EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

TECHNICAL REPORT

EXPERT ADVISORY GROUPS ON HUMAN H5N1 VACCINES

Public Health and Operational 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 (EMEA). 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.

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

This section summarises the answers produced by EAG2. The answer to each question is further developed with supporting evidence and discussion in Section 5. It should be underlined that this expert group made its advice based on the assumption that an H5N1 vaccine with some (even limited) effect actually existed.

The answers provided by the Expert Advisory Groups (EAGs) to the questions compiled 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.

When answering the questions it was necessary to make some assumptions. To qualify the answers given to the following questions, a number of definitions were assumed. These can be seen in Appendix 1.

This document contains ECDC scientific opinion following consultation with appropriate experts, and as such the information and conclusions should be taken as background information to assist Member States and EU bodies in making decisions. Certainly they are not rules and are not binding for Member States. It is not within ECDC's remit to determine national or EU positions and the approach may vary across Member States since decisions over purchasing these – likely costly – vaccines will most likely be taken at national or even regional levels. Rather, the purpose of this document and the accompanying EAG1 Report is to create a common understanding of the scientific and public health rationale for these vaccines which may make national positions and decisions converge in the EU. This does not preclude Member States or European Union bodies developing a common position through other mechanisms but that is beyond ECDC's remit (ECDC Founding Regulations).

4.11. Which groups should be immunised? Rationale for each (with special reference to children, adolescents and healthcare workers) with the desired population coverage

The group that would most benefit from vaccination with an H5N1 vaccine will change with the evolving profile of the developing pandemic and also depend on the timingof use of the vaccine. It could be appropriate to vaccinate poultry workers and/or veterinarians should the decision be taken to roll out vaccination whilst the virus remains predominantly infectious to birds. There are benefits in vaccinating healthcare workers (HCW) and laboratory staff, social care and other 'front-line' staff, and other vulnerable groups. There is a strong argument that children are the most potent spreaders of influenza in the community and that vaccinating them may influence the size and duration of the epidemic overall. There are epidemiological and ethical considerations regarding all these groups and the decision may vary between Member States. Herd immunity is unlikely to occur because of the low quantity of H5N1 vaccine likely to be available.

4.12. What might be the defined trigger points for applying the intervention in different groups?

The trigger points will vary for each group according to resources and organisation of care and therefore will be particularly likely to vary between Members States, but should be defined in advance as far as possible. It should be noted that while for some categories like HCWs the trigger points can be identified easily (they should be immunised earlier than other groups), more evidence would be needed for others and that can only be gathered during the early stages of the pandemic.

4.13. 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)?

Vaccinating twice as many individuals with only one dose will only be worth considering if clinical studies prove that one dose provides some degree of protection. Preliminary modelling studies suggest that there may be some theoretical advantage (e.g. reduced infections) to offering reduced antigen (two doses at a lower antigen concentration) to a greater number of people than a higher amount of antigen to fewer people. (See also the report from EAG1.)

4.14. What is the cost and the likely cost-benefit in the event of an H5N1-based pandemic?

It is difficult to answer this question without making assumptions and the cost will vary between Members States. Assuming a pre-pandemic vaccine can offer protection against the next pandemic strain, investment in such a project would be justified.

Preliminary modelling data and early economic assessment indicate that a substantial continuous investment is needed in order to reduce the impact of a pandemic through pre-pandemic vaccination but that it may be cost-effective. Further economic research at the EU level is needed to better formulate when such an investment would be justified.

4.15. When should the H5N1 vaccine be given?

Since the probability of an H5 pandemic is impossible to quantify, the EAG2 does not recommend that an H5N1 vaccine should be administered to any large population groups prior to the emergence of an H5-based pandemic. However, certain at-risk groups (for example, poultry workers) should be vaccinated as soon as sufficient amounts of a safe vaccine are available. It should be stressed that this policy requires that the country has the capacity to deliver mass vaccine in a very short time, ideally prior to the emergence of the virus in that country.

4.16. What systems are needed for rapid assessment of a developing pandemic to determine whether to deploy the vaccine and to whom?

A system for gathering and sharing the epidemiological information needed should be planned in advance and tested during a normal seasonal influenza epidemic. ECDC in conjunction with MS, WHO EURO and EMEA has been planning these activities as part of the 'Surveillance in a Pandemic' project. It is expected that relevant information like vaccine effectiveness, case fatality rate by age and risk group, as well as other data, are produced and shared in a timely way within Europe.

4.17. What systems are needed for rapid detection, assessment and investigation of adverse events?

Systems exist in most Member States, for example the EudraVigilance system in the European Economic Area (EEA), which was launched in December 2001. EMEA in conjunction with relevant partners is developing specific guidance for the safety management of pre-pandemic and pandemic vaccines. In addition, ECDC, through a call for tender, is planning to assess the national adverse events following immunisation (AEFI) reporting systems and to develop specific guidance and training material on the investigation of AEFI.

4.18. What systems are needed for rapid assessment of effectiveness when the vaccine is deployed?

Pre-planned trials in key groups and routine seasonal influenza vaccine systems should be able to address this. EMEA already has mechanisms in place to monitor post-marketing efficacy, and a call for tender for a project from ECDC addressing the special problems of the pandemic situation should help the implementation of epidemiological tools to estimate vaccine effectiveness through observational studies.

5. DISCUSSION AND SUPPORTING EVIDENCE

This section provides the background for the short answers given in Section 4, above. It should be underlined once more that this expert group made its advice based on the assumption that an H5N1 vaccine with some (even limited) effect actually existed.

