



# **TECHNICAL REPORT**

## **EXPERT ADVISORY GROUPS ON HUMAN H5N1 VACCINES**

**Scientific Questions  
Stockholm, August 2007**



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## 1. BACKGROUND

A number of pharmaceutical companies have reported that they are developing human H5N1-based influenza vaccines, and some European national authorities are considering stockpiling these 'pre-pandemic vaccines'. The rationale is that, unlike a specific 'true' pandemic vaccine, these can be made ahead of the emergence of a pandemic virus. If there is an H5N1-based pandemic, the strategy of having a stockpiled vaccine (and possibly deploying it in advance), even if incompletely matched to the pandemic virus (perhaps giving very low protection), may prevent more infections and deaths than waiting for specific 'true' pandemic vaccines (Ferguson et al, 2006; Germann et al, 2006). There are substantial benefits in developing H5N1 pre-pandemic vaccines as data and knowledge from clinical trials of newly developed H5N1 human vaccines represents an important addition to pandemic preparedness. However, there are a number of technical difficulties and uncertainties that need to be resolved before these vaccines can be deployed with confidence (see below).

At a meeting of ECDCs Advisory Forum in September 2006 Dr Terhi Kilpi (Finland) presented the scientific and public health thinking behind that country's decision to invest in enough human H5N1 vaccine to offer a single dose to its entire population in the event of an H5N1 pandemic. The Advisory Forum strongly recommended that ECDC should establish an Expert Advisory Group (EAG) to rapidly identify evidence relating to the most prominent questions, and to report back to ECDC and Member States that are considering whether to use such vaccines. After consideration, and following consultation with some experts, the Scientific Advice Unit identified two sets of questions:

1. Highly technical **scientific questions** over whether, and how well and safely, a vaccine prepared against the current H5N1 antigens will work against an H5-based pandemic.
2. **Public health and operational questions** concerning when such vaccines might be used, including the specific triggers, and for which groups in the population.

Therefore ECDC convened two Expert Advisory Groups (Human H5N1 Vaccines), EAGs 1 and 2, with inter-group liaison being achieved through the two chairpersons. Membership included technical representation from the European Commission (C3) and the European Agency for the Evaluation of Medicinal Products (EMA). Communication was also established with the World Health Organization (WHO) which is also considering these topics and will draw on the work of the ECDC groups (WHO, 2006). Membership of the two EAGs is detailed in Appendix 3.

### 1.1. Specific remit and questions of EAG1: (Human H5N1 Vaccines – Scientific)

- (a) To consider, refine and prioritise the proposed questions with the chair of EAG2 to ensure all important questions are covered.
- (b) To seek evidence to the questions, to identify those best suited to analyse the available data, and to make recommendations on actions including research to be undertaken.
- (c) To produce a detailed report on the scientific data on the vaccines by May 2007 and to report back to ECDC and its Advisory Forum.



EAG1 was tasked with addressing the following ten questions:

1. What antigen content is needed for response?
2. What is the added value of a number of adjuvants in terms of improving response?
3. How many doses are needed for protection?
4. How long is protection likely to last?
5. For the previous four questions, determine the response also for children.
6. What is the shelf-life of a pre-produced H5N1 vaccine?
7. What is the risk of immunologic 'mal-reaction' between the vaccine strain used and the pandemic strain – the 'dengue effect'?
8. What is the risk of other adverse events from the vaccine and potential new adjuvants likely to be used?
9. What is the probability of cross protection between the strain used in a pre-produced H5N1 vaccine and a pandemic H5N1 strain?
10. What could be the expected efficacy?

At the third meeting of EAG1, a further question (question 15) was referred from EAG2: 'When should the H5N1 vaccine be given?' EAG1 discussed the issue and passed comments to EAG2 via the ECDC observer.

## **1.2. Specific remit and questions of EAG2: (Human H5N1 Vaccines – Public Health)**

- (a) To consider, refine and prioritise the proposed questions with the chair of EAG1 to ensure all important questions are covered.
- (b) To seek answers to the questions, to identify those best suited to answer the questions, and to make recommendations on actions including research to be undertaken.
- (c) To produce a detailed report on the scientific issues around these vaccines by May 2007 and to report back to ECDC and its Advisory Forum.

EAG2 was initially tasked with addressing the following ten questions:

### **Social science (including mathematical and economic modelling)**

11. Which groups should be immunised? Rationale for each (with special reference to children, adolescents and healthcare workers) with the desired population coverage.
12. What is the cost and the likely cost-benefit of vaccination with a human H5N1 vaccine in the event of an H5N1-based pandemic?
13. How is the public likely to respond to a low efficacy vaccine with and without an imminent threat?
14. How and when should countries go public about this strategy?
15. What methods should be used for communicating with different groups?

## Operational

16. When should the H5N1 vaccine be given?
17. What might be the defined trigger points for applying the intervention in different groups?
18. What systems are needed for rapid assessment of a developing pandemic to determine whether to deploy the vaccine and to whom?
19. What systems are needed for rapid detection, assessment and investigation of adverse events?
20. What systems are needed for rapid assessment of effectiveness when the vaccine is deployed?

At their meeting, EAG2 agreed that they did not have the necessary specialist expertise to answer questions 13–15 above concerning public reaction and communication to the public. These questions were thus not addressed at this stage. EAG2 did, however, identify a further relevant question which was addressed: 'With a given amount of antigen available, what is the trade-off between giving a few people a high dose (or two doses) versus giving many people a lower dose (or only one)?'

Therefore the questions answered by EAG2 became:

11. Which groups should be immunised? Rationale for each (with special reference to children, adolescents and healthcare workers) with the desired population coverage.
12. What might be the defined trigger points for applying the intervention in different groups?
13. With a given amount of antigen available, what is the trade-off between giving a few people a high dose (or two doses) versus giving many people a lower dose (or only one)?
14. What is the cost and the likely cost-benefit of vaccination with a human H5N1 vaccine in the event of an H5N1-based pandemic?
15. When should the H5N1 vaccine be given?
16. What systems are needed for rapid assessment of a developing pandemic to determine whether to deploy the vaccine and to whom?
17. What systems are needed for rapid detection, assessment and investigation of adverse events?
18. What systems are needed for rapid assessment of effectiveness when the vaccine is deployed?

## 1.3. Imponderable questions

The following questions were identified as highly relevant to the discussions but outside the scope of the expertise of the EAGs and so were not tackled at this time. The most important question is that concerning the risk of an H5-based pandemic; the interim ECDC risk assessments have noted that this risk cannot be quantified but that it could not be said to be zero (ECDC, 2006).



- What is the probability of future influenza pandemics?
- How big and severe could it become?
- What is the probability that it will be caused by an H5N1 strain?
- What is the risk of litigation?
- What is the possibility of developing a 'generic' influenza vaccine against all subtypes?

## **1.4. The reports**

Two separate reports have been produced, one containing the conclusions of EAG1's meetings and the other containing the outcome of EAG2's discussions. Both reports contain a common introduction (sections 1 to 3) and common appendices and references. The reports differ in the central portion, in that this report contains the answers to EAG1's questions.

Both reports have been considered by the ECDC Advisory Forum. Additions, amendments and clarifications have been provided where requested by the chairs of each EAG in discussion with the members where necessary.

## **2. PROCESS**

The process by which the EAGs operated is described in Appendix 4. Members' declarations of interest are listed in Appendix 5.

## **3. REFERENCES CONSIDERED**

References are embedded in the text as appropriate and listed in full in Appendix 6.

## 4. SUMMARY ANSWERS

The answers provided by the EAGs to the questions posed by ECDC represent the best view based on the evidence available at the time of writing. The EAGs fully expect and acknowledge that the science will change rapidly. The EAGs are not able to speculate on what is not yet known or may yet be discovered. No assumptions can be made at this stage about the possible evolution of further clades or sub-clades of H5N1 or the repercussions that such developments might have on vaccines. The EAGs felt it would be advisable for the groups to re-convene periodically in order to review any new data.

