Use of Vaccines against Pandemic Influenza

Scientific Evidence Base Review

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Use of Vaccines against Pandemic Influenza

Scientific Evidence Base Review

Prepared by the Immunisation Team. A draft of this paper was circulated to members of the Joint Committee on Vaccination and Immunisation Influenza (JCVI) sub-committee, officials at the Medicines and Healthcare products Regulatory Agency (MHRA) and comments received incorporated into a revised draft. The Scientific Advisory Group on Pandemic Influenza (SPI) have reviewed and endorsed an updated version of this review. The review will be updated periodically to reflect any additions to the scientific literature that might alter any of its conclusions.

Contents

Executive summary

1. This paper summarises scientific information on pre-pandemic and pandemic influenza vaccines. It is an update of an earlier paper provided to the Scientific Advisory Group on Pandemic Influenza that was published in 2007[1] that has been modified in light of scientific studies published since that time[2,3]. This is an active area of scientific research and future developments may appreciably modify current scientific knowledge. Most work on pre-pandemic vaccines prior to the emergence of the 2009 H1N1v pandemic has focussed on the production of vaccines against the highly pathogenic avian influenza A H5N1 strains.

2. The most significant development since the original paper was prepared has been the emergence in 2009 of the pandemic 2009 H1N1v influenza virus and the production and use of pandemic vaccines against that influenza strain. This has provided experience of the process of producing pandemic vaccines and implementing a pandemic influenza vaccination programme. However, the evidence that is accumulating on the performance of the vaccines developed to provide protection against the pandemic 2009 H1N1v influenza virus may not be generally applicable to considerations about vaccines against pandemic influenza viruses. This is because studies suggest that a significant proportion of the population, with the proportion increasing with age, had existing immunity to the pandemic 2009 H1N1v strain[4,5]. Therefore, a significant proportion of the population may have been at least partially protected from the virus and primed for vaccination, which

1 Department of Health (2007) Pre-pandemic and pandemic vaccines http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_077276?ssSourceSiteId=ab (accessed 25/10/10)

2 As well as the studies reviewed in the original paper, relevant studies were identified using the PubMed search engine and the following search terms in the title and abstract fields: pre-pandemic / pandemic vaccine / immunisation, pandemic vaccine / immunisation and reactogenicity / safety / immunogenicity / effectiveness / efficacy / cross-reactivity with new studies published between January 2007 and June 2010 (inclusive) considered. Data from studies on vaccines cited in the earlier paper were from abstracts of conference presentations or press releases. Many of the vaccines have been studied further and are the subject of full published reports referred to in this paper.

3 A draft of this paper was circulated to members of the Joint Committee on Vaccination and Immunisation Influenza sub-committee, officials at the Medicines and Healthcare products Regulatory Agency and the Scientific Advisory Group on Pandemic Influenza and comments received incorporated into a revised draft.

4 Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. *N Engl J Med.* 362, 1708-1719.

5 Miller *et al* (2010) Incidence of 2009 pandemic influenza H1N1 infection in England: a cross-sectional serological study. *Lancet.* 375: 1100-1108.

may not be the situation in future pandemics. Furthermore, the properties of a future pandemic influenza virus, for which there is very little or no existing immunity, may be very different from the relatively mild nature of the pandemic 2009 H1N1v strain. A review of the strategic response to the 2009 H1N1v pandemic that included an examination of the planning and implementation of the vaccination programme has been published[6].

3. As there are likely to be many studies of the 2009 H1N1v influenza pandemic that have yet to be published, data may emerge that may improve current understanding of pandemic influenza and the development, production and use of influenza vaccines for pandemics.

Pandemic-specific influenza vaccine

4. Pandemic-specific influenza vaccines are manufactured against the pandemic strain (or an engineered derivative of the pandemic virus) once it has been identified. Since a specific vaccine against a pandemic influenza strain cannot be produced in advance of a pandemic, the European Medicines Agency (EMA) has introduced an authorisation process for pandemic vaccines to allow pandemic-specific vaccines to be developed and introduced rapidly[7].

5. This process involves the assessment of prototype ('mock up') vaccines developed against influenza strains to which the population is immunologically naïve in terms of vaccine quality, immunogenicity and safety. Provided certain criteria are met, the 'mock up' vaccine is authorised. The licence remains dormant until a pandemic influenza virus emerges when the strain in the 'mock up' vaccine is replaced with the pandemic strain and a variation to the licence made. Since the manufacture, construction and intended use of each 'mock up' vaccine and the corresponding pandemic specific vaccine are similar, the data obtained with the 'mock up' vaccine are assumed to be broadly

6 The 2009 influenza pandemic: an independent review of the UK response to the 2009 influenza pandemic. http://www.cabinetoffice.gov.uk/media/416533/the2009influenzapandemic-review.pdf (accessed 25/10/10)
7 EMA pandemic influenza authorisation procedures. http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000468.jsp&mid=WC0b01ac05801dbba0&murl=menus/special_topics/special_topics.jsp&jsenabled=true (accessed 25/10/10)

predictive of the immunogenicity and safety of the pandemic-specific vaccine. Although this process shortens the time to authorisation, the manufacture of pandemic-specific vaccine still takes some months. For this reason, it is unlikely that sufficient pandemic-specific vaccine would be available before the end of the first wave of infections in an influenza pandemic. This proved to be the case during the 2009 H1N1v influenza pandemic when vaccine only became available within the second epidemic wave in the UK following several months of development and production with initial supplies of vaccine limited.

6. Due to the close match between the pandemic virus and the viral components in a pandemic-specific vaccine, these vaccines are expected to be effective against the circulating virus.

7. A number of 'mock up' vaccines have been licensed by the EMA[8].

Pre-pandemic influenza vaccine

8. Pre-pandemic vaccines are vaccines prepared from influenza viruses considered to have pandemic potential that are intended for use before or just after a pandemic is declared. They are the only clinical countermeasure with the potential to develop population protection before a pandemic virus emerges. Mathematical modelling suggests that depending on the severity and transmissibility of the pandemic influenza strain, use of a pre-pandemic vaccine could reduce attack rates even if the vaccine was of low effectiveness[9].

9. The effectiveness of a pre-pandemic vaccine will be a function of (i) its ability to induce, in an immunologically naïve population, a persistent potentially protective immune response specific to the viral strain used to produce the vaccine, (ii) the extent to which the immune response elicited against the strain used in the pre-pandemic vaccine is able to provide

8 EMA Pandemic influenza vaccines http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000462.jsp&murl=menus/special_topics/special_topics.jsp&mid=WC0b01ac058004b9ac&jsenabled=true (accessed 25/10/10)
9 Lee *et al.* (2009) Combination strategies for pandemic influenza response – a systematic review of mathematical modelling studies. *BMC Medicine*. 7; 76-83.

cross-protection against the eventual pandemic strain and (iii) the coverage of vaccination achieved before the pandemic influenza strain is circulating widely within the population.