5.11. Which groups should be immunised? Rationale for each (with special reference to children, adolescents and healthcare workers) with the desired population coverage

Relevance: *With limited amounts of vaccine available or affordable, it may be necessary to prioritise different segments of the population. This can only be based upon our knowledge of previous pandemics and of seasonal influenza. It may vary for different Member States, according to the parameters of a specific pandemic (an H5-based vaccine is unlikely to be effective with a pandemic based on an H1 or H3 influenza virus) and/or even change during the course of the pandemic*.

Information gathering on the epidemiological parameters, genetic characteristics and behaviour of the pandemic strain in relation to these vaccines would be part of more general gathering of data on the pandemic (*Surveillance in a Pandemic*) rather than a separate exercise in relation to H5N1 vaccines.

Should infection of domestic birds with H5N1 become more widespread in Europe, but remaining predominantly an animal infection, it would be reasonable to consider poultry workers and veterinarians for vaccination with H5N1 vaccine, but probably no other group would warrant vaccination. There are strenuous efforts being made by veterinary authorities across the EU to prevent a wider spread in poultry, and to date those efforts have succeeded despite repeated challenges from infected wild birds, but the possibility has to be considered. However, there are difficulties in defining exactly who are poultry workers and especially what to do over people with small backyard and hobby flocks who could be most at risk (ECDC 2006).

If the situation develops so that human-to-human transmission becomes a more important and maybe predominant mode of transmission, poultry workers and veterinarians would probably no longer be a priority group.

The four groups that have been considered for targeted use of the vaccine and the *rationale* for this are:

(a) Healthcare workers and laboratory staff – *more likely to be exposed.*
(b) Social care and other 'front-line' staff (having face-to-face contact with the public) – *more likely to be exposed.*
(c) **Vulnerable populations** (akin to those who are currently recommended for seasonal vaccine, i.e. the elderly, those with chronic medical conditions) – *can be anticipated to be especially vulnerable.*
(d) **Children** – may play a special role in the amplification of some pandemics.

Finally, there are approaches of immunising the **whole population** and, indeed, immunising children can be seen as a variant of these.

Epidemiological considerations in the choice of groups to be immunised

The choice of who should be vaccinated depends on the strategy chosen, the characteristics of the disease, the characteristics of the vaccine, the characteristics of the target groups, and how many doses are available, as well as a host of operational and ethical questions. Restricting attention to the epidemiological characteristics, the following should be borne in mind:

(i) Healthcare workers and those working in laboratories are a particularly important target group as they are most likely to be exposed, have a critical function in caring for others and should be able to expect reasonable precautions to be taken to protect them from the hazards of their work.

(ii) If a relatively small number of doses has been purchased then a vaccination programme would not be expected to generate significant indirect (*herd immunity*) effects. Under these circumstances, targeting those most at risk of complications and deaths would bring the most health benefits assuming these groups are able to mount an effective immune response. The target group would probably be (a subset of) the group currently recommended for epidemic influenza vaccination. However, it cannot be assumed that any pandemic would behave in the same way as seasonal influenza. In the 1918–19 pandemic, for instance, young adults were also at higher risk and a health economic approach emphasising preserving healthy life-years (rather than minimising the number of deaths) might lead to altered prioritisation towards young adults. Equally, observations of the age-profile of the human infections with H5N1 in its current form show severe infections in all age-groups but with some countries experiencing more in young age-groups (WHO, 2006). However, it is considered by some that this latter observation may simply reflect the fact that younger people have more contact with sick poultry in the affected countries. This emphasises the variability of pandemics and the importance of collecting early data on age- or risk-group-specific complication rates and of maintaining a degree of flexibility in plans for vaccine roll-out.

(iii) If large numbers of doses have been purchased (e.g. sufficient to vaccinate 20–30% of the population), then some indirect protection of unimmunised individuals might be expected to occur. Under these circumstances it may be advisable to target those who are most likely to spread the infection. Recent (unpublished) work in the UK supports earlier observations that vaccination of children could prevent far more cases, and may prevent numbers of deaths comparable with vaccination of the elderly, even when age-specific mortality rates increase sharply with age. The reduction of disease in the elderly would be the result of a general reduction in the incidence of influenza, as a consequence of vaccinating children (Ferguson et al, 2006; Germann, 2006).

These extrapolations rely on assumptions about how different age groups mix within and with each other and therefore are not certain. For example, recent (unpublished) work has tried to estimate how different age groups interact. The study showed a connection between people aged 30–40 and children, which is hardly surprising, but this connection could be skewed if schools were to close during a pandemic and children stay with grandparents, for example.

Different effects again would be observed should an age group be totally removed from the transmission chain (for example, by vaccinating everyone in that age group with a vaccine of 100% efficacy) or removing a part of an age group. In addition, vaccinating children first may not be the most effective strategy since the 30–40 year age group is larger in size. Therefore, even if children have a high contact rate with the elderly, the higher number of individuals aged 30–40 years could result in a higher total number of infectious exposures from this group than from children. In contrast, a study using contact data from the Netherlands (Wallinga et al, 2006) suggested that a disproportionate number of people might be infected through contact with 13–19 year-olds, assuming there is no immunity in any age group.

The variety of possible outcomes of employing these different approaches and methods highlights the concern that the scientific evidence on this issue is vague and that while there are increasing numbers of modelling studies there are few observations of how pandemic or even seasonal influenza actually spreads on which such studies can be based. In a diverse region such as Europe it quite possible that there are important differences between and within countries. In addition, there is the uncertainty as to how the next pandemic, and specifically an H5-based pandemic, might behave. The three pandemics of the 20th century all differed in their transmission profiles (Glass, 2006). Given all these uncertainties it is hard to say how best to allocate a limited supply of vaccine to achieve the best herd immunity and the ultimate strategy would be to offer immunisation to the entire population. At least one EU country has stated that this is the approach it will take, though of course the investment required for this is considerable.