When answering the questions posed by ECDC, it was necessary to make certain assumptions. To qualify the answers given to the following questions, a number of definitions were assumed. These can be seen in Appendix 1. The summary answers given below are supported with further evidence and discussion in Section 5.

This document contains ECDC scientific opinion following consultation with appropriate experts, and as such the recommendations should be taken as guidelines rather than rules and are not binding for Member States. The approach taken for an EU position would not be consistent across all Member States since decisions would likely be taken at national or more local level.

### 4.1. What antigen content is needed for response?

This is highly dependent upon the individual vaccine formulation and the presence of an adjuvant. In general terms, split and sub-unit vaccines (the types in use in the EU as seasonal influenza vaccines) are likely to require very high doses of antigen per dose (90µg) without an adjuvant, 30µg or more if using alum adjuvant, but potentially in the range of 3.8–7.5µg if newer adjuvants are used. Data from a whole virus non-adjuvanted vaccine (using wild-type H5N1 strain and grown in cell culture) suggest that 7.5µg per dose will be needed. Lower doses of many developmental vaccines may be evaluated in the future. At the current time and with the current level of technology, it will be expensive and take time to produce a pre-pandemic or pandemic vaccine in sufficient amounts for effective use.

### 4.2. What is the added value of a number of adjuvants in terms of improving response?

Adjuvants have been used successfully to reduce the amount of antigen required with most (but not all) developmental human H5N1 vaccines. Adjuvants appear essential in split and sub-unit vaccines to keep the amount of antigen at or below the quantities used in seasonal influenza vaccines (15µg). Adjuvants may also affect the ability of the immune response to recognise antigenically variant strains and impact on the duration of the immune memory.



### **4.3. How many doses are needed for protection?**

One dose may have some positive effects (e.g. immune priming) but as far as we can tell, two doses are needed for protection. A two-dose strategy might be delivered in a number of different ways:

- zero doses of pre-pandemic vaccine + two doses of pandemic vaccine;
- one dose of pre-pandemic vaccine + one dose of pandemic vaccine;
- two doses of pre-pandemic vaccine + zero doses of pandemic vaccine.

Further data (and a consideration of issues relating to availability and logistics) are required before any conclusions can be drawn about which of these regimens would be most appropriate in practice. In addition, much may depend upon the timing between pre-pandemic vaccination and pandemic vaccination, and the degree of heterogeneity between the vaccine viruses used. Member States may have differing capacities and abilities to undertake the strategies over differing time periods, e.g. a rapid 'catch-up' style campaign may not be achievable by all Member States.

### **4.4. How long is protection likely to last?**

It is assumed that this will be at least as long as the persistence of detectable antibodies. The data vary by product, but periods of up to 16 months have so far been recorded. Immune memory is expected to persist much longer than measurable circulating antibodies but the precise duration has not been established and this memory may, or may not, provide protection. The timing of a priming dose is a matter of fine judgement in relation to variables in relation to the strength of immune memory and ongoing antigenic drift.

### **4.5. For the previous four questions, determine the response also for children**

So far, there are no data available for H5N1 vaccines in children under two years old, but the limited data available on older children indicate that their response to human H5N1 vaccines is likely to be similar to that in young adults. It is important to note that only very limited data are available about the response of children to adjuvanted influenza vaccines. However, it is important to bear in mind that virtually all children routinely receive alum-adjuvanted vaccines from an early age as part of the childhood vaccination schedules in operation across Europe, thus alum has a long and safe history in relation to childhood vaccines. Concerning novel adjuvants, favourable safety data are available in infants for a malaria vaccine containing AS adjuvant, and in toddlers and newborns for CMV and HIV vaccines respectively, both containing MF59.

### **4.6. What is the shelf-life of a pre-produced H5N1 vaccine?**

At least one year, based on data from seasonal influenza vaccines. Vaccine stored in bulk may have an even longer potency (refer to individual manufacturer data). Theoretically, the presence of adjuvant may also affect shelf-life. Shelf-life issues are entangled with delivery issues, and it must be remembered that shelf-life runs from the date the bulk was assembled, not when the vial was filled or the purchase/delivery date.

#### **4.7. What is the risk of immunologic 'mal-reaction' between the vaccine strain used and the pandemic strain – the 'dengue effect'?**

Based on the experience of seasonal influenza vaccination and animal challenge models with H5N1 vaccines the risk is considered rather low, but cannot be ignored completely. Surveillance to monitor adverse events is key.

#### **4.8. What is the risk of other adverse events from the vaccine and potential new adjuvants likely to be used?**

There is presently no evidence of an unacceptable adverse event profile with any of the human H5N1 vaccines so far evaluated. In general terms most human H5N1 vaccines will be adjuvanted, increasing the risk of reactogenicity. Widespread population deployment on the scale anticipated for an H5N1 vaccine will lead to the reporting of adverse events, and/or the perception of adverse events, or vaccine failures. Preparations must be taken to handle these eventualities in a timely manner.

#### **4.9. What is the probability of cross-protection between the strain used in a pre-produced H5N1 vaccine and a pandemic H5N1 strain?**

There are early encouraging signs that some cross-protection is likely. Studies using human sera indicate some cross-neutralisation, yet challenge studies in mice and ferrets show very good cross-protective activity between viruses of clades 1 (vaccine strain) and those in clades 2 and 3 of the Asian H5N1 lineage. However, these are preliminary data. A wide immunological cross-reaction against currently available H5N1 strains will more likely induce some protection against a future H5N1 pandemic strain. The probability of cross-protection is likely to decrease with the increased antigenic distance between the pre-pandemic vaccine strain and the pandemic strain. The use of adjuvants such as MF59 and AS have both shown evidence of improved cross-reaction of sub-unit and split virion vaccines, respectively, against divergent H5N1 strains. Preliminary data have shown that a (cell culture-derived) whole virus wild type vaccine can induce a cross-reactive immune response without the use of an adjuvant.

#### **4.10. What could be the expected efficacy?**

Efficacy and effectiveness are unknown and measuring both will be difficult (but not impossible) for individual products even after a pandemic virus has emerged and vaccines are being deployed widely. However, the data from animal models are so far encouraging, as are bio-mathematical models which indicate a likely effectiveness of a vaccine even when of modest efficacy, provided that it is administered in good time and coverage is adequate. It should be clear, however, that there may not be very much better data in the future, on which to base any decision to purchase or not to purchase the vaccine.



## 5. DISCUSSION AND SUPPORTING EVIDENCE

### 5.1. What antigen content is needed for response?

*Relevance: It will be expensive and time consuming to produce a pre-pandemic or pandemic vaccine in sufficient amounts for effective use. To make whatever amount is available go further, it would be advantageous to lower the amount of antigen in the vaccine, thus enabling vaccination of more individuals. Adjuvants may further reduce the amount of antigen needed.*

The answer to this question is not necessarily straightforward. The word 'response' could apply to a range of criteria used in vaccinology (for example, a response indicative of immunological priming is not necessarily equivalent to a response indicative of full protection). For the purposes of the consultation it was assumed that the question referred to a response in human subjects, sufficient to meet the current EMEA Committee on Human Medicinal Products (CHMP) criteria for the annual update of human seasonal influenza vaccines (see Appendix 2). Although the current CHMP criteria have been adopted by the EMEA for the assessment of both 'mock-up'<sup>1</sup> pandemic vaccines and pre-pandemic vaccines, the criteria were originally designed for the assessment of seasonal influenza vaccines and may not necessarily be the most appropriate criteria for assessment of H5 vaccines (EMEA/CPMP/VEG/4717/03 and EMEA/CHMP/VWP/263499/2006).