10. The clinical study data required for approval of a vaccine for pre-pandemic use are greater than those required for approval for use only in a pandemic situation when a variation to an existing marketing authorisation is sought. Once approved, pre-pandemic vaccines are specifically indicated for active immunisation against the influenza virus type in the vaccine (e.g. influenza A H5N1) with no restriction of use to any specific WHO pandemic phase.

11. At the time of writing, one pre-pandemic vaccine against influenza A H5N1 has been licensed by the EMA[8,10]. Currently this vaccine is licensed for use in those aged 18 years and older. Recent horizon scanning by the Joint Committee on Vaccination and Immunisation (JCVI, June 2010)[11] identified another pre-pandemic vaccine that may be submitted for licensure within the next two years for use in those aged six months and older.

Vaccine efficacy on the basis of assumed correlates of protection

12. In advance of use of any new influenza vaccine, efficacy can only be assessed on the basis of the immune response elicited against the virus used to manufacture the vaccine as well as any measurable response there may be against drifted variants of that virus and against more distantly related influenza viruses in clinical trials and experimental studies. The immune response in terms of the amount of antibody elicited in response to the vaccine may be assessed by means of haemagglutination inhibition [HI] assays, single radial haemolysis [SRH] assays and/or neutralising antibody (NA) assays. For the

10 EMA pre-pandemic vaccine http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001015/human_med_000985.jsp&mid=WC0b01ac058001d124&murl=menus/medicines/medicines.jsp&jsenabled=true (accessed 25/10/10)
11 JCVI, horizon scanning paper for the meeting on 16th June. http://www.dh.gov.uk/ab/JCVI/DH_118735 (accessed 25/10/10)

purpose of assessing the immunogenicity of seasonal, pre-pandemic and pandemic vaccines, the EMA defines the seroprotection rate as the percentage of adult subjects with an HI titre ≥ 1:40 or a SRH zone >25mm^2 [12]. Criteria are laid down regarding post-vaccination seroprotection rates, seroconversion rates (defined according to pre-vaccination serostatus) and increases in geometric mean titres from pre- to post-vaccination that should be achieved in response to vaccination.

13. However, there are scientific uncertainties around the validity of these criteria to reliably predict the efficacy of seasonal influenza vaccines and they are of uncertain relevance when applied to responses against pre-pandemic or pandemic vaccines. The criteria were derived from evidence of some degree of reduction in seasonal influenza disease following vaccination of subjects who were very likely to have some degree of pre-existing immunity. Subjects without detectable antibody prior to vaccination in HI or SRH assays might still have some degree of protection against circulating strains as a result of earlier priming of the immune system.

14. These criteria are not definitive predictors of protection for seasonal influenza vaccines and may not be reliable for predicting protection against pandemic strains for which the majority of people would have no immunological priming. Studies in animal models (e.g. ferrets and mice) have examined the immune response to candidate pre-pandemic or pandemic influenza vaccines and the protection provided when the animals are subsequently challenged with an influenza strain[13]. These studies can provide some supporting evidence that elicitation of a measurable immune response to vaccination could provide some protection against infection or, at least, against clinically apparent disease[14]. However, data from animal studies cannot be extrapolated directly to the human situation of influenza circulating in a community.

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12 Committee for Medicinal Products for Human Use (CHMP) Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (revision) http://www.ema.europa.eu/pdfs/human/vwp/471703en.pdf (accessed 25/10/10) and Committee for Proprietary Medicinal Products (CPMP) Note for guidance on harmonisation of requirement for influenza vaccines. http://www.ema.europa.eu/pdfs/human/bwp/021496en.pdf

13 A range of animal studies were reviewed in the original paper: Department of Health (2007) Pre-pandemic and pandemic vaccines http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_077276?ssSourceSiteId=ab (accessed 25/10/10)

14 Bodewes *et al.* Animal models for the preclinical evaluation of candidate influenza vaccines. *Expert Rev. Vaccines.* 2010; 9: 59-72.

15. Cohort studies of the proportion of clinically, and preferably virologically confirmed, influenza in vaccinated and non-vaccinated individuals provide the best indication of vaccine effectiveness. However, such studies are dependent on the presence of significant levels of disease in the population, and, as it may take months to accrue sufficient data, would only allow assessment of the effectiveness of a pre-pandemic vaccine later in, or for a pandemic-specific vaccine, after a pandemic.

16. Evidence from the 2009 pandemic suggests that effective vaccines were produced when authorisation criteria based on these correlates were applied to the assessment and licensing of pandemic 2009 H1N1v vaccines (see later). However, the evidence also suggests that there had been a significant degree of immunological priming against this pandemic virus in the general population[4,5] so the experience gained may not be relevant to any future pandemic in which this situation does not apply.

Cross-protection

17. Since influenza viruses are unstable and drift, it is important that a pre-pandemic vaccine provides some degree of cross-protection, or at least cross-priming, against drifted variants of the same influenza subtype. Therefore, it is highly desirable that high and durable antibody titres are demonstrated against drifted variant strains of the same influenza type since the virus used to manufacture the vaccine is unlikely to be identical to the circulating pandemic strain. In addition, it is very desirable that evidence of cross-priming is obtained based on observation of booster responses when those vaccinated are later exposed to drifted variants that may emerge over time.

18. It cannot be expected that the virus used to manufacture a specific pre-pandemic vaccine would elicit any useful degree of immunological priming against other influenza sub-types. However, the cross-antigenicity of each of the haemagglutinin and neuraminidase antigens could be used to assess the degree of potential priming[15].

15 Rimmelzwaan & McElhaney. Correlates of protection: novel generations of influenza vaccines. *Vaccine.* 2008; 265: D41-D44.

19. Cross-protection is also a useful, though not essential, property of pandemic-specific vaccine in order to provide protection as well as priming against drifted variants of the original pandemic strain in the years following the onset of the pandemic. It is expected that informative long-term data may be accumulated on the immune responses to seasonal influenza vaccines containing drifted variants of the pandemic strain given in subsequent years to subjects who received pandemic 2009 H1N1v vaccine.