Ethical considerations in the choice of groups to be immunised

As well as affecting the individual, pandemic influenza impacts on the community as a whole. In principle, everyone in the community should have equal access to preventive and therapeutic measures. However, in the context of an influenza pandemic, it is unlikely that even in well-resourced countries such as those in Europe there will be sufficient stocks of human H5 vaccine for the whole population. This is a more general issue concerning pandemics: who should receive limited intensive care, etc. Therefore, the best ethical principles and a solid scientific knowledge of the different possible impact scenarios of a pandemic need to be integrated into a well justified rationale to prioritise the allocation of limited resources (WHO, 2007b). Much of the debate about vaccines during a pandemic is over how to deal with time constraints (the rapid emergence of a pandemic) when a specific pandemic vaccine only becomes available later from a system with restricted global capacity. Pre-purchase of human H5 vaccines overcomes some of these issues but there are still many relevant discussions on ethical issues in the WHO document (2007b). Indeed, ECDC-led assessments have found that several EU countries are actively considering ethical issues that emerge in relation to pandemics, for example by establishing independent groups to consider these matters, either drawing on pre-existing structures or creating special ones for pandemic preparation. As already mentioned, the issues are complicated by the fact that it is impossible to predict the impact of a future pandemic on different subgroups of the population. In previous pandemics the highest risk of mortality has varied from the young working-age population (1918) to the groups more traditionally affected by the annual seasonal influenza

epidemics with particular emphasis on children in 1957 and across most age groups in 1968 (Glass, 2006; ECDC, 2007).

Ethical decision-making should consider issues such as individual liberty; efficiency; transparency; reasonability; reciprocity; equity; and utility.

Decision-makers assessing access to health care and distribution of vaccines or antivirals need to find a balance between equity and achieving maximal health benefits in the population. The generic objective is to prevent adverse health effects, i.e. illness, hospitalisation and death. However, these are not of equal value for ethical decision-making, and need to be further elaborated to reach a justifiable basis for prioritisation. Preventing death, the irreversible outcome, is usually the primary objective. Saving *expected years of life* values the prevention of death in young people higher than preventing death in the aged. Saving *quality-adjusted life years*, which assesses the value of the remaining life span, incorporates co-morbidities, commonly seen in the elderly, in the decision model. The aim to save *productive quality-adjusted life years* emphasises the social or societal added value of the remaining years of life. Determining quality and productivity in this context may be difficult in such a way that would be transparent and acceptable to the population as a whole.

Treatment of influenza patients by healthcare workers places that worker at risk of acquiring the disease and of death. Maximal personal protective equipment (PPE) will not be available at every contact with a patient with confirmed or suspected influenza. Indeed some operational studies find that a balance has to be struck between personal protection and being able to carry out tasks: some PPE is simply incompatible with carrying out normal duties on a general level (HPA, 2007). Due to the rapid escalation of the threat many healthcare workers will not have had appropriate training to fully meet the professional requirements to avoid acquiring the infection. Ultimately a pragmatic balance must be struck between maximal protection and delivering health care since some of the procedures are cumbersome and difficult to apply when managing large numbers of patients (US Congress, 2006). In the event of a pandemic, ameliorating the adverse health effects depends to a great extent on the healthcare personnel fulfilling their ethical and professional obligation to take care of the patients, at the same time exposing themselves to the risk of infection. This makes healthcare personnel encountering (potential) influenza patients a priority group for vaccination and other preventive measures, based on the ethical principle of reciprocity.

Arguments can be made that countries should incorporate in their national influenza pandemic preparedness planning a process to develop the principles of prioritising limited preventive and therapeutic measures in different pandemic scenarios, based on the universal ethical principles and the key societal values of the country. These principles can then be applied in decision-making when sufficient information becomes available on the properties of the actual pandemic virus and its impact on different population groups. Any model needs to operate rapidly on new issues as they arise in a pandemic.

A WHO-coordinated 'Project on addressing ethical issues in pandemic influenza planning' has produced a comprehensive four-part document on general ethical issues related to a pandemic (WHO, 2007b) and as mentioned, a number of individual EU countries have also established groups to address these issues prior to and during pandemics.

5.12. What might be the defined trigger points for applying the intervention in different groups?

Relevance: *Due to limited availability of vaccine, it may be necessary to vaccinate different groups at different stages. Therefore it will be essential to identify the trigger points in advance in order to use the vaccine most effectively*.

Defined general and specific trigger points for deploying the stockpiled vaccine are needed. The general conditions that would need to be met are described above. Unless Member States purchased enough vaccine for every citizen they presumably will have determined their strategies for restricting the offer of immunisation to the groups they have selected such as those suggested under Question 11.

The triggers could be relatively simple. For instance, a trigger for protecting those working with poultry would be the increased appearance of H5N1 among domestic poultry. There would be advantages in Member States coming up with criteria that were comparable across the EU and taking a collective decision using the pre-existing mechanism that enables this in the veterinary field.

Should the importance of human-to-human transmission increase, triggers for offering the vaccines to a) **healthcare workers and laboratory staff**, and to b) **social care and other 'front line' staff** should involve them and their representatives in the first instance, but to whom to offer the vaccine within these broad groups remains to be defined. This would have to be pre-planned and there would again be advantages in Member States coming up with criteria that were comparable across the EU.

For group c) **vulnerable populations**, the trigger would again be early studies of case fatality rate (CFR) observations, i.e. where in the spectrum the pandemic was acting between being a classical seasonal virus or more like the virus that caused the pandemic of 1918–19 where an unusually high mortality was observed including in the young adult age-group. The latter scenario would cause a reappraisal, entailing some difficult ethical choices (see Question 5.11: ethical consideration). Particular care will need to be taken over how the early CFRs are measured as there will probably be reasons why they will be biased upwards (as happened for SARS), especially if serology is not used to detect mild and asymptomatic infections.