***The EAG recommends that consideration be given to appropriate CHMP criteria for H5 vaccines.***

Current data, largely derived from use of a reverse genetics (RG) vaccine virus, indicate that non-adjuvanted H5N1 sub-unit and split vaccines will need high doses of antigen (up to 90µg) to induce an adequate response. Alum-adjuvanted split vaccines would require doses higher (30µg or more) than those used in seasonal vaccination (15µg) while the use of certain adjuvants allows reduction of doses to 7.5µg (MF59) or 3.8µg (AS). The effect of alum may depend upon the precise formulation used but it is still likely to be of benefit (compared with no adjuvant) for egg-grown whole virus and split vaccines (Lin et al, 2006). Exceptionally, one alum-adjuvanted whole virus vaccine appears to be immunogenic after only one dose (Vajo et al, 2007). The results of a vero cell-derived whole virus (wild type) H5N1 vaccine, have shown that non-adjuvanted formulation with antigen doses of 7.5µg and 15µg were more immunogenic when the same product was formulated with alum. A direct comparison of this observation with the egg-derived Japanese and Chinese whole virus vaccines is not possible as these studies did not include non-adjuvanted formulations.

The likely antigen requirement for an adequate immune response for various possible types and formulations of H5N1 human vaccine are broadly as follows (see table, below). The vaccines in the table have all shown immunogenicity and have the potential to become licensed products.

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<sup>1</sup> A mock-up pandemic influenza vaccine is a vaccine that mimics the future pandemic influenza vaccine in terms of its composition and manufacturing method (EMEA/501557/2006).

Vaccine type and formulation	Dose
†Split virion H5N1, no adjuvant	2 x 90µg (Treanor et al, 2006)
Split virion H5N1, with alum	2 x 30-45µg (Bresson et al, 2006)
‡Whole virus H5N1 (egg grown), with alum	2 x 10-15µg (Hehme et al, 2006; Lin et al, 2006; Tashiro et al, 2006) 2 x 15 µg (EPAR Daronix) 1 x 6 µg (Vajo et al, 2007)
Subunit H5N3, with MF59	2 x 7.5µg* (Nicholson et al, 2001)
‡Subunit H5N1 with MF59	2 x 7.5 µg (commercial in confidence, March 2007; EPAR Focetria)
Vero cell whole virus H5N1 (wild type), no adjuvant	2 x 7.5µg* (presented, Vienna 2006)
Split H5N1 vaccine with AS	2 x 3.8µg* (Borkowski et al, 2006)

† already licensed in the USA; ‡ already licensed in Europe.

\*doses lower than this not evaluated so far in humans.

The EAG emphasised three important caveats to this general conclusion:

(1) The assays used to assess immunogenicity of influenza vaccines are not standardised and a high level of inter-laboratory variability has been reported. It is difficult to compare different vaccine trials. WHO is taking steps to improve assay standardisation. It must be stressed that correlates of protection for H5N1 vaccines have not yet been established, hence the current reliance on CHMP criteria for seasonal influenza vaccines which are widely considered to be suboptimal. The receptor requirements for H5N1 may mean that current biological assays used to assess immunogenicity (haemagglutination inhibition (HI) and neutralisation tests (neut)) may not reflect the true immunogenicity of current developmental H5N1 vaccines. Although clinical field efficacy trials of pandemic vaccine candidates cannot be undertaken, it is nevertheless theoretically possible to perform controlled clinical challenge studies with volunteers, held under strict confinement and medical observation, challenged with de-pathogenised/ attenuated H5N1 virus after having been immunised with a candidate pandemic vaccine. These may generate useful clinical data on correlates of protection.

(2) The dose/ response relationship for many currently available H5 vaccines with adjuvants has not yet been fully described. This arises partly as a result of limited dose selection for clinical trials and an unpredictable effect of adjuvant in relation to antigen content (some vaccines with low quantities of antigen appear to perform worse with alum than without adjuvant which is somewhat counterintuitive (data submitted for publication)). In general, the optimal antigen-adjuvant ratio has not yet been fully quantified for most products (Bresson et al, 2006; Nicholson et al, 2001). Additionally, data based on HI evaluation of immunogenicity



may not be the correct basis upon which to establish dose-response for H5N1 vaccines. It is still possible that lower doses of antigen (with adjuvant) will be shown to be effective in the future, especially in relation to immunological 'priming'.

(3) Immunological priming describes the first encounter of a 'naïve' immune system with a specific antigen, leading to a *primary immune response*. This response may impact on and shape the immunological reactivity pattern to subsequent exposures to similar or closely related antigens. Thus, priming is a very important concept that could lead to only one vaccine dose inducing some protective immunity in a pandemic situation. Yet, currently there are only limited data concerning the amount of antigen, the antigen formulation or how closely related the antigens would have to be in order to induce a favourable and protective immune response associated with a second antigen encounter (vaccine or wild virus). It is possible, but not yet proven in humans, that priming with lower doses of antigen will generate an immune response or immune memory which will ensure protection in the event of subsequent challenge over a year or several years later. It is not yet fully clear how successful heterologous priming (e.g. priming with vaccine derived from one clade of H5N1 viruses, followed by re-vaccination with vaccine virus derived from a different clade or challenge with an H5N1 pandemic virus from a different clade) is likely to be. Nevertheless, the early data from the trials of recombinant H5 HA vaccine (Goji et al, 2006) and H5N3 vaccine with the MF59 adjuvant are promising (Stephenson et al, 2003a; 2005). For example, subjects who were vaccinated eight years previously with an H5N1 clade 3 sub-unit vaccine showed higher immune responses after being vaccinated with 90µg of a non-adjuvanted H5N1 clade 1 vaccine compared with those vaccinated for the first time (Goji et al, 2006).

No data on the inter-changeability of current candidate H5N1 human vaccines are currently available.

## **5.2. What is the added value of a number of adjuvants in terms of improving response?**

*Relevance: Adjuvant can reduce the amount of antigen required in a vaccine ('dose sparing') and/ or increase the breadth of the immune response. Both actions would be beneficial when developing H5N1 vaccines for either pandemic or pre-pandemic use.*

Adjuvants could play two different roles: improvement of immune responses and/ or dose sparing. There are currently three main candidates: alum, MF59 and AS. All, so far, have demonstrated evidence of enhancement of immune response, but the data for MF59 and AS are the most encouraging. There are also many other potential proprietary new adjuvants which have not yet been adequately explored in relation to H5N1 human vaccines and which are not yet licensed for use. Current data, for non-adjuvanted split and sub-unit vaccines, indicate poor responses and suggest that for these types of vaccine an adjuvant will be required.

### ***The EAG recommends the funding of further work on human H5N1 vaccine adjuvants***

The adjuvants so far used in H5N1 human vaccines have all demonstrated antigen sparing ability (based on HI titres). However, this EAG again stresses that the response to the various

adjuvants is neither fully predictable nor fully quantified in relation to antigen content. Adjuvants may also affect the quality of the immune response such as recognising variant H5N1 strains (and possibly the balance between the humoral and cellular response). The EAG consider that a vaccine containing small quantities of antigen (and an adjuvant) which does not produce detectable levels of antibody, may still be adequate to achieve immunological priming; however further data are required.

The EAG wished to stress that the 'value' of adjuvants will remain a difficult question to address as long as understanding of the immune correlates of protection remains incomplete.

### 5.3. How many doses are needed for protection?

*Relevance: If supplies of H5N1 vaccine are limited, it is essential that what is available is used most appropriately and effectively. Points to consider include whether to vaccinate fewer individuals with two doses or greater numbers with one dose. There are a variety of two-dose strategies that could be employed.*

In general the population of the EU will be immunologically naïve to a pandemic virus. Therefore, based on existing data, at least two doses (pandemic or pre-pandemic strategy) will be needed to induce an antibody response consistent with CHMP standards. This is currently the case for children vaccinated for the first time against seasonal influenza. A number of developmental H5N1 vaccines appear to give an adequate response (CHMP criteria) after two doses (e.g. Bresson et al, 2006; Lin et al, 2006; Treanor et al, 2006) but exceptionally one such alum-adsorbed whole virus vaccine is immunogenic after only one dose (Vajo et al, 2007). However, it should be recognised that different segments of the population may require different vaccination strategies; some data exist to support a different immune response to novel sub-types of influenza according to age group (Stephenson et al, 2003b).

