-derived, whole virus clade 2 H5N1 (A/Indonesia/05/2005) influenza vaccine. *Vaccine* 2012;30(2):329–335.
40. Ehrlich HJ, Muller M, Fritsch S, Zeitlinger M, Berezuk G, Low-Baselli A, et al. A cell culture (Vero)-derived H5N1 whole-virus vaccine induces cross-reactive memory responses. *The Journal of Infectious Diseases* 2009;200(7):1113–1118.
41. van der Velden MV, Aichinger G, Pöllabauer EM, Löw-Baselli A, Fritsch S, Benamara K, et al. Cell culture (Vero cell) derived whole-virus non-adjuvanted H5N1 influenza vaccine induces long-lasting cross-reactive memory immune response: homologous or heterologous booster response following two dose or single dose priming. *Vaccine* 2012;30(43):6127–6135.
42. Nolan TM, Richmond PC, Skeljo MV, Pearce G, Hartel G, Formica NT, et al. Phase I and II randomised trials of the safety and immunogenicity of a prototype adjuvanted inactivated split-virus influenza A (H5N1) vaccine in healthy adults. *Vaccine* 2008;26(33):4160–4167.
43. Nolan T, Richmond PC, Formica NT, Hoshler K, Skeljo MV, Stoney T, et al. Safety and immunogenicity of a prototype adjuvanted inactivated split-virus influenza A (H5N1) vaccine in infants and children. *Vaccine* 2008;26(50):6383–6391.
44. Bresson J-L, Perronne C, Launay O, Gerdil C, Saville M, Wood J, et al. Safety and immunogenicity of an inactivated split-virion influenza A/Vietnam/1194/2004 (H5N1) vaccine: phase I randomised trial. *The Lancet* 2006;367:1657–1664.
45. Keitel WA, Campbell JD, Treanor JJ, Walter EB, Patel SM, He F, et al. Safety and immunogenicity of an inactivated influenza A/H5N1 vaccine given with or without aluminum hydroxide to healthy adults: results of a phase I-II randomized clinical trial. *The Journal of Infectious Diseases* 2008;198(9):1309–1316.
46. Leroux-Roels I, Van der Wielen M, Kafaja F, Vandermeulen C, Lazarus R, Snape MD, et al. Humoral and cellular immune responses to split-virion H5N1 influenza vaccine in young and elderly adults. *Vaccine* 2009;27(49):6918–6925.
47. Chotpitayasunondh T, Thisyakorn U, Pancharoen C, Pepin S, Nougarede N. Safety, humoral and cell mediated immune responses to two formulations of an inactivated, split-virion influenza A/H5N1 vaccine in children. *PLoS ONE* 2008;3(12):e4028.
48. Patel SM, Atmar RL, El Sahly HM, Cate TR, Keitel WA. A phase I evaluation of inactivated influenza A/H5N1 vaccine administered by the intradermal or the intramuscular route. *Vaccine* 2010;28(17):3025–3029.
49. Patel SM, Atmar RL, El Sahly HM, Guo K, Hill H, Keitel WA. Direct comparison of an inactivated subvirion influenza A virus subtype H5N1 vaccine administered by the intradermal and intramuscular routes. *The Journal of Infectious Diseases* 2012;206(7):1069–1077.
50. Leroux-Roels I, Borkowski A, Vanwolleghe T, Drame M, Clement F, Hons E, et al. Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial. *The Lancet* 2007;370(9587):580–589.
51. Chu DW, Hwang SJ, Lim FS, Oh HM, Thongcharoen P, Yang PC, et al. Immunogenicity and tolerability of an AS03(A)-adjuvanted prepandemic influenza vaccine: a phase III study in a large population of Asian adults. *Vaccine* 2009;27(52):7428–7435.