For targeting group d) **children**, the trigger should come from early studies on the pandemic virus characteristics, showing that children could be acting as pandemic amplifiers. For example, the information that children are contributing to more than X% + 20% of transmissions, where X% represents the proportion of the population represented by children, could trigger vaccinating them.

A trigger to *not* deploy, or to withdraw a human H5 vaccine would presumably be the detection of plausible and convincing associations with clinically significant adverse events following early vaccine use that changed the risk-benefit argument to one against vaccination. This is especially the case since the vaccine here is likely to have lower efficacy than a specific vaccine and it may be offered to individuals (such as children) to reduce transmission generally rather than to protect those individuals against disease.

Further discussion of triggers, specifically about when to immunise are discussed below under Question 15.

5.13. 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 dose)?

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. This is also considered in 5.3 (see Report from EAG1).*

There are two scenarios to consider: either that the vaccine only protects against disease in the vaccinated, or that it also protects against transmission from a vaccinated but still (clinically or sub-clinically) infected person.

It is, however, generally held that killed and parenterally-administered influenza vaccines of today will not protect against infection per se, and if so, only to a marginal degree due to a vaccine-induced boosting of an IgA memory from previous infections. As the H5N1 vaccine will be given to a naive population, we can safely assume that no anti-H5N1 IgA will be present at mucosal surfaces, and thus not offer any protection against the infection as such. However, systemically available vaccine-induced IgG antibodies will dampen the replication process (and thus give a milder clinical outcome). Also, it is safe to assume (based on data from animal studies) that the viral infection could cause leakage of IgG through mucosal surfaces and thus to some degree neutralise virus and reduce the viral load in the airways, thereby reducing infectiousness. If an inactivated parenterally-given vaccine elicits mainly an antibody response, and little if any cytotoxic response, then it would follow that reducing clinical illness (presumably through a reduced number of viral replication cycles), should lead to a reduced viral load in the airways and thus reduce infectiousness. (The use of inactivated intranasal vaccines may change this argument.)

In the event that only a limited amount of vaccine has been purchased or there is an actual shortage, antigen sparing strategies (such as giving a single dose to twice as many individuals) might be considered. The use of vaccines in this way may not be in agreement with the licensed indication. Recent preliminary modelling suggests that there may be some overall benefit of lower infection attack rates by administering lower individual antigen doses to a greater number of people. For three H5N1 vaccines (described in 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. This was achieved modelling a two dose, rather than one dose, strategy. While reducing the antigen dosage may still protect people against illness to some degree, it does not automatically follow that complications or deaths will be similarly reduced. This effect would be influenced by the groups targeted for vaccination; for example, the elderly, very young or physically vulnerable from having chronic medical conditions may respond poorly to a reduced antigen dose (Riley

et al, 2007). There are other considerations which depend on the characteristics of the vaccine and the numbers of doses available and some of these are outlined below.

Antigen-sparing strategies should be informed by immunogenicity and, preferably, challenge, studies in an appropriate animal model, such as the ferret or macaque. If such studies suggest that two doses are required to offer protection against severe clinical outcome, then a strategy in which twice as many are given only one dose may reduce illness to a lesser degree. If a degree of protection is offered from a single dose, then it may be appropriate to investigate the marginal benefit of an antigen sparing strategy. In doing so, any such strategy should also consider the immunogenicity of a single dose strategy in the marginal groups at highest risk.

If large numbers of doses are available, then indirect protection (or herd immunity) might be expected to be generated via a vaccination programme. Under these circumstances the marginal benefits of an antigen sparing strategy need to be very carefully evaluated with reference to an appropriate transmission model. In terms of reduced cases and deaths it may well be better to provide solid protection in those most likely to spread the infection (for example children), than offer a lower level of protection to a wider number of people. This would be particularly the case if a single dose did not prevent infectiousness, but only offered protection against disease, whereas two doses prevented infectiousness as well as disease. Under these circumstances it is unlikely that an antigen sparing strategy would offer more population-level protection than an appropriately targeted vaccination programme that takes into account the infection dynamics.

Having a large stockpile of vaccines with a 15% efficacy after two doses used in a large population could prevent a number of deaths, even if herd immunity in the population would not be achieved unless the influenza strain has a basic reproductive number $R_0 < 1.17$ (assuming a randomly mixing population and discarding age or spatial structure). This seems unlikely when compared with the reproductive numbers estimated for the three pandemics in the 20th century which were all higher (Hall, 2007).

Some modelled estimate of the population effect of having a vaccine, which only prevents serious illness and death is illustrated below. Assuming:

- a population of 10 million with random mixing and no age/space structure;
- 2.5% lethality from the virus in an unprotected population;
- a vaccine efficacy of 15% after two doses;
- a vaccine coverage of 40%,

one can calculate that mortality would be reduced by 8 000 – 12 000 by the vaccination campaign (see Figure 5.13.1).