EAG1 noted that protection could be achieved with a variety of two dose strategies:

- zero doses of pre-pandemic vaccine + two doses of pandemic vaccine;
- one dose of pre-pandemic vaccine + one dose of pandemic vaccine;
- two doses of pre-pandemic vaccine + zero doses of pandemic vaccine,

but further data (and a consideration of issues relating to availability and logistics) are required before any conclusions can be drawn about which of these regimens would be most appropriate in practice. In addition, much may depend upon the timing between pre-pandemic vaccination and pandemic vaccination, the degree of heterogeneity between the vaccine viruses used and the differences between the vaccine viruses and the pandemic virus. The third strategy will be particularly affected by antigenic heterogeneity, as only pre-pandemic vaccine is used. Limited data from animal studies, clinical studies and mathematical modelling suggest that adequate protection can be achieved despite some heterogeneity (see 5.9; 5.10). However, if the pre-pandemic vaccine is prepared from an H5N1 virus and the pandemic is caused by a virus from another subtype (ie H2N2), no protection is likely.

One may also foresee a scenario where only one dose of a pre-pandemic vaccine will be given, either due to time constraints or insufficient quantities of available vaccine. Recent



preliminary modelling indicates that there may be some community benefit of reduced infections, by administering lower individual antigen doses (i.e. less than the recommended dose for maximum protection) to a greater number of people. For the three developmental H5N1 vaccines described above (Bresson et al, 2006; Lin et al, 2006 and Treanor et al, 2006), increased population vaccine coverage by lowering the antigen dose indicated a lower theoretical infection attack rate (Riley et al, 2007). However, this study did consider two doses of reduced antigen content, rather than one dose of maximal content.

The interval between doses is mainly based on convenience. The interval between priming doses tends to be between 21–28 days. However, this interval should not be reduced to below 14–21 days since the peak IgG response for naïve subjects (children) is not achieved until this time (El-Madhun et al, 1998). With pandemic vaccination, the smallest interval possible is likely to be chosen to ensure delivery to the maximum number of people within a short time frame.

#### **5.4. How long is protection likely to last?**

*Relevance: It cannot be predicted when the next pandemic will occur, therefore decisions about procurement and administration need to be made with the best possible understanding about how long protection will last.*

At present the only real assessment of duration of protection is made using the persistence of circulating antibody after vaccination. It is reasonable to assume that the higher the antibody titre immediately after vaccination, the longer the titre will remain above the level assumed to be protective (Hobson et al, 1972; Stephenson et al, 2003a), ranging typically from six months to over one year. There is evidence that circulating antibodies generated in response to an H5N3 vaccine with MF59 adjuvant persist up to 16 months (Nicholson et al, 2001; Stephenson et al, 2003a).

However, even without detectable levels of serum antibodies, there may be some immunological memory that could reduce illness severity or even offer protection in the event of a subsequent challenge by a pandemic virus.

Commercial companies are currently investigating the persistence of antibodies prior to boosting, and more information should be available over the next few years. These follow-up studies should be extended for periods longer than the minimum required by regulatory criteria.

***The EAG recommends that ECDC should track progress and actively revisit this area***

There are insufficient data about the duration of immunological memory (Goji et al, 2006), but from first principles an assumption can be made that priming will produce some degree of immune memory and is likely to be worthwhile. The question will remain difficult to answer until the immune correlates of protection are better understood. In addition to affecting the quality of the immune response, adjuvant also appears to prolong its duration.

Memory is expected to persist much longer than the detectability of circulating antibodies but development of memory and its precise duration is not yet established. The timing of a priming dose is a matter of fine judgment in relation to variables in relation to the strength of immune memory and ongoing antigenic drift. The rate of antigenic drift may also have a

significant impact on longevity of protection induced by priming and the effect of subsequent re-vaccination. It may prove necessary to give future booster vaccinations with homologous or heterologous strains.

## **5.5. For the previous four questions, determine the response also for children**

*Relevance: Children may be particularly vulnerable to the next pandemic virus, and it is known that children sometimes react differently to vaccines when compared with adults. It is important to consider known information about children and vaccines, and extrapolate this, where relevant, to H5N1 vaccines.*

At least 16 manufacturers from 10 countries are known to be developing human vaccines against H5N1 avian influenza, with five also involved in the development of vaccines against other novel avian influenza viruses (H9N2, H5N2, H5N3, H7N7 and H7N1). Over 40 clinical trials have been completed or are ongoing; most focusing on healthy adults, although some have progressed further to clinical trials in the elderly and children (NIH, 2007; WHO 2007a). All were well tolerated in all age groups tested.

There are no data available for H5N1 vaccines in children under two years old, but the limited data available on older children indicates that the response to human H5N1 vaccines in these older children is likely to be similar to that in young adults (Campbell et al, 2007). Since small children (<2 years old) may react differently in terms of the quality of their immune response, it cannot be automatically assumed (without supporting data) that children will respond to H5N1 vaccine in a similar manner as young adults.

There are no recent data on the use of adjuvanted influenza vaccines in children. The EAG wished to stress that although in the past influenza vaccines containing alum had produced high rates of adverse reactions in children, (Miles et al, 1982) these data originated from use of an old technology vaccine which would now be considered very impure. The vaccine itself (as opposed to the adjuvant used) may well have been responsible for the effects seen and no inferences should be drawn from these data in respect of the latest developmental human H5N1 vaccines.

It is important to note that only very limited data are available about the response of children to adjuvanted influenza vaccines. However, data in infants are available for a malaria vaccine containing AS adjuvant (Macete et al, 2007a; 2007b), and in toddlers for CMV vaccines (Mitchell et al, 2002) and newborns for HIV vaccines (Borkowsky et al, 2000; Cunningham et al, 2001; McFarland et al, 2001) containing MF59. Virtually all children routinely receive alum-adjuvanted vaccines from an early age as part of the childhood vaccination schedules in operation across Europe, thus alum has a long and safe history in relation to childhood vaccines.

## **5.6. What is the shelf-life of a pre-produced H5N1 vaccine?**

*Relevance: If Member States are planning to stockpile H5N1 vaccine, shelf-life of the vaccine is of high importance. It is of lesser importance if the vaccine will be used for other purposes, such as immediate priming of (part of) the population.*



There are reassuring data based on monovalent bulk and formulated seasonal influenza vaccines (H1N1, H3N2, B) from most manufacturers that vaccine potency remains stable for at least one year (at 2–8°C). There is little evidence of stability over longer periods, as the stability protocols tend not to be extended past 15 months due to the use of these vaccines for a specific season and the probability that a new vaccine will be prepared for the following season (Gerdil, 2003).

In some cases, vaccine stored in bulk (ready for packaging and filling at a later date) may have an even longer shelf-life. For example, in an H5N3 vaccine trial the final product (antigen + MF59 in the same syringe) remained fully potent at 16 months. Notwithstanding, no generalisation about stability can be drawn between individual manufacturers and individual products. The EAG noted that the NIBRG14 vaccine H5N1 virus produced through a process of reverse genetics by the National Institute of Biological Standards and Control (NIBSC), UK, has a lower proportion of haemagglutinin protein on its surface than the normal virus, leading to a lower vaccine yield. It is not known if this might affect subsequent degradation of produced vaccine. The type and presence of adjuvant, may also affect shelf-life.