20. For the reasons outlined above, it is not possible to predict the level of cross-protection induced by pre-pandemic vaccines against a future pandemic virus. The potential cross-protection can only be extrapolated on the basis of induction of cross-reacting antibody titres, which cannot be relied upon to accurately predict the likely protection the vaccine will provide. Animal studies may provide some supporting data on the potential cross-protection produced by vaccination against one influenza strain following challenge with other influenza strains[14,16]. However, again extrapolating data from animal studies to humans is difficult.

Evidence of immunogenicity, cross-protection and safety of vaccines against pandemic influenza

21. Published clinical trials on influenza A H5N1 vaccines are summarised in Annex 1, table 1. As there are differences between studies in vaccination schedule, dosage of antigen, the use of adjuvant, the assays used to assess immunogenicity, the assessment of reactogenicity and the evaluation of cross-protection, it is difficult to compare studies directly or compare the performance of specific vaccines. Nevertheless, it is possible to draw general conclusions from the data (see Annex 1, table 1 and references therein) which suggest that:

16 Forrest *et al.* Single- and multiple-clade influenza A H5N1 vaccines induce cross-protection in ferrets. *Vaccine.* 2009; 27: 4187-4195.

- immunogenicity varies widely between different products and formulations. However, as laboratories use their own assays and in the absence of standardisation of assays, it is difficult to make direct comparisons between the results produced by different laboratories
- generally two doses of vaccine are required to produce an immune response that meet EMA criteria
- the use of adjuvant increases the antibody response and it may also lead to an antibody response that may be more durable and more broadly reactive
- the optimal amount of antigen (and adjuvant) may vary by age group
- the use of adjuvant reduces the dosage of antigen needed and is therefore dose sparing
- the immune responses produced suggest that vaccines elicit variable degrees of cross-immunogenicity and cross-priming against drifted variant strains
- antibody levels following two doses of vaccine wane significantly over time but may be boosted by further vaccination
- some local and systemic but transient reactogenicity is common. The addition of adjuvant increases the local and systemic reactogenicity. The size of the trials are unlikely to identify rare reactions
- most of the data are from clinical trials in healthy adult populations
- comparisons between vaccines can only be made in head-to-head trials using the same assays. Such data have not been generated.

22. A recent meta-analysis[17] and a systematic review[18] of clinical trials of influenza A H5N1 vaccines concluded that the use of an adjuvant was advantageous and there is a need for two doses of vaccine.

23. Published studies of pandemic 2009 H1N1v vaccines are summarised in Annex 1, table 2 and also in a 2010 review by WHO[19] (although there are likely to be many data yet to be published) show that:

17 Manzoli *et al.* Immunogenicity and adverse events of avian influenza A H5N1 vaccine in healthy adults: multiple-treatments meta analysis. *Lancet Infect. Dis.* 2009; 9: 482-492.
18 Prieto-Lara & Llanos-Mendez. Safety and immunogenicity of prepandemic H5N1 influenza vaccines: a systematic review of the literature. *Vaccine.* 2010; 28: 4328-4334.

- these vaccines produced immune responses in healthy groups of people including young children indicative of seroprotection
- the vaccines were well tolerated producing mild or moderate transient adverse reactions
- use of adjuvant can be antigen dose sparing
- one dose of vaccine was sufficient to induce an immune response indicative of seroprotection.

24. However, it may not be possible to extrapolate directly the findings of studies on pandemic influenza A 2009H1N1v vaccines to vaccines produced against other pandemic strains for the reasons explained earlier. It therefore may not be assumed that a one dose strategy for future pandemic vaccines would provide adequate protection on the basis of the findings of studies on 2009 H1N1v vaccines.

25. The WHO have compiled a database of both published and unpublished data from 160 clinical trials of pandemic vaccines submitted to it mostly on vaccines against the influenza A H5N1 and H1N1v strains but also data on vaccines against H2, H3, H7 and H9 strains[20]. The database is available at: http://www.who.int/entity/vaccine_research/immunogenicity/immunogenicity_table.xls (accessed 25/10/10). General conclusions similar to those in paragraphs 20 and 22 above can be drawn from inspection of these data.

26. Safety monitoring during the use of pandemic 2009 H1N1v vaccines in the UK suggests that these vaccines have a favourable safety profile[21]. Furthermore, following a review of safety data collected from pandemic influenza A 2009 H1N1v vaccination programmes worldwide, the WHO Global Advisory Committee on Vaccine Safety concluded (June 2010) that the safety profile of pandemic influenza A 2009 H1N1v vaccines was

19 6th WHO Meeting on Evaluation of Pandemic Influenza Vaccines in Clinical Trials, 18-19 February 2010, Geneva. http://www.who.int/vaccine_research/diseases/influenza/meeting_18_19Feb2010/en/index.html (accessed 25/10/10)
20 Initiative for Vaccine Research Tables on clinical trials of pandemic influenza prototype vaccines (06/08/10) http://www.who.int/vaccine_research/diseases/influenza/flu_trials_tables/en/index.html (accessed 25/10/10)
21 MHRA 2010. Suspected adverse drug reaction (ADR) analysis swine flu vaccines - H1N1 (Celvapan and Pandemrix) - Final Public Summary - 1 April 2010 http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON078911 (accessed 25/10/10)

reassuring with most adverse events reported after vaccination not serious with no unexpected safety concerns identified[22].

Strategies for use of pre-pandemic and pandemic vaccines

27. Vaccines against pandemic influenza could be used:

- during the inter-pandemic period in anticipation of an influenza pandemic at some point in the future
- in the pre-pandemic period when there is evidence that an influenza pandemic may be arising and / or
- during an influenza pandemic.

28. Use of pre-pandemic vaccine during the inter-pandemic phase was considered by the WHO Strategic Advisory Group of Experts (April 2009)[23]. It concluded there is insufficient scientific evidence to recommend the use of influenza A H5N1 vaccines, or to propose that such vaccines be made available in the inter-pandemic period for the general global population, either to prime them or immunise them against infection with a potential pandemic influenza H5N1 virus. Similarly, JCVI also advised (June 2009) against inter-pandemic use of an unlicensed pre-pandemic vaccine[24]. This was because the risk of a pandemic needed to be balanced against the risk of adverse reactions to the vaccine and the latter were unknown at the time.