52. Langley JM, Frenette L, Ferguson L, Riff D, Sheldon E, Risi G, et al. Safety and cross-reactive immunogenicity of candidate AS03-adjuvanted prepandemic H5N1 influenza vaccines: a randomized controlled phase 1/2 trial in adults. *The Journal of Infectious Diseases* 2010;201(11):1644–1653.
53. Kitada S, Kobayashi K, Ichiyama S, Takakura S, Sakatani M, Suzuki K, et al. Serodiagnosis of *Mycobacterium avium*-complex pulmonary disease using an enzyme immunoassay kit. *American Journal of Respiratory and Critical Care Medicine* 2008;177(7):793–797.
54. Hwang SJ, Chang SC, Yu CJ, Chan YJ, Chen TJ, Hsieh SL, et al. Immunogenicity and safety of an AS03(A)-adjuvanted H5N1 influenza vaccine in a Taiwanese population. *Journal of the Formosan Medical Association* 2011;110(12):780–786.
55. Chu DW, Kwong AS, Tsui WW, Wang JH, Ngai CK, Wan PK, et al. Cross-clade immunogenicity and safety of an AS03A-adjuvanted prepandemic H5N1 influenza vaccine in Hong Kong. *Hong Kong Medical Journal* 2011;17(1):39–46.

56. Yang PC, Yu CJ, Chang SC, Hsieh SM, Drame M, Walravens K, et al. Safety and immunogenicity of a split-virion AS03A-adjuvanted A/Indonesia/05/2005 (H5N1) vaccine in Taiwanese adults. *Journal of the Formosan Medical Association* 2012;111(6):333–339.
57. Langley JM, Risi G, Caldwell M, Gilderman L, Berwald B, Fogarty C, et al. Dose-sparing H5N1 A/Indonesia/05/2005 pre-pandemic influenza vaccine in adults and elderly adults: a phase III, placebo-controlled, randomized study. *The Journal of Infectious Diseases* 2011;203(12):1729–1738.
58. Heijmans S, De Meulemeester M, Reynders P, Giet D, Demanet E, Devresse PY, et al. Immunogenicity profile of a 3.75-mug hemagglutinin pandemic rH5N1 split virion AS03A-adjuvanted vaccine in elderly persons: a randomized trial. *The Journal of Infectious Diseases* 2011;203(8):1054–1062.
59. Diez-Domingo J, Garces-Sanchez M, Baldo JM, Planelles MV, Ubeda I, JuBert A, et al. Immunogenicity and safety of H5N1 A/Vietnam/1194/2004 (Clade 1) AS03-adjuvanted prepandemic candidate influenza vaccines in children aged 3 to 9 years: a phase ii, randomized, open, controlled study. *Pediatric Infectious Disease Journal* 2010;29(6):e35–46.
60. Leroux-Roels I, Bernhard R, Gerard P, Drame M, Hanon E, Leroux-Roels G. Broad clade 2 cross-reactive immunity induced by an adjuvanted clade 1 rH5N1 pandemic influenza vaccine. *PLoS ONE* 2008;3(2):e1665.
61. Nagai H, Ikematsu H, Tenjinbaru K, Maeda A, Drame M, Roman FP. A phase II, open-label, multicentre study to evaluate the immunogenicity and safety of an adjuvanted prepandemic (H5N1) influenza vaccine in healthy Japanese adults. *BMC Infectious Diseases* 2010;10:338.
62. Lasko B, Reich D, Madan A, Roman F, Li P, Vaughn D. Rapid immunization against H5N1: a randomized trial evaluating homologous and cross-reactive immune responses to AS03(A)-adjuvanted vaccination in adults. *The Journal of Infectious Diseases* 2011;204(4):574–581.
63. Gillard P, Caplanusi A, Knuf M, Roman F, Walravens K, Moris P, et al. An assessment of prime-boost vaccination schedules with AS03(A)-adjuvanted prepandemic H5N1 vaccines: a randomized study in European adults. *Influenza and Other Respiratory Viruses* 2013;7(1):55–65.