Shelf-life is a fundamental issue for Member States and is entangled with delivery issues. It must be borne in mind that shelf-life runs from the date the bulk was assembled, not when the vial was filled or the purchase/delivery date. With the current shelf-life of 12 months, stockpiling will be difficult and expensive and thus only feasible for limited amounts or when authorities are considering priming the population almost immediately. H5N1 vaccine could be stored either as the purified bulk antigen or as the prepared mix (either in bulk or pre-filled vials). Manufacturers of H5N1 vaccines for pre-pandemic use plan to investigate the stability of the monovalent bulks and H5N1 vaccines over a longer period (extended stability protocol up to 18 months for the monovalent bulk and 36 months for the vaccine). It is therefore possible, but not guaranteed, that the shelf-life of stockpiled H5N1 bulks and vaccines will be extended, subsequent to submission of the relevant supporting evidence from ongoing stability studies to EMEA for approval.

Authorities planning to stockpile either H5N1 bulks or vaccines should discuss, as part of their contract negotiations, the length of the stability protocols<sup>2</sup> and the commitment to submit variation applications to extend the shelf-life when data become available. Ideally the shelf-life of the bulks and vaccines should exceed 18 months and three years, respectively, for stockpiling.

***The EAG recommends that research to investigate the extended shelf-life (past 12 months) of the monovalent antigen and bulk formulations should be undertaken.***

## **5.7. What is the risk of immunologic 'mal-reaction' between the vaccine strain used and the pandemic strain – the 'dengue effect'?**

Relevance: *The virus that causes the next pandemic may be drifted from the vaccine strain; this may increase the risk of adverse events as per the 'dengue effect'. In humans H5N1*

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<sup>2</sup> For extended storage periods, there may be a need to conduct additional clinical or non-clinical testing (EMEA/CHMP/VWP/263499/2006)

*infection appears to produce a more vigorous immunological response than seasonal influenza. Coupled with the fact that widespread vaccination with an H5N1 vaccine has never been undertaken, this raises further theoretical concerns which need to be considered.*

N.B. From a technical perspective, it should be noted that the 'mal-reaction' referred to in this question (i.e. between the vaccine strain and the pandemic strain) is not actually the process which occurred when the 'dengue effect' was observed (see below).

While disease enhancement due to vaccine-driven immuno-pathological events has been reported for RSV and dengue, there is no evidence that this is the case for influenza. The underlying mechanisms for RSV-driven effects and dengue are different in nature; 'enhancing antibodies' are the key regulating molecules which drive the 'dengue-effect'. Primary infection with any of the four dengue serotypes results in lifelong immunity to the same serotype, but the individual remains susceptible to sequential secondary infections with other dengue subtypes, possibly leading to enhanced disease. The 'dengue-effect' is mediated by cross-reactive, non-neutralising antibodies which enhance viral infection as well as cross-reactive T-cells (Bashyam et al, 2006). On the other hand, early studies of RSV vaccine response have shown that on rare occasions the vaccine has augmented an unfavourable cellular response resulting in a serious clinical outcome when the vaccinee meets the wild type virus (de Swart et al, 2002; Osterhaus, 2004).

However, evidence from both the H5N1 in South-East Asia and the 1918 H1N1 pandemic indicates that the immune response in animal models to those viruses is different to that observed with normal seasonal influenza and may involve a cytokine storm.

In light of the frequently observed severe clinical outcome seen for many of the zoonotic H5N1 cases (de Jong et al, 2006), there is a theoretical risk that the offending pandemic virus could boost an inappropriate cell-mediated response elicited by the pandemic vaccine itself. It is known that some epitopes have a detrimental impact on viral clearance and have important implications for the development of vaccination strategies designed to provide protection against subsequent influenza virus challenge (Crowe et al, 2005; 2006). A recently published paper has described such a response in a porcine model but it should be noted that this was using a DNA vaccine against the M2 protein which is highly dissimilar to current developmental human H5N1 vaccines (Heinen et al, 2002).

With currently produced seasonal influenza vaccines (including one product which contains adjuvant (MF59)), there is no evidence of such a phenomenon even though extremely large quantities of such vaccines are given every year. However, this evidence was not obtained in immunologically naïve individuals, so may not be relevant to the immune enhancement seen with RSV. In the event of an H5N1 pandemic virus with similar and therefore unusually severe pathogenic properties such as the current strains in South-East Asia, the reassuring experience from seasonal adjuvanted and non-adjuvanted vaccines used against the epidemic strains of today, may not be fully relevant. Nevertheless, there are encouraging data from animal challenge models using adjuvanted H5N1 vaccines (Ruat et al, 2006), and a cell culture (vero) derived whole virus (H5N1) vaccine based on wild-type virus (data submitted for publication) to suggest that this phenomenon does not occur. Further data are awaited from other developmental vaccines containing different (non-alum) adjuvants.



## **5.8. What is the risk of other adverse events from the vaccine and potential new adjuvants likely to be used?**

*Relevance: Vaccines and adjuvants have the potential to cause adverse events. Widespread vaccination with H5N1 has never occurred. The public may be more or less accepting of adverse events, and consequently to vaccination per se, depending on the perceived level of risk at the time of vaccination.*

EAG1 is not able to, and would not wish to, draw conclusions on, or make comparisons of the current range of developmental vaccines, other than agreeing that there is a broad signal from the small number of studies undertaken to date, that there is no evidence of an unacceptable adverse event profile with any of the vaccines so far evaluated. That said, the majority of pandemic vaccines are likely to be adjuvanted, and thus more likely to be reactogenic compared to seasonal influenza vaccines (Treanor et al, 2006). However, the safety of an MF59 adjuvanted seasonal influenza vaccine has been shown to be comparable to the equivalent non-adjuvanted product from the same manufacturer in the elderly although local reactions were more frequent when adjuvant was present (Podda, 2001).

When a vaccine is used on a large scale, rare events may become a public health issue, due to the large numbers of recipients involved. The risk is not theoretical and adverse events will happen. We should be prepared for unexpected results and be prepared to manage them. The most important aim is to manage over-reactions such as the one which occurred in 1976 with the widespread administration of a vaccine against H1N1 swine-flu and its reported association with Guillain-Barre Syndrome (Langmuir et al, 1984; Safranek et al, 1991).

Regardless of the true scientific picture, deployment of a novel vaccine at speed across the EU will result in public and media stories about adverse events, and it will be difficult to refute these without good post-marketing surveillance and adequate communication. There may also be a change in public perception depending on the level of pandemic threat at the time of vaccination. For example if the public does not perceive any clear threat (in WHO Phase 3), they may not accept minor reactions such as a sore arm, but once a pandemic seems imminent (in WHO Phase 5), minor reactions may be accepted in the expectation of protection.

The EAG noted that the adverse event profile may vary when the vaccine is used with vulnerable groups such as children, the elderly, pregnant women, or the immuno-suppressed. Whilst there is no evidence for an increased risk of adverse events associated with seasonal influenza vaccination, vaccine trials tend to exclude pregnant women. On the other hand, there are major concerns about pregnant women and pandemic influenza; the death rate among pregnant women in the 1957 pandemic was higher than in non-pregnant women of the same age (Freeman and Barno, 1959).

The EAG felt that there would always be a level of risk in relation to reactogenicity, or an unforeseen major adverse event, since the contribution of the adjuvant to the safety profile can never be fully evaluated during clinical trials.

In the past, whole virus vaccines tended to be responsible for more reactogenicity than subunit or split-virion vaccines as explained earlier. However, this comparison may be less relevant now due to modern purification processes.

The results of H2N2 and H9N2 studies (Hehme et al, 2002; 2004) as well as the Chinese and the Japanese studies with egg-derived whole virus candidate vaccines have not indicated marked differences in tolerability compared to that of split virus preparations. A study with a vero cell-derived H5N1 whole virus (wild type) candidate vaccine has shown that the safety profile is not dissimilar to licensed seasonal influenza split vaccines and to H5N1 split virus candidate vaccines (data submitted for publication).