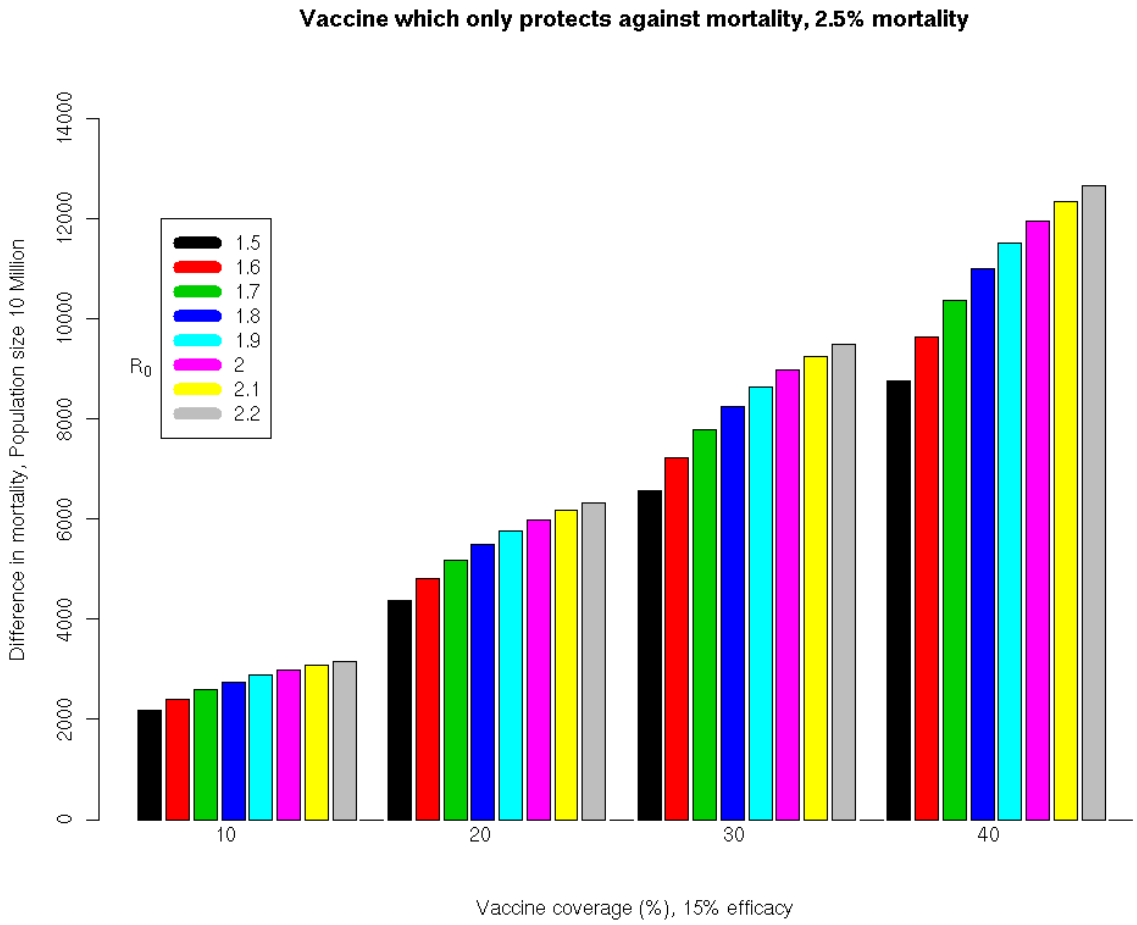

Figure 5.13.1. The expected number of deaths prevented by giving a vaccine which prevents serious disease and death, but gives no protection from infection. *The different colours represent various assumed values for R_0.*

This theoretical reasoning could be expanded by assuming that the vaccine not only prevents serious illness and death, but that it also stops any further transmission from an infected individual. If this were the case, mortality would be reduced by a further 8 000 – 17 000 (see Figure 5.13.2). As can be seen from that graph, the main benefits from a vaccine that not only protects the immunised, but also prevents further transmission, are achieved for low values of R_0. This is explained by observing the real value of R_0, taking into account the population immunity and the potential for spread. If R_0 is large, the difference between the effects of these two types of vaccine is small, but when R_0 approaches 1 the additional effect on further spread of infection can be considerable, especially when the vaccine coverage increases.