64. Banzhoff A, Gasparini R, Laghi-Pasini F, Staniscia T, Durando P, Montomoli E, et al. MF59-adjuvanted H5N1 vaccine induces immunologic memory and heterotypic antibody responses in non-elderly and elderly adults. *PLoS ONE* 2009;4(2):e4384.
65. Bihari I, Panczel G, Kovacs J, Beygo J, Fragapane E. Assessment of antigen-specific and cross-reactive antibody responses to an MF59-adjuvanted A/H5N1 prepandemic influenza vaccine in adult and elderly subjects. *Clinical and Vaccine Immunology* 2012;19(12):1943–1948.
66. Vesikari T, Karvonen A, Tilman S, Borkowski A, Montomoli E, Banzhoff A, et al. Immunogenicity and safety of MF59-adjuvanted H5N1 influenza vaccine from infancy to adolescence. *Pediatrics* 2010;126(4):e762–770.
67. Beran J, Abdel-Messih IA, Raupachova J, Hobzova L, Fragapane E. A phase III, randomized, open-label study to assess the tolerability and immunogenicity of an H5N1 influenza vaccine administered to healthy adults with a 1-, 2-, 3-, or 6-week interval between first and second doses. *Clinical Therapeutics* 2010;32(13):2186–2197.
68. Vesikari T, Forsten A, Herbinger KH, Cioppa GD, Beygo J, Borkowski A, et al. Safety and immunogenicity of an MF59®-adjuvanted A/H5N1 pre-pandemic influenza vaccine in adults and the elderly. *Vaccine* 2012;30(7):1388–1396.
69. Lopez P, Caicedo Y, Sierra A, Tilman S, Banzhoff A, Clemens R. Combined, concurrent, and sequential administration of seasonal influenza and MF59-adjuvanted A/H5N1 vaccines: a phase II randomized, controlled trial of immunogenicity and safety in healthy adults. *The Journal of Infectious Diseases* 2011;203(12):1719–1728.
70. Fragapane E, Gasparini R, Schioppa F, Laghi-Pasini F, Montomoli E, Banzhoff A. A heterologous MF59-adjuvanted H5N1 prepandemic influenza booster vaccine induces a robust, cross-reactive immune response in adults and the elderly. *Clinical and Vaccine Immunology* 2010;17(11):1817–1819.
71. Bernstein DI, Edwards KM, Dekker CL, Belshe R, Talbot HK, Graham IL, et al. Effects of adjuvants on the safety and immunogenicity of an avian influenza H5N1 vaccine in adults. *The Journal of Infectious Diseases* 2008;197(5):667–675.
72. Walker WT, Faust SN. Monovalent inactivated split-virion AS03-adjuvanted pandemic influenza A (H1N1) vaccine. *Expert Review of Vaccines* 2010;9(12):1385–1398.

73. Nazareth I, Tavares F, Rosillon D, Haguinet F, Bauchau V. Safety of AS03-adjuvanted split-virion H1N1 (2009) pandemic influenza vaccine: a prospective cohort study. *BMJ Open* 2013;3(2):pii=e001912.
74. Arnheim-Dahlstrom L, Hallgren J, Weibull CE, Sparen P. Risk of presentation to hospital with epileptic seizures after vaccination with monovalent AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine (Pandemrix): self controlled case series study. *BMJ: British Medical Journal* 2012;345:e7594.
75. Andrews N, Stowe J, Al-Shahi Salman R, Miller E. Guillain-Barre syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: self-controlled case series. *Vaccine* 2011;29(45):7878–7882.
76. De Wals P, Deceuninck G, Toth E, Boulianne N, Brunet D, Boucher RM, et al. Risk of Guillain-Barré syndrome following H1N1 influenza vaccination in Quebec. *JAMA, The Journal of the American Medical Association* 2012;308(2):175–181.
77. Nohynek H, Jokinen J, Partinen M, Vaarala O, Kirjavainen T, Sundman J, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. *PLoS ONE* 2012;7(3):e33536.