***The EAG recommends that, in due course, when more data are available, it would be worthwhile to undertake comparison of adverse events using a meta-analysis of candidate vaccines of various formulations with and without adjuvants.***

In addition to the issue of adverse events attributable to adjuvant, there will inevitably be instances of vaccine failure, as no vaccine is ever 100% effective. These events will also require careful handling in the context of massive public expectation from a vaccine during a pandemic.

## **5.9. What is the probability of cross-protection between the strain used in a pre-produced H5N1 vaccine and a pandemic H5N1 strain?**

*Relevance: At best, it is anticipated that the virus that causes the pandemic will have drifted from the vaccine strain. The pandemic strain may even be from a different clade to the vaccine strain. Cross-protection between clades would therefore be highly beneficial. The degree of protection achieved will depend on the type of vaccine used but even sub-optimal protection (i.e. only preventing severe symptoms such as death) would be beneficial. If the next pandemic arises from a non-H5 subtype, an H5N1 vaccine will probably offer no protection at all.*

Clinical trials with developmental H5N1 human vaccines have so far indicated some cross-neutralising activity between viruses of clades 1 and 2 (Höschler et al, 2006) and vaccine efficacy studies in mice and ferrets show survival after infection with highly pathogenic H5N1 virus, when the vaccine is prepared from a different H5N1 clade to that of the challenge virus (Govorkova et al, 2006; Lipatov et al, 2006; Lu et al, 2006; and data submitted for publication). However, these are preliminary data and in clinical trial sera, the degree of cross-reaction decreases with increased heterogeneity between the vaccine virus and the cross-reacting virus. If a wide immunological cross-reaction against currently available H5N1 strains can be demonstrated, it is more likely that protection will be induced against a future H5N1 pandemic strain.

The probability of cross-protection is likely to decrease with the increased antigenic distance between the pre-pandemic vaccine strain and the pandemic strain. The use of adjuvants such as MF59 (Stephenson et al, 2005) and AS (personal communication, M Denis) has shown evidence of improved cross-reaction of sub-unit and split virion vaccines against H5N1 strains.



Whole virus vaccines may induce a slightly different spectrum of antibody cross-reactions. Indeed the nature of the immune response raised against a whole virus vaccine, (including T-cell responses) may be broader. Data from clinical trials of whole H5N1 vaccines so far suggest a stronger antibody response than split or subunit formulations, hence being more likely to cross-react with variant strains. Additionally, there are indications that whole virus vaccines may elicit a response skewed towards a more prominent cellular immune response, as may future experimental virosomal formulations (Huckriede et al, 2005).

The correlation between cross-reactivity and cross-protection in humans can only be established once a pandemic is underway.

There is some evidence of antibody to H5N1 virus in the sera of elderly populations, which may contribute some degree of priming or protection against H5N1 but the significance of this finding in relation to immunisation strategy is at present unclear (Hoffenbach, 2007; personal communication, M Zambon).

***The EAG stressed the need for better data using the ferret model to provide more definitive answers to this question.***

Again, it is emphasised that although the current CHMP criteria have been adopted by EMEA for the assessment of both 'mock-up' pandemic vaccines and pre-pandemic vaccines, the criteria were originally designed for the assessment of seasonal influenza vaccines and may not necessarily be the most appropriate criteria for assessment of H5 vaccines (EMEA/CPMP/VEG/4717/03 and EMEA/CHMP/VWP/263499/2006).

## **5.10. What could be the expected efficacy?**

*Relevance: Any pandemic or pre-pandemic vaccine should be efficacious and effective, however it is unlikely that this can be determined before the pandemic occurs. There are different measures for effectiveness that should be considered by Member States.*

'Efficacy' is defined as the extent to which a specific intervention produces a beneficial result under ideal (usually experimental clinical trials) conditions. In contrast, 'effectiveness' is defined as the extent to which a specific intervention, deployed under field conditions, does what it is intended to do for a defined population (Fedson, 1998; Last, 1988).

In relation to a human H5N1 vaccine, its efficacy is to be determined by the inherent characteristics of the vaccine itself and the host response to the vaccine. Since there will be no available data on the protective efficacy of an H5N1 vaccine in humans (as judged by protection against clinical illness, complication rates and/or mortality) until a pandemic virus begins to circulate, immunogenicity is considered a proxy measure of likely efficacy. Generally, immunogenicity is studied by means of measuring anti-haemagglutinin antibodies, according to the CHMP criteria. Since these criteria were developed to assist the annual re-licensure of seasonal vaccines, there are many caveats to the CHMP criteria in relation to their appropriateness for an H5N1 vaccine and in relation to the correlates of protection (as discussed earlier in this report). The possibility of different host responses and the exploration of alternative immunological parameters should also be considered. In addition, data from animal challenge studies indicate that protective efficacy is likely to be high (Govorkova et al,



2006; Lipatov et al, 2006; Lu et al, 2006; Baxter data submitted for publication on cell culture (vero) derived whole virus (H5N1) wild type vaccine); providing useful information concerning the expectations of pandemic vaccines in the event of a pandemic.

In the event of a pandemic it is most likely that the effectiveness and not the efficacy of vaccination will be measured, as field trials are unlikely to be conducted. The effectiveness of human H5N1 vaccination would relate not only to the intrinsic efficacy of the vaccine (inherent characteristics and host response) but also to wider factors relating to conditions in the field. These additional factors might include:

- the exact choice of regimen (see 4.3);
- target population, in relation to possible variations in clinical protection to be achieved by age group;
- target population, in relation to possible secondary effects on virus shedding;
- the proportion of the population that is vaccinated (vaccination coverage and potential herd immunity);
- degree of matching (and therefore cross-protection) between the vaccine virus and the circulating wild type;
- the virulence of the pandemic strain, the attack rate (i.e. the new cases per population at risk) and its development over subsequent waves.

Effectiveness might thus be judged not just in terms of protection against clinically apparent illness, but also against outcomes which are meaningful in a public health context such as reductions in mortality, hospitalisations, healthcare utilisation, costs, complications and secondary spread. Contrary to seasonal influenza vaccination, these vaccines will be used population-wide, with likely significantly greater vaccination coverage. Therefore, the non-vaccinated population may benefit from this wide-spread vaccination coverage to a larger extent than in a normal winter epidemic situation (herd effect).

Vaccine effectiveness cannot be judged in advance and will be dependent on factors such as the vaccination strategy chosen by individual Member States. Bio-mathematical modelling data suggest that an appropriate vaccine, even if of relatively low efficacy, given in advance of a pandemic, would prove to be more effective (in public health terms) than a vaccine of much higher efficacy, but not widely available until after a pandemic was underway (Ferguson et al, 2006).

Given the importance of timely vaccination and adequate coverage, procurement decisions on human H5N1 vaccines (i.e. to proceed or not to proceed) should not be delayed based on a view that by waiting, greater certainty over efficacy and effectiveness will emerge in advance of a pandemic.



## 6. AREAS WHERE ADDITIONAL RESEARCH IS PARTICULARLY NEEDED

The subject of human H5N1 vaccines is a generally data-poor area and further studies are needed 'across the board'. However, areas flagged by EAG1 as needing particular attention were:

- appropriate CHMP criteria for H5 vaccines;
- studies addressing the correlates of protection against influenza in humans, especially H5N1;
- standardisation of assays to address immunogenicity;
- studies on priming strategies against H5N1;
- development of novel adjuvants for H5N1 vaccines;
- duration of protection;
- studies in children, especially those <2 years old;
- further cross-reactivity studies;
- H5N1 vaccine inter-changeability studies (sequential use of different products);
- shelf-life of monovalent and bulk formulations (beyond those required for regulatory purposes);
- economic research to assess the level of investment needed and cost-effectiveness of different vaccine strategies.