22 WHO Global Advisory Committee on Vaccine Safety meeting 16-17 June 2010 (2010) *Weekly epidemiological record.* 85; 285-292. http://www.who.int/vaccine_safety/wer2010_wer8530.pdf (accessed 25/10/10)
23 WHO (2009) Strategic Advisory Group of Experts: recommendations on the use of licensed human H5N1 influenza vaccines in the interpandemic period *Weekly epidemiological record*. 84; 237-248. http://www.who.int/wer/2009/wer8424.pdf (accessed 25/10/10)
24 JCVI Influenza sub-committee minutes of March 2009 meeting. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_103575.pdf (accessed 25/10/10)

29. A number of different vaccination strategies can be envisaged for the use of pandemic influenza vaccines when a potential pandemic is emerging / during a pandemic:

    (i) use of pandemic-specific vaccine, once available, during a pandemic (the situation in the 2009 pandemic)
    (ii) use of pre-pandemic vaccine when a potential influenza pandemic is emerging or in the early stages of an influenza pandemic or
    (iii) (i) and (ii) combined ('prime-boost strategy')

30. The effectiveness of a vaccination strategy is dependent on the effectiveness of the vaccine, the interval between vaccination and exposure to the pandemic virus, the quantity of vaccine available and the rate at which it becomes available, the rate at which a vaccination programme can be implemented and delivered and the coverage of vaccination.

31. In relation to (i), the experience of the 2009 H1N1v pandemic showed clearly that, with current production methods, adequate quantities of pandemic specific vaccine are unlikely to become available until during the second pandemic wave, limiting the impact of vaccination.

32. In relation to (ii), a pre-pandemic vaccine could potentially provide adequate protection against a pandemic strain if the strain used to produce the vaccine closely matched that of the pandemic virus, otherwise its impact may be limited or absent.

33. In relation to (iii), vaccines could be used in a 'prime-boost' strategy where one or two doses of pre-pandemic vaccine are given before or early in a pandemic, followed by one dose of pandemic specific vaccine, once available. The currently licensed pre-pandemic influenza A H5N1 vaccine is for use in adults in a two dose schedule. The licence suggests that in the event of an influenza pandemic, those previously vaccinated with one or two doses of pre-pandemic vaccine may receive a single dose of pandemic vaccine instead of the two doses required in previously unvaccinated individuals if the pre-pandemic vaccine is derived from a different clade of the same influenza subtype as the pandemic influenza strain[10].

34. For a 'prime-boost' strategy to be effective, the pre-pandemic vaccine would need to provide sufficient priming to minimise disease and to allow a pandemic-specific vaccine boosting dose to be effective. Whilst the priming doses can be given before or early in a pandemic, pandemic-specific vaccine is unlikely to be available until after the first pandemic wave has passed. Therefore, it would be important that sufficient protection can be induced by the pre-pandemic vaccine.

35. A 'prime-boost' strategy that includes a single rather than two doses of pre-pandemic vaccine would need to be based on the assumption that a single dose of vaccine would provide sufficient priming and protection. However, available data (see Annex 1, table 1 and references therein) indicate that a single dose of influenza A H5N1 vaccine may often not be sufficient to produce a large (nor potentially lasting) immune response and therefore, two doses of pre-pandemic vaccine may be required. Furthermore, the use of vaccines in a single dose prime boost strategy may not conform to current licensing of pre-pandemic vaccines, which is based on evidence of immune responses following two doses rather than a strategy of a single dose of pre-pandemic vaccine to 'prime' for a subsequent 'boost' with a different pandemic-specific vaccine. However, the EMA has asked for clinical data on the vaccines used in such a strategy[25].

36. There is evidence from a number of studies that have explored the impact of a priming and boosting strategy (see Annex 1, box 1 and references therein) that the immune response induced by a priming influenza vaccination can be boosted several years later by a subsequent influenza vaccination.

37. Targeting or prioritising vaccination to sub-populations may significantly improve the impact of a pre-pandemic and / or pandemic-specific vaccination programme. Sub-populations that might be prioritised / targeted for vaccination could include children, who are generally efficient transmitters of influenza, and/or the elderly and/or those with in clinical risk groups with medical conditions that make them at increased risk of the complications from influenza. This could include pregnant women who were shown to be at increased risk from the pandemic 2009 H1N1v strain[4] and who, if vaccinated, are likely

25 CHMP recommendations for the Core Risk management Plan for influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier.

to provide some passive immunity to their newborn for whom the use of pre-pandemic and pandemic vaccines is not licensed. The risk to different clinical risk groups is unlikely to be equal with some groups at greater risk than others, as was found during the 2009 pandemic with mortality greatest in those with chronic neurological disease or immunosuppression[26]. In addition, front line health and social care workers might be targeted to enhance the resilience of the health and social care services during a pandemic.

38. JCVI suggested (October 2007)[27] that groups that might be targeted in a pre-pandemic vaccination programme could include, in no particular order: health and social care workers, children under 16 years and vulnerable groups such as those identified for seasonal influenza vaccination. However, the committee noted that these groups might be subject to modification or internal re-ordering in the light of scientific developments, vaccine availability at the time and real time knowledge of the scientific and clinical impact of the pandemic virus. A modelling study of vaccination strategies for pandemic-specific vaccine during the 2009 pandemic, showed that an approach of prioritising / targeting vaccination to be advantageous[28].

39. A key influence on the effectiveness of a vaccination strategy is the rate of uptake and coverage of vaccination in the sub-populations targeted with higher coverage of vaccination more likely to be effective in lowering transmission, morbidity and mortality. Data on the uptake of pandemic 2009 H1N1v vaccine showed coverage in England of around 35-40% in those in clinical risk groups and 40% amongst frontline healthcare workers by the end of the pandemic[29]. Vaccination coverage will partly depend on the swift and effective implementation of a vaccination programme and the delivery of vaccinations. It will also be strongly dependent on the importance that the groups targeted place on being vaccinated. This will be driven by perceptions amongst the

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http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003872.pdf (accessed 25/10/10)

26 Pebody *et al.* (2010) Pandemic influenza A (H1N1) 2009 and mortality in the United Kingdom: risk factors for death, April 2009 to March 2010. *Eurosurveillance.* 15, 19571.

27 JCVI minutes of October 2007 meeting: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_095066.pdf (accessed 25/10/10)

28 Baguelin *et al.* (2010) Vaccination against pandemic influenza A/H1N1v in England: a real-time economic evaluation. *Vaccine.* 28: 2370-2384.

29 Reports on H1N1 pandemic vaccine uptake. DH/HPA

target groups and the wider public of the risk of pandemic influenza to them and on the safety and ability of the vaccine to protect them. Good understanding of the behavioural drivers for vaccination, which may differ between target groups, could inform the design of vaccination and communications strategies that may be more likely to lead to higher uptake rates and coverage.