78. Wijnans L, Lecomte C, de Vries C, Weibel D, Sammon C, Hviid A, et al. The incidence of narcolepsy in Europe: before, during, and after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns. *Vaccine* 2013;31(8):1246–1254.
79. Miller E, Andrews N, Stellitano L, Stowe J, Winstone AM, Shneerson J, et al. Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis. *BMJ: British Medical Journal* 2013;346.
80. Candela S, Pergolizzi S, Ragni P, Cavuto S, Nobilio L, Di Mario S, et al. An early (3–6 weeks) active surveillance study to assess the safety of pandemic influenza vaccine Focetria® in a province of Emilia–Romagna region, Italy—part one. *Vaccine* 2013;31(10):1431–1437.
81. Moro ML, Nobilio L, Voci C, Di Mario S, Candela S, Magrini N. A population based cohort study to assess the safety of pandemic influenza vaccine Focetria® in Emilia–Romagna region, Italy—part two. *Vaccine* 2013;31(10):1438–1446.
82. Parretta E, Ianniello B, Ferrazin F, Rossi F, Capuano A. Italian post-marketing surveillance for adverse event reports after MF59-adjuvanted H1N1v vaccination. *Vaccine* 2011;29(20):3708–3713.
83. Banzhoff A, Haertel S, Praus M. Passive surveillance of adverse events of an MF59-adjuvanted H1N1v vaccine during the pandemic mass vaccinations. *Human Vaccines* 2011;7(5):539–548.
84. Tsai TF, Crucitti A, Nacci P, Nicolay U, Della Cioppa G, Ferguson J, et al. Explorations of clinical trials and pharmacovigilance databases of MF59®-adjuvanted influenza vaccines for associated cases of narcolepsy. *Scandinavian Journal of Infectious Diseases* 2011;43(9):702–706.
85. Pasternak B, Svanström H, Mølgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, et al. Risk of adverse fetal outcomes following administration of a pandemic influenza A(H1N1) vaccine during pregnancy. *JAMA, The Journal of the American Medical Association* 2012;308(2):165–174.
86. Puleston R, Bugg G, Hoschler K, Konje J, Thornton J, Stephenson I, et al. Multi-centre observational study of transplacental transmission of influenza antibodies following vaccination with AS03(A)-adjuvanted H1N1 2009 vaccine. *PLoS ONE* 2013;8(1):e47448.
87. Huang WT, Chen WC, Teng HJ, Huang WI, Huang YW, Hsu CW, et al. Adverse events following pandemic A (H1N1) 2009 monovalent vaccines in pregnant women—Taiwan, November 2009 – August 2010. *PLoS ONE* 2011;6(8):e23049.
88. Heikkinen T, Young J, van Beek E, Franke H, Verstraeten T, Weil JG, et al. Safety of MF59-adjuvanted A/H1N1 influenza vaccine in pregnancy: a comparative cohort study. *American Journal of Obstetrics and Gynecology* 2012;207(3):177 e171–178.
89. Australian Technical Advisory Group on Immunisation. ATAGI statement: use of multi-dose vials in vaccination programs. Why has Australia chosen to use multi-dose vials for the H1N1 program? In. Canberra: Australian Government Department of Health and Ageing; 2009.
90. WHO Strategic Advisory Group of Experts. Use of licensed H5N1 influenza vaccines in the interpandemic period: report of the H5N1 SAGE working group to the April 2009 meeting of the Strategic Advisory Group of Experts. Geneva; 2009.

91. Wood J, McCaw J, Becker N, Nolan T, MacIntyre CR. Optimal dosing and dynamic distribution of vaccines in an influenza pandemic. *American Journal of Epidemiology* 2009;169(12):1517–1524.
92. Riley S, Wu JT, Leung GM. Optimizing the dose of pre-pandemic influenza vaccines to reduce the infection attack rate. *PLoS Medicine* 2007;4(6):e218.