## 7. OTHER ISSUES DISCUSSED

### 7.1. Live virus vaccine

In an ad hoc supplementary session to meeting one, EAG1 briefly discussed live influenza virus vaccines. Live attenuated influenza vaccines offer greater potential than their inactivated counterparts, for producing a pandemic vaccine which will be available quickly, and in large quantities. However, there are theoretical risks in relation to genetic reassortment between the vaccine virus and a wild-type virus which would need to be carefully weighed up, if such a vaccine were ever to be considered for pre-pandemic use.

Live virus vaccines, based on attenuated backbones, are in use and licensed for children in the USA and Russia. There are very few data relating to use of live vaccines in elderly populations. Live H5N1 and H5N2 vaccines have been trialled in animal models and the little data currently available show high levels of protection against subsequent infection (Desheva et al, 2006; Lu et al, 2006; Suguitan et al, 2006). Live H5N1 vaccine trials in humans are currently in progress but the preliminary data suggest that the low level of virus replication *in vivo* in humans may limit immunogenicity. Data are available from NIH and showed marginal antibody responses to H5N1, but better immune responses were induced with a live H5N2 vaccine developed in Russia. No live seasonal influenza vaccines are currently licensed in the EU.

## APPENDIX 1: DEFINITIONS

**Adverse event:** Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

**Adverse reaction:** All untoward and unintended responses to an investigational medicinal product related to any dose administered.

**Reactogenicity:** Events that are considered to have occurred in causal relationship to the vaccination. These reactions may be either local or systemic.

**Serious adverse event or serious adverse reaction:** Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

**Unexpected adverse reaction:** An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

**Immune response:** In addition to the pre-existing and non-specific **innate** immune system providing immediate front line defence, the **adaptive** system responds specifically to the infectious agent, antigen or vaccine in question. There is close collaboration and cross-stimulation between the innate and adaptive systems. In general, immune responses are characterised by the recognition stage (identification of the pathogen or the vaccine) and the effector stage.

The adaptive response has a **humoral** arm generating tailor-made antibodies that will neutralise the infectious agent. Such antibodies will be found in blood and tissue fluids. Depending on the immunising route (e.g. nasal/oral) used for vaccines, antibodies can also be found at mucosal sites such as the airways. The **cellular** arm of the adaptive immunity refers to specialised white blood cells being made to destroy infected cells. There is a high degree of cross-stimulation between the humoral and cellular arms.

**Immunisation** is the process of manufacturing immune defence, by artificially helping the body to defend itself using effector mechanisms (cellular and humoral). A long-term immune memory response is desired.

**Herd immunity** is the indirect protection of a (sub-)population generated via a vaccination programme, i.e. the lowering of the risk of infection in the un-immunised proportion of the population due to the protection of some of the population by vaccination.

An **adjuvant** is a substance that when mixed with an isolated antigen (e.g. influenza viral protein) increases its immunogenicity. Adjuvants cause local inflammation, draw immune cells to the site of injection and affect the interplay of antigen-presenting cells with specific



immune cells responsible for long-term immune memory (i.e. humoral and cellular immune responses).

**Efficacy** is defined as the extent to which a specific intervention produces a beneficial result under ideal (usually experimental clinical trials) conditions by reducing the chance or odds of developing clinical disease after vaccination relative to the chance or odds when unvaccinated. Vaccine efficacy thus measures direct protection (i.e. protection induced by vaccination in the vaccinated population sample). By contrast, **effectiveness** is defined as the extent to which a specific intervention, deployed under field conditions, does what it is intended to do for a defined population. For vaccines this means the protection rate conferred by vaccination in a certain population. Vaccine effectiveness thus measures direct and indirect protection (i.e. protection to non-vaccinated persons by the vaccinated population) in field trials. Vaccine effectiveness is also determined by vaccination coverage, correlation of vaccine strains with circulating strains and selection of strains not included in the vaccine following introduction of the vaccine in that population. When field trials are impossible, difficult or unnecessary to undertake, surrogate laboratory markers may be employed. Such serum analyses are also used for clinical trials of pandemic vaccine candidates, although in this case it is not known to which degree these parameters will correspond to field protection.

**Priming:** Immunological priming describes the first encounter of a 'naïve' immune system with a specific antigen, leading to a *primary immune response*. This response will impact on and shape the immunological reactivity pattern to subsequent exposures to similar or closely related antigens.

**Protection:** A range of possible endpoints might be used to measure protection elicited by an influenza vaccine: the occurrence of infection (whether or not symptomatic), the occurrence of clinical illness; hospitalisation; or death. For the purposes of this report, it was assumed that the word 'protection' as used in the questions referred mainly to protection of humans against clinical illness due to a pandemic virus where the progenitor virus was of the H5N1 Asian lineage.

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## APPENDIX 2: CHMP CRITERIA

The current EMEA Committee on Human Medicinal Products (CHMP) criteria for the annual update of human seasonal influenza vaccines have also been applied to 'mock-up' pandemic vaccines. These criteria were designed for the assessment of seasonal influenza vaccines and although adopted by EMEA for the assessment of 'mock-up' pandemic vaccines and pre-pandemic vaccines, are recognised as not necessarily being the most appropriate criteria.

The criteria are used to assess the immunogenicity of influenza vaccines for seasonal strain changes as well as initial licensure. Sera are assayed using either haemagglutinin inhibition (HI) or single radial haemolysis (SRH) tests to determine the titre and frequency of anti-haemagglutinin (HA) antibody responses.

It is assumed that an HI titre of at least 40 (or an area  $\geq 25\text{mm}^2$  for SRH) correlates with protective levels of antibody. This is based on the assumption of a correlation with a reduction in influenza-like illness when most of the vaccinated population has some degree of pre-existing immunity against seasonal strains.

Pre- and post-vaccination sera are titrated simultaneously and in duplicate. The titre assigned to each sample is the geometric mean of two independent determinations.

CHMP uses three criteria to assess the antibody response to influenza vaccines:

- Seroconversion rate: the percentage of subjects (sera) with negative pre-vaccination HA titre and post-vaccination titre of  $\geq 40$  or, for sera with positive pre-vaccination titre, at least a four-fold increase in HA titre. In SRH tests, seroconversion corresponds to negative pre-vaccination serum and post-vaccination are of  $\geq 25\text{mm}^2$ , or for sera with positive pre-vaccination SRH tests, at least a 50% increase in area.
- Seroprotection rate: the percentage of subjects achieving a post-vaccination HA titre of at least 40 or SRH area of  $\geq 25\text{mm}^2$ .
- Mean geometric increase: the mean geometric increase in titre.

For seasonal influenza vaccines, at least one of the following serological criteria must be met in the following age groups (each of at least 50 individuals):

	<b>Adults 18–60 yrs</b>	<b>Adults <math>\geq 60</math> yrs</b>
Seroconversion rate	$\geq 40\%$	$\geq 30\%$
Seroprotection rate	$\geq 70\%$	$\geq 60\%$
Mean geometric increase	$\geq 2.5$	$\geq 2.0$

For 'mock-up' pandemic vaccines and pre-pandemic vaccines, it is expected that all three criteria will be met.