Immune response of population subgroups to vaccination

40. There will be inter-individual variation in immune response to vaccination, especially between different age groups of the population with immune system senescence in the elderly[30] and a lack of potential priming in younger age groups should there have been exposure to a similar virus in the past[4,31] and also between those that are immunocompetent and those in clinical risk groups that are immunocompromised[32]. While two doses of candidate pre-pandemic and pandemic vaccines have been demonstrated to induce an adequate immune response in healthy adults, the data base is more limited for children, older adults and clinical risk groups. However, should the immune response be poor in these groups, it is likely to be improved by additional doses of vaccine.

41. Limited published data on the effectiveness of the pandemic 2009 H1N1v vaccine in the UK, where the vaccine was used mainly in clinical risk groups and pregnant women, suggests that use of a single dose of vaccine may have been reasonably effective[33]. This was in a situation where there may have been at least some priming from previous exposure to a similar virus, especially in older age groups[4,5]. This situation may be somewhat similar to circumstances where pandemic-specific vaccination is preceded by

30 Webster. Immunity to influenza in the elderly. *Vaccine.* 2000; 18; 1686-1689.
31 Groothuis *et al.* Safety and immunogenicity of a purified haemagglutinin antigen in very young high-risk children. *Vaccine.* 1994; 12: 139-141.
32 Kroon *et al.*(2000) Antibody response after influenza vaccination in HIV-infected individuals: a consecutive 3--year study. *Vaccine*. 18:3040-3049.
33 Simpson *et al.* Vaccine effectiveness in pandemic influenza – primary care reporting (VIPER): an observational study to assess the effectiveness of the pandemic influenza A (H1N1)v vaccine. 2010. NIHR research report. http://www.netscc.ac.uk/supporting_research/flu_project_portfolio/098490.asp (accessed 25/10/10)

pre-pandemic vaccination. There are no published data on the comparative effectiveness of pandemic 2009 H1N1v vaccines in different age or different clinical risk groups of the population.

Development of new vaccines

42. Most of the viral components (split virion, whole cell, subunit) in current vaccines against pandemic influenza are produced in hens eggs or mammalian cell lines. Current methods of production take some months to produce sufficient quantities of vaccine of the required quality to support a vaccination programme, as was demonstrated in the 2009 H1N1v pandemic. Work to develop new methods to produce larger quantities of vaccines more rapidly and different formulations of vaccine using recombinant technologies (recombinant protein vaccines, virus-like particle vaccines, DNA vaccines, viral vector vaccines) are still largely at an early experimental stage[34,35]. Development of a universal influenza vaccine targeting conserved regions on the surface of the influenza virus has proved difficult. However, a recent approach that involves priming with a DNA vaccine coding haemagglutinin and then boosting with conventional seasonal flu vaccine has shown promise in pre-clinical studies, producing antibodies to the conserved stem of haemagglutinin and providing protection against a range of influenza strains[36].

43. The need for more rapid manufacturing of vaccines against pandemic influenza viruses and the design of vaccines which are of greater potency, are capable of conferring protection after a single dose and protect against a broad range of influenza viruses has been highlighted by the World Health Organization (WHO)[37]. The WHO Initiative for Vaccine Research most recently (November 2009) considered novel technologies for the development of new influenza vaccines: virus-like particle-based vaccines, live viral vectors, virus matrix protein 2-based vaccines, novel production methods, and novel

34 Singh *et al.* Avian influenza pandemic preparedness: developing prepandemic and pandemic vaccines against a moving target. *Expert. Rev. Mol Med.* 2010; 12: 14-27.
35 Kreijtz *et al.* Vaccination strategies and vaccine formulations for epidemic and pandemic influenza control. *Hum. Vacc.* 2009; 5: 126-135.
36 Wei *et al.* (2010) Inductaion of broadly neutralizing H1N1 influenza antibodies by vaccination. *Science.* 329: 1060-1064.
37 WHO (2006) Global pandemic influenza action plan to increase vaccine supply http://www.who.int/vaccines-documents/DocsPDF06/863.pdf (accessed 25/10/10)

delivery systems. It was concluded that little is known on the potential protective efficacy of most of these new types of vaccines in humans, and much more has to be learnt on their immunogenicity and principal characteristics before they can be registered for human use. However, if successful, these new technologies could bring forward the goal of a universal influenza vaccine[38].

Risks with vaccination strategies

44. There are a number of risks in pursuing a vaccination strategy to ameliorate the effects of a pandemic. Firstly, whilst most work has been directed at the production of candidate vaccines against an avian influenza A H5N1 strain, a future pandemic strain may not, as was the case with the 2009 H1N1v pandemic, be of avian influenza A H5N1 origin. In the longer term, this risk might be mitigated by a combined H2/H5/H7/H9 vaccine or a vaccine that provides protection against most or all influenza strains (potentially such vaccines could be included within seasonal influenza vaccine programmes). However, currently there appear to be no such candidate pandemic vaccines at an advanced stage in clinical trials (although higher valency seasonal influenza vaccines are in clinical trials).

45. Secondly, if the pandemic is caused by an avian influenza A H5N1 strain or a strain against which pandemic vaccines are available, the vaccine may not be as effective as anticipated as the correlates of protection used for licensure may not have given a good indication of the effectiveness of the protection conferred by the vaccine. However, this risk did not materialise in relation to the 2009 H1N1v pandemic.

46. Thirdly, even if a pandemic vaccine is effective, a pre-pandemic vaccine based on a related but drifted strain may not be effective. The scientific basis of cross-reactivity between strains is not well understood and for this reason the extent of cross-reactivity cannot be reliably predicted[39]. However, this risk may be (partially) mitigated by a pre-pandemic vaccine that shows good evidence of cross-protection against a breadth of

38 WHO Initiative for Vaccine Research Fourth meeting on influenza vaccines that induce broad spectrum and long-lasting immune responses, London, 9-10 November 2009. http://www.who.int/vaccine_research/diseases/influenza/meeting_09_10Nov09/en/index.html (accessed 25/10/10)

drifted variants. Furthermore, a strategy that involves separate stockpiling of antigen and adjuvant with the manufacturer able to replace the antigen at relatively short notice, should a divergent strain arise could also mitigate this risk.

47. Fourthly, a pandemic specific vaccine may only be developed and produced in sufficient quantities relatively late in a pandemic thus limiting the impact it may have on reducing transmission, morbidity and mortality. This risk may be mitigated by advances that allow more rapid production of large quantities of pandemic specific vaccine.