93. Chlibek R, Anca I, Andre F, Bakir M, Ivaskeviciene I, Mangarov A, et al. Central European Vaccination Advisory Group (CEVAG) guidance statement on recommendations for 2009 pandemic influenza A(H1N1) vaccination. *Vaccine* 2010;28(22):3758–3766.
94. Van Kerkhove MD, Vandemaële KA, Shinde V, Jaramillo-Gutierrez G, Koukounari A, Donnelly CA, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. *PLoS Medicine* 2011;8(7):e1001053.
95. McVernon J, McCaw J, Glass K, Mercer G, Wood J, McBryde E. Mathematical modelling to inform response to the H1N1 influenza 09. Canberra; 2010.
96. Mylius SD, Hagenaars TJ, Lugner AK, Wallinga J. Optimal allocation of pandemic influenza vaccine depends on age, risk and timing. *Vaccine* 2008;26(29–30):3742–3749.
97. Conway JM, Tuite AR, Fisman DN, Hupert N, Meza R, Davoudi B, et al. Vaccination against 2009 pandemic H1N1 in a population dynamical model of Vancouver, Canada: timing is everything. *BMC Public Health* 2011;11:932.
98. Matrajt Jr L, Longini IM. Optimizing vaccine allocation at different points in time during an epidemic. *PLoS ONE* 2010;5(11):e13767.
99. Newall AT, Wood JG, Oudin N, MacIntyre CR. Cost-effectiveness of pharmaceutical-based pandemic influenza mitigation strategies. *Emerging Infectious Diseases* 2010;16(2):224–230.
100. Lee VJ, Tok MY, Chow VT, Phua KH, Ooi EE, Tambyah PA, et al. Economic analysis of pandemic influenza vaccination strategies in Singapore. *PLoS ONE* 2009;4(9):e7108.
101. Partridge J, Kieny MP. Global production of seasonal and pandemic (H1N1) influenza vaccines in 2009–2010 and comparison with previous estimates and global action plan targets. *Vaccine* 2010;28(30):4709–4712.
102. Hatta M, Kawaoka Y. The continued pandemic threat posed by avian influenza viruses in Hong Kong. *Trends in Microbiology* 2002;10(7):340–344.
103. Koopmans M, Wilbrink B, Conyn M, Natrop G, van der Nat H, Vennema H, et al. Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in commercial poultry farms in the Netherlands. *The Lancet* 2004;363(9409):587–593.
104. Influenza A (H3N2) variant virus-related hospitalizations: Ohio, 2012. *MMWR Morbidity and Mortality Weekly Report* 2012;61:764–767.
105. Glass K, Davis S, Martich L, Mercer GN. Development of decision support documents to assist decision making during a pandemic influenza response: public health measures. Canberra: DoHA; 2013.
106. Khazeni N, Hutton DW, Garber AM, Owens DK. Effectiveness and cost-effectiveness of expanded antiviral prophylaxis and adjuvanted vaccination strategies for an influenza A (H5N1) pandemic. *Annals of Internal Medicine* 2009;151(12):840–853.
107. Rockman S, Brown LE, Barr IG, Gilbertson B, Lowther S, Kachurin A, et al. Neuraminidase-inhibiting antibody is a correlate of cross-protection against lethal H5N1 influenza virus in ferrets immunized with seasonal influenza vaccine. *Journal of Virology* 2013;87(6):3053–3061.
108. Van Kerkhove MD, Broberg E, Engelhardt OG, Wood J, Nicoll A. The consortium for the standardization of influenza seroepidemiology (CONSISE): a global partnership to standardize influenza seroepidemiology and develop influenza investigation protocols to inform public health policy. *Influenza and Other Respiratory Viruses* 2013;7(3):231–234.
109. Katz J, Hancock K, Veguilla V, Zhong W, Lu XH, Sun H, et al. Serum cross-reactive antibody response to a novel influenza A (H1N1) virus after vaccination with seasonal influenza vaccine. *MMWR Morbidity and Mortality Weekly Report* 2009;58(19):521–524.