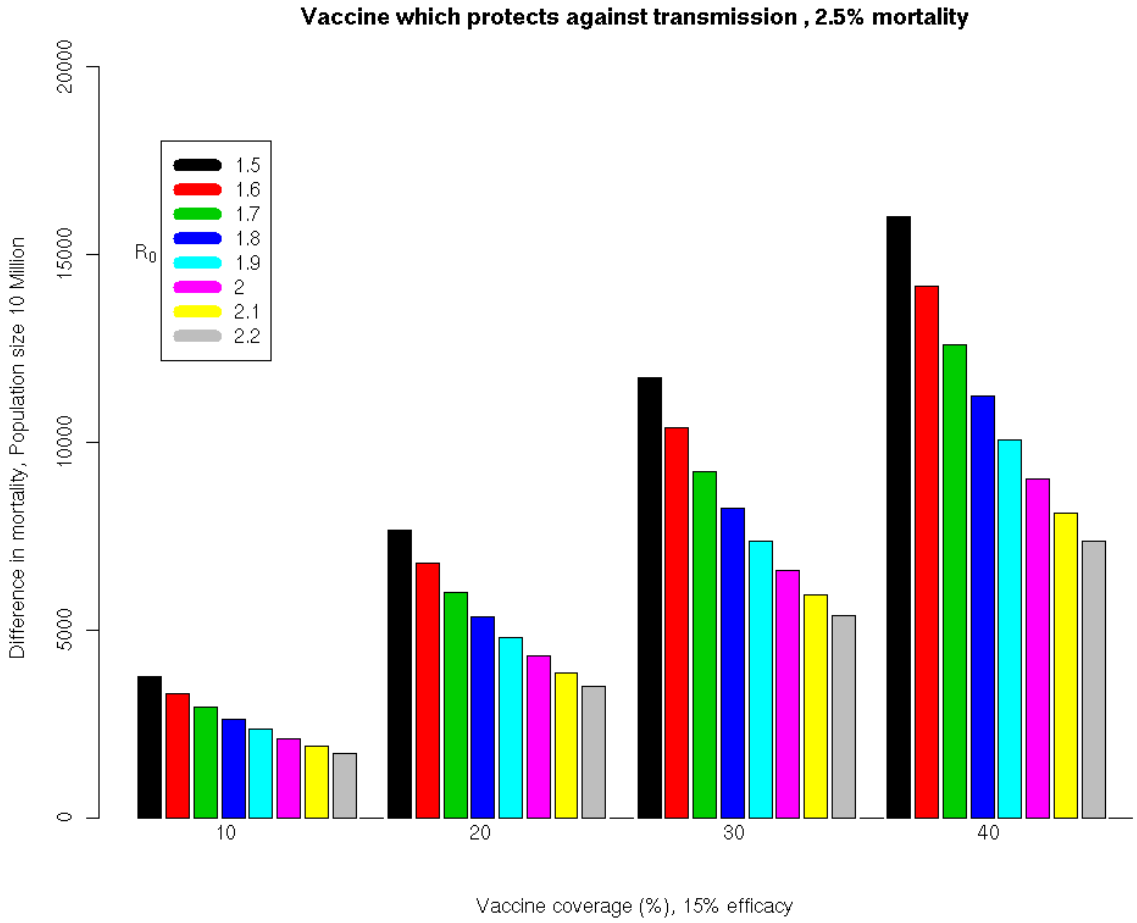

Figure 5.13.2. Additional number of deaths prevented compared to the graph in Fig. 5.13.1 if the vaccine used not only prevents serious disease and death, but also stops transmission of disease from an infected individual. *The different colours represent various assumed values for R_0.*

5.14. What is the cost and the likely cost-benefit in the event of an H5N1-based pandemic?

Relevance: *It is essential that the potential cost of a pandemic and cost-benefit of various interventions, including pre-/ pandemic vaccination, are considered. Such evaluations may help decisions on funding among Member States and specifically the issue of purchasing these vaccines compared to other priorities for limited national budgets.*

This difficult question cannot be answered without making many assumptions which may not be relevant to all Member States. Furthermore, the choice of assumptions will greatly influence the answers generated.

The cost of an influenza pandemic could be very large (US Congress, 2006). Assuming a human H5N1 vaccine can offer protection against the next pandemic strain, then simple economic analysis suggests that significant investment in such a policy may well be justified. Of course investment in development of a vaccine that can offer protection against all of the most likely pandemic strains (those based on H1–3, H7 and H9 as well as H5) may well be a prudent use of public resources, though such a 'holy grail' of influenza control is not considered an immediate prospect by vaccine experts.

Economic arguments

Estimating the cost-benefit of vaccination strategies is complicated and difficult since there are a number of possible epidemiological scenarios (e.g. the pandemics of the 20th century had very different impacts) and an unknown time period until the next pandemic, both of which affect the estimated present value of the cost of a pandemic. The specific difficulty is that while almost everyone agrees that another pandemic is inevitable, there is no certainty that the next one will be H5-based (ECDC, 2006). In addition, there are a number of alternative vaccination strategies, the effectiveness and cost of which are, at present, unknown. There are also special difficulties in the EU because of its economic and social diversity. This argues for countries developing these discussions but applying the general arguments such as those which are outlined below, drawing on work in the UK as an illustration.

It is impossible to estimate the total cost to society from a future pandemic and the entire reasoning in the remainder of this question thus becomes highly theoretical. However, as a starting point, one could use recent estimates from a UK exercise, where it was assumed that the cost of a pandemic would be in the range of 0.8–1.5% of annual GDP. (Estimates from the US Congressional Committee are significantly higher, largely as they assume longer periods of absence from work (US Congress, 2006).).

Providing a rough cost estimate can be simplified by setting a threshold of the costs and effects of a vaccination strategy under which they might be acceptable given the range of possible epidemiological scenarios:

- If the basic reproduction number (R_0) for the next strain of influenza is approximately 2 (which appears to have been the case for previous pandemics), then a universal pre-pandemic vaccination programme that achieves >50% immunity (that is if everyone is vaccinated then the efficacy of the vaccine must exceed 50%) should prevent a major epidemic from occurring.
- If $R_0 = 3$, then this threshold level of immunity will be 67%. At such levels of population immunity a pandemic would still be expected to incur some costs, since cases will still occur, but these might be expected to be insignificant in comparison with the costs of an uncontrolled epidemic.
- Epidemic theory suggests that there would be an approximately linear relationship between the level of population immunity achieved and the size of the epidemic (see Figure 5.14.1). If the costs scale accordingly, then the threshold level of investment needed to achieve this reduction in cases through immunisation can be derived.

- The final complicating factor concerns the starting date of the epidemic, since the costs of stockpiling vaccination accrue now, whereas the epidemic occurs some time in the future (future costs are valued less than those that occur today, using a discount rate, frequently in the range of 3–5% per annum).

The figure can then be used to estimate the maximal level of investment that should be made into vaccination programmes (the analysis can be extended to other mitigation strategies). For instance, if a vaccination programme results in >50% population immunity (and $R_0 = 2$), then the savings resulting from this if the epidemic occurred immediately would be between 0.8% and 1.5% of GDP (the difference between cost of the pandemic with the intervention and the cost with no intervention, or 0% immune).

If the pandemic occurs in 30 years' time (the risk of a pandemic can be estimated at roughly 3% per year[1]), then the investment needed should be up to 0.2% and 0.6% (depending on the discount rate) of GDP in a universal pre-pandemic vaccination programme.

Preventing a pandemic completely may be unfeasible due to the difficulties of producing a vaccine that will cross protect, and of vaccinating widely enough. Hence if it is only possible to achieve 20% of the population effectively immunised then the figure suggests that investment needed would be from 0.1% to 0.35% of annual GDP into a pre-pandemic vaccination programme (assuming the pandemic occurs in 30 years' time). If investment in other strategies to reduce the epidemic size have already been made, then investment in vaccines should be scaled down accordingly.