48. Fifthly, it is possible that the risk/benefit ratio for pandemic or pre-pandemic vaccines when they are deployed in a public health programme may not be favourable (i.e. unacceptable reactogenicity profile given the degree of protection afforded). However, safety studies of influenza A H5N1 vaccines in clinical trials (see Annex 1, table 1 and references therein) and from the wide use of pandemic 2009 H1N1v vaccines in the UK[21] and worldwide[22] suggests that the risk of a unfavourable safety profile may be low, although it cannot be ruled out. Safety monitoring of those vaccinated during a vaccination programme would allow the size of the safety database to accrue and this would be enhanced if safety data from a number of different countries were pooled.

49. Lastly, the effectiveness of a vaccination strategy is highly dependent on the uptake of vaccine by the sub-populations targeted. If uptake is low, the success of the strategy will be compromised. The risk of low uptake may be mitigated by advance planning of the implementation and delivery of a pandemic vaccination programme. It may also be mitigated by clear, effective and timely communications about the reasons for, benefits and risks of, vaccination.

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39 Boon & Webby. Antigenic cross-reactivity among H5N1 viruses. *Curr. Top. Microbiol. Immunol.* 2009; 333: 25-40.

Summary

- There is already considerable published and ongoing research into the development of pandemic vaccines and further scientific advancements may appreciably modify vaccination strategies. Furthermore, full study of the 2009 H1N1v pandemic and the impact of the vaccines that were used has not yet been completed.
- Data on the 2009 H1N1v vaccines may not be readily or generally extrapolated to other pre-pandemic or pandemic vaccines.
- All pre-pandemic and 'mock up' pandemic-specific vaccines need to meet EMA immunogenicity, safety and quality criteria before authorisation. A number of vaccines have been authorised.
- Vaccines meeting authorisation criteria may, but are not guaranteed to, prevent influenza symptoms and prevent severe illness and death in a large proportion of those exposed in the event of a pandemic.
- Whilst candidate vaccines can be produced against one (or possibly more) particular strain of influenza virus with pandemic potential, a future pandemic may arise from a very different strain of influenza virus.
- Data suggest that influenza A H5N1 pre-pandemic (and pandemic) vaccines may need to be given in two doses to provide adequate protection in healthy adults. Data from clinical trials on the response to vaccination of young children, elderly adults is more limited and very few data are available of the immune response to vaccination of clinical risk groups.
- It is not possible to know or predict in advance, the level of cross-protection offered by a pre-pandemic vaccine against a future pandemic virus. However, good evidence of cross-reactivity against a wide breadth of virus variants will increase the chances of cross-protection against related strains.
- There is some evidence to suggest that the immune response induced by priming doses of pre-pandemic vaccine may be boosted by vaccination with pandemic specific vaccine potentially years following priming.
- Under current manufacturing methods and capacities, a pandemic-specific vaccine is unlikely to be available until after the first pandemic wave.

- Experience with influenza A H5N1 vaccines in clinical trials and from the very wide use of pandemic 2009 H1N1v vaccines suggests that the risk of an unfavourable safety profile for a pandemic vaccine may be low, although it cannot be ruled out.
- Key uncertainties and challenges are summarised in the table below:

Area of uncertainty	**Key uncertainties / challenges**
Pandemic characteristics	• Timing • Severity • Aetiology (H5N1 or other type) • Geographical origin • Timing of arrival and spread in the UK
Pandemic influenza characteristics	• Presence of existing population immunity • Transmissibility • Attack rate • Case-fatality ratio • Relative risks of complications by age and clinical group
Pre-pandemic vaccine performance	• Cross-protection against pandemic strain (in general population and in age and risk groups) • Priming for pandemic-specific vaccination (in general population and in age and risk groups) • Duration of protection and priming (in general population and in age and risk groups) • Occurrence of rare adverse reactions
Pandemic-specific vaccine performance	• Speed of development and production of vaccine • Protection against pandemic strain (in general population and in age and risk

	groups) • Dosage required (may be partially dependent on use of pre-pandemic vaccine) • Occurrence of rare adverse reactions
Implementation and coverage of vaccination	• Speed of implementation and delivery of vaccinations • Acceptance of vaccination by target populations
Future developments	• More rapid production of vaccine • Development of higher valency or universal vaccines

Annex 1 – Summaries of studies

Table 1: Illustrative data from clinical trials of influenza A H5N1 vaccines (see also the much larger WHO database on clinical trials of pandemic influenza prototype vaccines[18]:
http://www.who.int/entity/vaccine_research/immunogenicity/immunogenicity_table.xls [accessed 25/10/10])

Vaccine	Adjuvant	Antigen (µg), doses	Subjects (n)	Immunogenicity*	Safety	Cross-protection against drifted strains	Ref
Inactivated whole virion H5N1 (Vietnam, clade 1)	Aluminium hydroxide	5, 10 or 15, two doses 28 days apart	Healthy adults aged 18-60 years (~100/dose group)	14 or 28 days after first dose: 10-42%(HI) and 24-47% (MN) seroconversion 28 days after second dose 42-82%(HI) and 62-89% (MN) seroconversion	34% of subjects reported ARs** (no USARs) all resolving within 73 hours	28 days following two 10 µg doses 34% (HI) seroconversion for Indonesia (claude 2.1) and Anhui (claude 2.3) 34% Turkey (clade 2.2) strains and ~ 50% (MN) seroconversion for all three strains	40

40 Wu *et al.* Immunogenicity, safety and cross-reactivity of an inactivated, adjuvanted, prototype pandemic influenza (H5N1) vaccine: a phase II, double-blind, randomised trial. *Clin. Infect. Dis.* 2009; 48: 1087-1095.

Vaccine	Adjuvant	Antigen (µg), doses	Subjects (n)	Immunogenicity*	Safety	Cross-protection against drifted strains	Ref
Inactivated split virion H5N1 (Vietnam, clade 1)	Oil and water (one group received unadjuvanted 7.5 µg dose vaccine)	1.9, 3.8, 7.5 or 15, two doses 21 days apart	Healthy adults aged 18-40 years (50/dose group)	21 days after first dose (HI) 24-40% seroconversion, 21 days after second dose 72-89% (HI) seroconversion for adjuvanted and 34% for unadjuvanted vaccines with responses generally increasing with dose	15-34% of subjects reported ARs (no USARs) with 86% resolving in 1-3 days	42 days following second dose adjuvanted vaccine 35-58% subjects with HI ≥1:8 and 4-23% subjects with HI ≥1:32 against Indonesia (clade 2) strain (titres much lower for unadjuvanted vaccine)	41

41 Levie *et al.* An adjuvanted, low-dose, pandemic influenza A (H5N1) vaccine candidate is safe, immunogenic, and induces cross-reactive immune responses in healthy adults. *JID.* 2008; 198: 642649.