110. Richmond P, et al. A study of the efficacy, safety and tolerability of CSL Limited’s influenza virus vaccine (CSL’s IVV) administered intramuscularly in healthy adults. Accessed on. Available from: www.clinicaltrials.gov/ct2/show/study/NCT00562484

111. McVernon J, Laurie K, Barr I, Kelso A, Skeljo M, Nolan T. Absence of cross-reactive antibodies to influenza A (H1N1) 2009 before and after vaccination with 2009 Southern Hemisphere seasonal trivalent influenza vaccine in children aged 6 months – 9 years: a prospective study. *Influenza and Other Respiratory Viruses* 2011;5(1):7–11.
112. Langley JM, Scheifele DW, Quach C, Vanderkooi OG, Ward B, McNeil S, et al. Safety and immunogenicity of 2010–2011 H1N12009-containing trivalent inactivated influenza vaccine in children 12–59 months of age previously given AS03-adjuvanted H1N12009 pandemic vaccine: a PHAC/CIHR Influenza Research Network (PCIRN) study. *Vaccine* 2012;30(23):3389–3394.
113. Garcia-Garcia L, Valdespino-Gómez JL, Lazcano-Ponce E, Jimenez-Corona A, Higuera-Iglesias A, Cruz-Hervert P, et al. Partial protection of seasonal trivalent inactivated vaccine against novel pandemic influenza A/H1N1 2009: case-control study in Mexico City. *BMJ: British Medical Journal* 2009;339:b3928.
114. Yin JK, Chow MY, Khandaker G, King C, Richmond P, Heron L, et al. Impacts on influenza A(H1N1)pdm09 infection from cross-protection of seasonal trivalent influenza vaccines and A(H1N1)pdm09 vaccines: systematic review and meta-analyses. *Vaccine* 2012;30(21):3209–3222.
115. Pebody R, Andrews N, Waight P, Malkani R, McCartney C, Ellis J, et al. No effect of 2008/09 seasonal influenza vaccination on the risk of pandemic H1N1 2009 influenza infection in England. *Vaccine* 2011;29(14):2613–2618.
116. Kelly HA, Grant KA, Fielding JE, Carville KS, Looker CO, Tran T, et al. Pandemic influenza H1N1 2009 infection in Victoria, Australia: no evidence for harm or benefit following receipt of seasonal influenza vaccine in 2009. *Vaccine* 2011;29(37):6419–6426.
117. Skowronski DM, De Serres G, Crowcroft NS, Janjua NZ, Boulianne N, Hottes TS, et al. Association between the 2008–09 seasonal influenza vaccine and pandemic H1N1 illness during spring–summer 2009: four observational studies from Canada. *PLoS Medicine* 2010;7(4):e1000258.
118. Rosella LC, Groenwold RH, Crowcroft NS. Assessing the impact of confounding (measured and unmeasured) in a case-control study to examine the increased risk of pandemic A/H1N1 associated with receipt of the 2008–9 seasonal influenza vaccine. *Vaccine* 2011;29(49):9194–9200.
119. Bodewes R, Fraaij PLA, Kreijtz JHCM, Geelhoed-Mieras MM, Fouchier RAM, Osterhaus ADME, et al. Annual influenza vaccination affects the development of heterosubtypic immunity. *Vaccine* 2012;30(51):7407–7410.
120. Bodewes R, Kreijtz JH, Rimmelzwaan GF. Yearly influenza vaccinations: a double-edged sword? *Lancet Infectious Diseases* 2009;9(12):784–788.
121. Hoschler K, Thompson C, Andrews N, Galiano M, Pebody R, Ellis J, et al. Seroprevalence of influenza A(H1N1)pdm09 virus antibody, England, 2010 and 2011. *Emerging Infectious Diseases* 2012;18(11):1894–1897.