If an H5N1 epidemic never occurs then the returns on the investment in such a vaccine will be very limited. Hence, investment in a pre-pandemic vaccine that covers all of the likely pandemic candidates (if and when that can be developed) is the best investment.

[1] This is on the basis of there having been three substantial pandemics in the 20th century

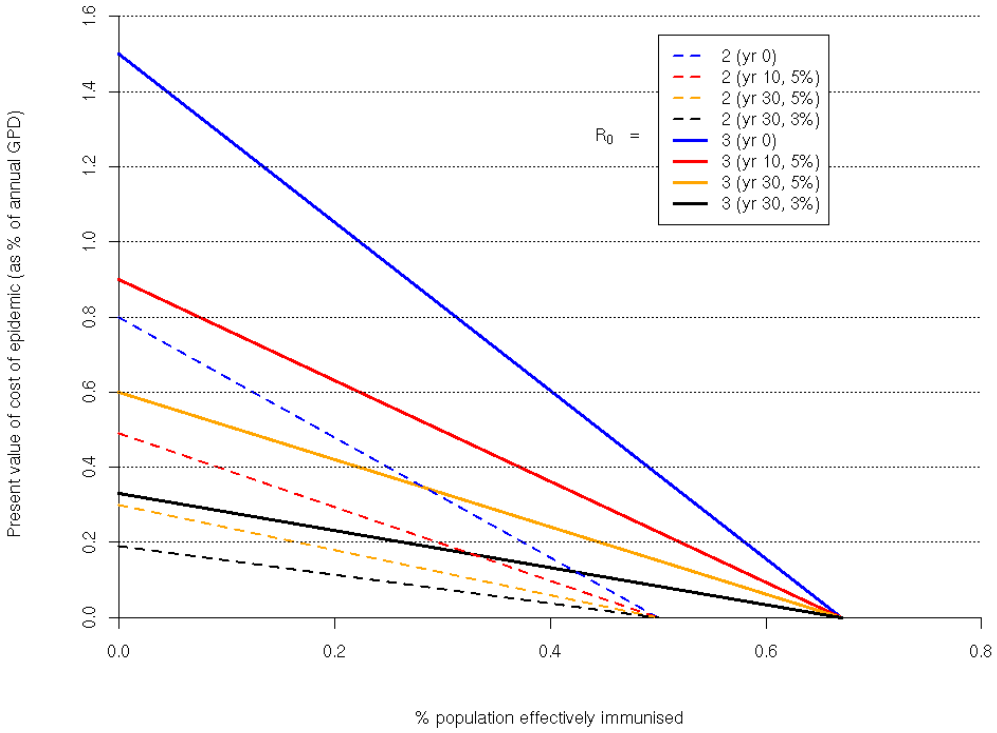

Figure 5.14.1. Theoretical model under a number of assumptions (see text) illustrating how R_0 (here assumed to be either 2 or 3), time to next pandemic(here assumed to either 0, 10 or 30 years) and discount rate (here assumed to be either 3 or 5%) influence the cost of a pandemic as a function of the proportion of population effectively immunised.

5.15. When should the H5N1 vaccine be given?

Relevance: *With an influenza vaccine targeted against a new subtype, it will be important that it is used at the optimum time*.

Here there are important difficulties some of which have already been mentioned under Question 11. A number of factors will contribute to decisions of Member States as to when to deploy vaccines, including the timing of priming doses if it seems important to give two doses to achieve an effect. These include the following:

1. How quickly does immunity develop in an individual? Certainly there is an important time factor with all active vaccines and an interval between an individual being vaccinated and developing protection (please refer to report from Expert Advisory Group 1).

2. How quickly can those selected be immunised? A country with a developed and tested plan for rapid mass immunisation may be able to defer immunisation better than one that relies on citizens going to their individual practitioners. The latter may need to make an earlier decision to start offering vaccines.

3. How far away from Europe can efficient human-to-human transmission be expected to start? Presently the most likely scenario for an H5-based pandemic is that human-to-human transmission starts in one of the countries where H5N1 is endemic in poultry. This allows for some delay for Europe, much more so than in the unlikely scenario that H5 becomes common in domestic poultry in Europe. However, caution is needed for several reasons: the nearest endemic country is Egypt; human infections travel quickly in the 21st century; and there is always the possibility that an H5 pandemic emerges undetected in one of the countries where veterinary and human surveillance for influenzas is weak (such as sub-Saharan Africa). In that case the appearance of efficiently transmitting H5 human infections in Europe or another industrialised region could be the first indication.

4. What will be the pattern of emergence of an H5-based pandemic? There is a well-known model whereby an influenza with pandemic potential moves through four phases from Phase 3 (where we are now) to Phase 6 (efficient human-to-human transmission) (WHO, 2005). Many countries have based their plans on this model describing the action to be taken at each phase. However, it must be appreciated that this is a model rather than a certainty. Phases 4 and 5 (when human-to-human transmission is becoming increasingly efficient) have never been recorded in previous pandemics (whether because they took place before modern epidemiological techniques were available or in resource-poor settings which did not lend themselves to investigation and description). It is quite possible that Europe first learns of a pandemic when WHO declares that the world is in Phase 6. Therefore, more realistically given factors 1 to 3 above, countries may need to take an early decision to deploy human H5 vaccines because either the Director of WHO declares that the world seems to be moving towards a pandemic or that a pandemic has emerged rapidly.