Vaccine	Adjuvant	Antigen (µg), doses	Subjects (n)	Immunogenicity*	Safety	Cross-protection against drifted strains	Ref
Inactivated split virion H5N1 (Vietnam, clade 1)	Oil and water or unadjuvanted	3.8, two doses, 21 days apart	Healthy adults aged 18-60 years (20/group)	86% HI seroconversion for adjuvanted vaccine	Most mild to moderate and transient. No USARs	75-85% (MN) seroconversion 21 days after second dose and 40-70% 6 months later for Indonesia (clade 2.1) Turkey (clade 2.2) and Anhui (clade 2.3) strains. No seroconversion with unadjuvanted vaccine	42,43

42 Leroux-Roels *et al.* Broad clade 2 cross-reactive immunity induced by an adjuvanted clade 1 rH5N1 pandemic influenza vaccine. *PLOS one*. 2008; 3: 1665-1670.
43 Leroux-Roels *et al.* Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial. *Lancet.* 2007: 18: 580-589.

Vaccine	Adjuvant	Antigen (µg), doses	Subjects (n)	Immunogenicity*	Safety	Cross-protection against drifted strains	Ref
Inactivated subunit H5N1 Vietnam (clade 1)	MF59 (oil and water)	7.5 or 15, two doses, 21 days apart and booster dose at 6 months	Healthy adults aged 18-60 and >60 years (~244/group)	Seroprotection (HI and SRH) 34-58% 21 days after first dose, 72-85% 21 days after second dose, 18-62% after 6 months, 84-90% 21 days after booster and 46-77% 6 months after booster	No USARs. Mild injection site pain most common AR (20-60% subjects)	28-77% seroprotection (HI and SRH) after second dose and 59-88% after booster dose to Turkey (clade 2.2) strain	44
Inactivated split virion H5N1 Vietnam (clade 1)	Aluminium phosphate or unadjuvanted	7.5, 15, 30, 45, two doses given 21 days apart and booster dose at 6 months	Healthy adults aged 18-64 years (100/dose group or 200/dose group for the two higher doses)	Seroresponse (HI ≥1:32) 21-31% 21 days after first dose, 37-59% 21 days after second dose, 4-11% 6 months later and 25-42% 21 days after booster. Similar seroprotection with MN assay	No USARs. 30% subjects with ARs, mostly mild	Seroresponse ~24% (MN ≥1:20) after second dose against H5N1 clade 2 strains (NIBRG-23 and INDO5/RG2)	45

44 Banzhoff *et al.* MF59-adjuvanted H5N1 vaccine induces immunologic memory and heterotypic antibody responses in non-elderly and elderly adults. *PLOS one*. 2009; 4: 4384-4393.
45 Nolan *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; 26:4160-4167.

Vaccine	Adjuvant	Antigen (µg), doses	Subjects (n)	Immunogenicity*	Safety	Cross-protection against drifted strains	Ref
Inactivated split virion H5N1 Indonesia (clade 2.1)	AS03a, AS03b (tocopherol) or unadjuvanted	3.75, two doses given 21 days apart	Healthy adults aged 18-64 years (~75-150/dose group)	Seroconversion (HI) 17% unadjuvanted and 49-97% adjuvanted vaccine 42 days after second dose and 3% unadjuvanted and 45-92% adjuvanted vaccine after 6 months.	No USARs. Mild injection site pain most common AR (~80% subjects with adjuvanted ~23% subjects with unadjuvanted vaccine)	Seroconversion (HI) adjuvanted vaccine 54-62% 42 days after second dose and 13-38% after 6 months against Vietnam (clade 1) strain. In a sub-study of about 150 subjects, seroconversion (NA) 89% and 79% 42 days after second dose and 61% and 2.1% after 6 months against Turkey (clade 2.2) and Anhui (clade 2.3) strains. No seroconversion for unadjuvanted vaccine	46

Vaccine	Adjuvant	Antigen (µg), doses	Subjects (n)	Immunogenicity*	Safety	Cross-protection against drifted strains	Ref
Inactivated split virion H5N1 Vietnam (clade 1)	AS03a or AS03b (tocopherol)	1.9 or 3.75, two doses given 21 days apart	Healthy children aged 3-5 or 5-9 years (~50/ group)	Seroconversion (HI) ~12-58%, 21 days after first dose, >95% 21 days after second dose and ~55-82% 6 months later	No USAR. Mild injection site pain most common AR (~60% subjects)	Seroconversion (HI) ~70-95% 21 days after second dose and <10-~70% after 6 months against Indonesia (clade 2) strain	47
Inactivated split virion H5N1 Vietnam (clade 1)	AS03 (tocopherol)	3.75, two doses given 21 days apart	Healthy adults aged 18-60 years (~600/group)	Seroprotection (HI) 94% 21 days after second dose	No USARs. Mild injection site pain most common AR	Seroprotection (HI) 50% against Indonesia (clade 2) strain	48

Vaccine	Adjuvant	Antigen (µg), doses	Subjects (n)	Immunogenicity*	Safety	Cross-protection against drifted strains	Ref
Inactivated split virion H5N1 Vietnam	None	7.5, 15, 45 or 90, two doses given 28 days apart	Healthy adults aged 18-64 years (~100/dose group)	At highest dose 28% (HI) and 17% (MN) seroprotection 28 days after first dose 57% (HI) and 53% (MN) seroprotection 28 days after second dose Poorer response with lower doses	No USARs. Mild injection site pain most common AR (~15-60% subjects increasing with dose)	ND	49
Inactivated split virion H5N1 Vietnam	Aluminium hydroxide or unadjuvanted	3.75, 7.5, 15 or 45, two doses given 28 days apart	Healthy adults aged 18-49 years (~60/dose group)	At highest dose seroprotection 25% and 33% (HI) and 58% and 51% (MN) with adjuvanted and unadjuvanted vaccine 28 days after second vaccination	No USARs. Mild injection site pain most common AR (~15-70% subjects, higher rates with adjuvanted vaccine)	ND	50

Vaccine	Adjuvant	Antigen (µg), doses	Subjects (n)	Immunogenicity*	Safety	Cross-protection against drifted strains	Ref
Reverse genetics derived H5N1 Indonesia	MF59 (oil and water) (0-100% of that usually in influenza vaccine)	3.75, 7.5 or 15, two doses 21 days apart	Healthy adults aged 18-40 years (~60/dose group)	Seroprotection ~10-80% (HI), with increasing concentration of adjuvant (similar levels for antigen doses) 21 days after second dose.	No USARs. Mild injection site pain most common AR (~20-65% subjects, higher rates with increasing concentration of adjuvant)	ND	51

*Seroprotection and seroconversion was defined in different ways in these studies but generally a seroprotection defined as e.g. ≥1: 40 HI and seroconversion defined as four-fold increase in HI or MN titres (e.g. from <1:10 to ≥1: 40 HI). In comparing the various vaccines on the basis of immune response, it needs to be borne in mind that the assays for measuring immune responses are not currently well standardised.