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## APPENDIX 3: EAG MEMBERS AND OBSERVERS

### EAG1: Meeting 1 (Hotel Bedford, Brussels, Belgium (1–2 March 2007))

#### *Members present*

**Dr Jonathan Nguyen-Van-Tam** Health Protection Agency, UK (Chairperson)  
**Dr Chloe Sellwood** Health Protection Agency, UK (Scientific Rapporteur)  
**Dr Martine Denis** GSK Biologicals, Belgium  
**Prof Lars R Haaheim** University of Bergen, Norway  
**Dr Agnes Hoffenbach** Sanofi Pasteur, France  
**Dr Terhi Kilpi** National Public Health Institute, Finland  
**Dr Otfried Kistner** Baxter, Austria  
**Dr Markus Maeurer** Karolinska Institutet and Smittskyddsinstitutet, Sweden  
**Dr John M Wood** National Institute for Biological Standards and Control, UK  
**Dr Maria Zambon** Health Protection Agency, UK

#### *Comments provided in absentia*

**Dr Bettie Voordouw** Medicines Evaluation Board, The Netherlands  
**Dr Giuseppe Del Giudice** Novartis Vaccines, Italy

#### *Observers*

**Dr Bruno Ciancio** ECDC, Sweden

### EAG1: Meeting 2 (ECDC, Stockholm, Sweden (29 March 2007))

#### *Members present*

**Dr Jonathan Nguyen-Van-Tam** Health Protection Agency, UK (Chairperson)  
**Dr Chloe Sellwood** Health Protection Agency, UK (Scientific Rapporteur)  
**Dr Martine Denis** GSK Biologicals, Belgium  
**Dr Giuseppe Del Giudice** Novartis Vaccines, Italy  
**Prof Lars R Haaheim** University of Bergen, Norway  
**Dr Terhi Kilpi** National Public Health Institute, Finland  
**Dr Markus Maeurer** Karolinska Institutet and Smittskyddsinstitutet, Sweden  
**Dr Bettie Voordouw** Medicines Evaluation Board, The Netherlands  
**Dr John M Wood** National Institute for Biological Standards and Control, UK  
**Dr Maria Zambon** Health Protection Agency, UK

#### *Comments provided in absentia*

**Dr Agnes Hoffenbach** Sanofi Pasteur, France  
**Dr Otfried Kistner Baxter** Austria

#### *Private sector contributors*

**Dr Martine Denis** GSK Biologicals, Belgium  
**Dr Giuseppe Del Giudice** Novartis Vaccines, Italy



**Mr Keith Howard Baxter** Austria

***Observers***

**Dr Bruno Ciancio** ECDC, Sweden

**EAG1: Meeting 3** (Thistle Kensington Gardens Hotel, London, UK (7 May 2007))

***Members present***

**Dr Jonathan Nguyen-Van-Tam** Health Protection Agency, UK (Chairperson)

**Dr Chloe Sellwood** Health Protection Agency, UK (Scientific Rapporteur)

**Prof Lars R Haaheim** University of Bergen, Norway

**Dr Terhi Kilpi** National Public Health Institute, Finland

**Dr Bettie Voordouw** Medicines Evaluation Board, The Netherlands

**Dr John M Wood** National Institute for Biological Standards and Control, UK

***Comments provided in absentia***

**Dr Markus Maeurer** Karolinska Institutet and Smittskyddsinstitutet, Sweden

**Dr Maria Zambon** Health Protection Agency, UK

***Observers***

**Dr Bruno Ciancio** ECDC, Sweden

**Dr Daniel Lavanchy** WHO, Geneva

**EAG2: Meeting 1** (ECDC, Stockholm, Sweden (21 December 2006))

***Members present***

**Dr Johan Giesecke** ECDC, Sweden (Chairperson)

**Dr Patrick Celis** European Agency for the Evaluation of Medicinal Products, UK

**Dr John Edmunds** Health Protection Agency, UK

**Dr Antoon Gijssens** European Commission (DG SANCO), Luxembourg

**Prof Liz Miller** Health Protection Agency, UK

**Prof Angus Nicoll** ECDC, Sweden

**Dr Petri Ruutu** National Public Health Institute, Finland

***Comments provided in absentia***

**Dr Nedret Emiroglou**, WHO EURO, Switzerland

**Dr Gérard Krause** Robert Koch-Institute, Germany

Further discussions of EAG2 were carried out by email.

Declarations of interest from both EAGs that are relevant to this work are listed in Appendix 5.

## APPENDIX 4: PROCESS OF CONSULTATION AND DISCUSSION

### Purpose of meetings

To answer the specific questions (a) by reference to scientific data in the public domain; (b) by drawing on the expert opinions of members of the EAG; and (c) through incorporating the broad messages from data which are still held commercially in confidence by EU vaccine manufacturers.

#### EAG 1

Three meetings of EAG 1 were held to consider the scientific questions on human H5N1 vaccines posed by ECDC. The meetings (March – May 2007) comprised selected public and private sector experts to consider scientific questions posed by the Advisory Forum of ECDC, in relation to the possible advance stockpiling of human H5N1 vaccines by Member States. Meeting One involved both public and private sector members acting as experts in their own right and not as representatives of individual companies or institutions. Meeting Two included restricted sessions during which only public sector members were present, to hear presentations from representatives of individual European vaccine manufacturers who wished to present confidential data to EAG1 (under confidentiality agreement) in the interests of ensuring that the final conclusions drawn related to the most up to date information. At the beginning and end of the meeting, the full membership (public and private sector individual experts) were present. The third and final meeting involved only public sector members. An observer from WHO was also present at the third meeting. This was to observe the process under which EAG1 operated, prior to a similar global consultation planned for autumn 2007.

The process was very successful and EAG1 reached consensus on the issues discussed. The rapid progress achieved is in no small part due to the presence of industry experts on EAG1 and through the process of being able to receive separate confidential presentations from individual companies. EAG1 demonstrated a successful and effective way of working, with open and frank discussions between the various industrial and public sector members. Also, through the use of a dedicated scientific rapporteur, EAG1 was able to concentrate on the scientific discussion. This could be considered for adoption by ECDC as the default *modus operandi* for future ECDC Expert Advisory Groups and Fora.

#### EAG 2

EAG 2 had one meeting at ECDC in Stockholm on 21 December 2006, the rest of the work being carried out through email contacts.

#### The final report

A meeting was held at ECDC, Stockholm on 22 May 2007 to bring together the separate reports of EAGs 1 and 2 (completed June 2007). Following submission of the combined EAG reports to the ECDC Advisory Forum in July 2007, it was agreed to separate the reports into their constituent parts. The introductory sections (1 to 3) and closing sections (section 6 to Appendix 6) are common to both reports. The only difference in the reports is the content of sections 4 and 5 which contain the specific outcomes of the discussions of EAG1 and EAG2. These are now available in two separate documents.

## APPENDIX 5: DECLARATIONS OF INTERESTS RELEVANT TO THIS WORK

Name	Current			Historical		
	Personal		Non-personal	Personal		Non-personal
	Specific	Non-specific		Specific	Non-specific	
Dr Patrick Celis						
Dr Martine Denis	GSK employee					
Dr John Edmunds						
Dr Nedret Emiroglou						
Dr Johan Giesecke						
Dr Antoon Gijssens						
Dr Giuseppe Del Giudice	Novartis Vaccines employee					
Prof Lars R Haaheim						
Dr Agnes Hoffenbach	Sanofi Pasteur employee					
Dr Terhi Kilpi	Principal investigator of KTL research projects supported by GlaxoSmithKline; KTL nominated member of an expert group established by EU Geriatric Medicine Society and supported by Sanofi Pasteur MSD Principal investigator of KTL research projects supported by Wyeth					

Name	Current			Historical		
	Personal		Non-personal	Personal		Non-personal
	Specific	Non-specific		Specific	Non-specific	
	Paid advice to Wyeth and GlaxoSmithKline on advisory boards					
Dr Otfried Kistner	Baxter employee					
Dr Gérard Krause						
Dr Markus Mæurer						
Prof Liz Miller						
Prof Angus Nicoll						
Dr Jonathan Nguyen-Van-Tam	Paid advice to Sanofi Pasteur MSD on pandemic business continuity			Sanofi Pasteur MSD employee (02/02–07/04)	Paid honoraria for public speaking	Support for attendance at scientific symposia (Sanofi Pasteur MSD)
Dr Petri Ruutu						
Dr Chloe Sellwood						
Dr Bettie Voordouw						
Dr John M Wood	Contracted work with Sanofi Pasteur					
Dr Maria Zambon	Lab work supported by various vaccine manufacturers				Paid honoraria for public speaking	



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