**Adverse reactions considered to be vaccine related. USARs – unexpected serious adverse reactions.

ND – not determined.

Table 2: Illustrative data from clinical trials of pandemic 2009 H1N1v vaccines (see also the much larger WHO database on clinical trials of pandemic influenza prototype vaccines[18]:

http://www.who.int/entity/vaccine_research/immunogenicity/immunogenicity_table.xls [accessed 25/10/10])

Vaccine and dosage	Subjects	Immune response*	Ref
One dose adjuvanted (5.25 µg antigen) or unadjuvanted split virion 2009 H1N1v vaccine (21 µg antigen)	healthy adults (n= ~65/group) aged 18 to 60 years	Seroconversion (HI) rates were 98 and 95% for adjuvanted and unadjuvanted vaccine, respectively after 21 days	52
Two doses either adjuvanted split virion (1.875 µg antigen) or non-adjuvanted whole virion (7.5 µg antigen) 2009 H1N1v vaccine	healthy children aged between 6 months and 3 years and between 3 and 13 years (n= ~200-230/group)	seroconversion (HI) rates were 98% and 80% for children aged between six months and below three years and 99% and 96% for children aged between three and below 13 years for the adjuvanted and unadjuvanted vaccine, respectively	53
Two doses of unadjuvanted split virion 2009 H1N1v vaccine containing 15 or 30 µg antigen 21 days apart	healthy children aged 6 months to below 9 years (n= ~180/dose group)	seroconversion (HI) rates were 86.8 and 94.2% for vaccine containing 15 or 30 µg antigen 21 days after first dose and 100% for both vaccines 21 days after the second dose, respectively	54
One dose of whole virion adjuvanted (aluminium phosphate) 2009 H1N1v vaccine (6 µg antigen)	healthy adults aged 18 to 60 years or older than 60 years (n= ~350)	seroconversion (HI) rates were 74 and 61% for adults aged 18 to 60 years or older than 60 years, respectively	55

One dose (7.5 to 30 µg antigen) 2009 H1N1v vaccine	children (n= 410) aged 6 months to nine years and adults aged 18 to more than 65 years (n= 724)	seroprotection (HI) rates were 45-50% of children aged six months to three years, 75-80% of children aged three to nine years, 95% of adults aged 18 to 64 years and 95% of adults aged more 65 years after 21 days	56
Two doses adjuvanted (3.75 or 7.5 µg antigen) or unadjuvanted (7.5 or 15 µg antigen) 2009 H1N1v vaccine 21 days apart	adults aged 18 to 50 years (n= 176)	seroconversion rates were 77-96% (HI) and 92-100% (MN) or 63-72% (HI) and 67-76% (MN) for adjuvanted or unadjuvanted vaccine, respectively 21 days after the first dose and 79-100% (HI) and 100% (MN) or 74-79% (HI) and 78-83% (MN) 21 days after a second dose for adjuvanted or unadjuvanted vaccine, respectively	57

*Seroprotection and seroconversion was defined in different ways in these studies but generally a seroprotection defined as e.g. ≥1: 40 HI and seroconversion defined as four-fold increase in HI or MN titres (e.g. from <1:10 to ≥1: 40 HI). In comparing the various vaccines on the basis of immune response, it needs to be borne in mind that the assays for measuring immune responses are not currently well standardised.

Box 1 – Summaries of studies exploring prime-boost vaccination strategy

A study compared the immune responses of adults (n= 48-60/group) aged 18-60 years given either one or two doses of adjuvanted pre-pandemic H5N1 influenza A/Vietnam/1194/2004 (clade 1) vaccine (3.75 µg antigen) followed six months later by a booster dose (3.75 µg antigen) of the same vaccine or a vaccine containing H5N1 A/Indonesia/05/2005 (clade 2) strain[58]. Similar levels of seroprotection were derived from two doses of A/Vietnam/1194/2004 vaccine irrespective of whether they were given 21 days (92.7-93.2%) or six months apart (89.6%). The levels of seroprotection were 92.5% against the A/Indonesia/05/2005 and 98.1% against the A/Vietnam/1194/2004 strains when a 'booster' dose of A/Indonesia/05/2005 vaccine followed a single 'priming' dose of A/Vietnam/1194/2004 vaccine.

In a study, adults (n=37) previously vaccinated around 1998 with two doses (either 25, 45 or 90 µg antigen) of unadjuvanted influenza A/Hong Kong (H5N1, clade 0) vaccine were vaccinated with one dose (90 µg antigen) of unadjuvanted influenza A/Vietnam (H5N1, clade 1) vaccine about a decade later[59]. Seroresponse rates were 23% and 43% (HI) and 10% and 41% (MN) 28 and 56 days following vaccination, respectively in those not previously vaccinated with H5N1 vaccine. In contrast, seroprotection rates in those previously vaccinated with H5N1 vaccine were 68% and 54% (HI) and 76% and 73% (MN) 28 and 56 days following vaccination, respectively.

A study compared the immune responses following vaccination of adjuvanted H5N1 A/Vietnam/1194/2004 clade 1 vaccine (two doses, 7.5µg antigen, 21 days apart) in groups of adults which had been vaccinated previously with adjuvanted (n= 12) or unadjuvanted (n= 12) influenza H5N3 A/duck/Singapore/1997 (clade 0) vaccine or had not been vaccinated (n= 30) during 1999–2001[60]. Each of the previously vaccinated ('primed') subjects had received two or three doses (containing 7.5, 15, or 30 µg antigen) of either non-adjuvanted or adjuvanted H5N3 vaccine. Seroconversion rates after two doses of H5N1 vaccine were highest in the group 'primed' with adjuvanted vaccine followed by the group 'primed' with unadjuvanted followed by the 'unprimed' group (100% versus 58% versus 23% HI; 100% versus 83% versus 50% SRH; 100% versus 92% versus 10% MN, respectively 21 days following vaccination and 92% versus 64% versus 8% HI; 100% versus 82% versus 50% SRH; 92% versus 45% versus 12%, respectively 202 days following vaccination.