However, there are plausible arguments that an H5N1 vaccine should not be administered prior to the emergence of an H5-based pandemic, or at least convincing evidence that the virus is moving towards Phase 6. Since there has never been an observed H5-based pandemic it is not inevitable that one will occur (ECDC, 2006). All vaccines have some adverse effects and the large-scale immunisation of populations at the present time (WHO Phase 3), though justifiable given factors 1 and 2 above, must carry some risk. It should be underlined that if countries that have decided to purchase these vaccines choose the option of delaying vaccination, they must consider their ability to deliver mass vaccine in a very short time prior to the emergence of the virus in that country (please also refer to the report from Expert Advisory Group 1).

Following the confirmed emergence of an H5-based pandemic by WHO there will need to be a rapid assessment of the genetic fit of the pandemic strain and whether it is close enough to the antigens used to produce the pandemic vaccine so as to reasonably expect some level of protection. The virus may have drifted so far from the genetic base of the antigens recommended by WHO that the protective effect might be very small (ECDC, 2007). This would not preclude use of the vaccine but it would be an important consideration. If the pandemic virus is not H5N1 (i.e. it has shifted), then an H5N1-based vaccine will not offer any protection.

Animal studies may give some early consideration as to whether the vaccines might be expected to work in humans, for example by challenging vaccinated and naïve members of a

susceptible species with the pandemic strain to see if there is a protective effect. Such studies would be undertaken early using a ferret or macaque model. This would not preclude use of the vaccine but would be another important consideration if, for example, there was seemingly no protective effect against the pandemic strain.

Early observations where the virus first emerged as to any protective benefit of the vaccines may help indicate whether the vaccine should be more widely used. There may be early trials taking place close to the areas of first appearance of the virus, though on ethical grounds these would need to be conducted in populations that would be expected to benefit from the intervention. This would be superior to animal model work.

5.16. What systems are needed for rapid assessment of a developing pandemic to determine whether to deploy the vaccine and to whom?

Relevance: *It will be essential to be able to rapidly assess the developing pandemic in order to be able to roll out vaccine in the most effective manner. This will be particularly pertinent in the case of a limited amount of vaccine and needed to prioritise at-risk groups.*

This system should not be separated from the general assessment of the *Surveillance in a Pandemic* work being undertaken by Member States with ECDC, WHO and other national bodies such as the US Centers for Disease Control and Prevention (CDC). Rather, some of the outputs from that work would be serving decisions for deployment of H5N1 vaccine. Even if information was available from other parts of the world, for example nearer to where the pandemic first emerged, there would still be a need to repeat some measurements, notably the case fatality rate and evaluation of which groups are experiencing transmission. This is because the virus may behave differently in a different demographic group and geographical region and previous pandemics have changed their genetics and behaviour with time and spread.

5.17. What systems are needed for rapid detection, assessment and investigation of adverse events?

Relevance: *It will be essential that adverse events associated with use of H5N1 vaccine can be rapidly detected, investigated and assessed to ensure the general population of Member States can be reassured about the safety of the vaccine*.

Such systems already exist in most Member States, but they are often slow, and rely on voluntary reporting of suspect adverse events following immunisation. EudraVigilance (http://eudravigilance.emea.europa.eu/human/index.asp) is a data processing network and management system for reporting and evaluating suspected adverse reactions during development, and following the marketing authorisation, of medicinal products in the European Economic Area (EEA). The first operating version of EudraVigilance was launched in December 2001.

However, both EMEA and ECDC are working to improve this situation. One reason for this joint work is that in many Member States issues around vaccines have traditionally been

addressed by the Public Health Institutes, often as part of their routine disease surveillance. The competencies of both these agencies and their constituencies are therefore needed.

EMEA is working on the development of the legal and technical framework for the pharmacovigilance of pre-pandemic and pandemic vaccines. Policy makers should refer to specific EMEA guidance that will be regularly updated. Experts from the Committee on Human Medical Products (CHMP), the Vaccine Working Party (VWP), the Pharmacovigilance Working Party (PhVWP), ECDC, DG SANCO and the European Vaccine Manufacturers association (EVM) contribute to the development of such guidelines. In addition to the routine passive reporting of adverse events, there will be some additional activities such as the monitoring of adverse events of special interest considered important to be monitored by documenting cases notified by healthcare professionals (neuritis, convulsions, severe allergic reactions, syncope, (myelo)encephalitis, thrombocytopenia, vasculitis, Guillain-Barré Syndrome, Bell's palsy, and other autoimmune diseases such as multiple sclerosis, optic neuritis, diabetes mellitus). Furthermore, the Risk Management Plan for each authorised vaccine should include the active follow-up of vaccinated individuals during the pandemic, and specific epidemiological studies to assess causality should be conducted.

ECDC, through a call for tender, is assessing the national adverse events following immunisation (AEFI) reporting systems and to develop specific guidelines and training material on the management of AEFI. More information should be available following completion of this process.

5.18. What systems are needed for rapid assessment of effectiveness when the vaccine is deployed?

Relevance: *It will be essential that the effectiveness of any human H5N1 vaccines can be rapidly assessed once deployed across Member States*.

The assessment of vaccine effectiveness can only be done during the pandemic. Vaccine efficacy data will be available before the pandemic, but they will only be based on immunogenicity tests and animal challenges. Vaccine effectiveness will have to be estimated under field conditions using observational studies that are currently used to measure vaccine effectiveness for seasonal influenza vaccines. ECDC has launched a call for tender to provide guidance on the various and most appropriate methods for estimating vaccine effectiveness through observational studies, with the goal of establishing a system around seasonal influenza and then using that system during a pandemic. That will be most relevant for the specific pandemic vaccine which will presumably be widely deployed, but it may have some value in relation to human H5N1 vaccines. However, if there is not widespread purchasing of the latter then individual Member States will need to ensure that arrangements are made for rapidly assessing effectiveness. Such efforts will be able draw on the ECDC-supported systems.

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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- WHO. Annex 1: Guidelines on clinical evaluation of vaccines: regulatory expectations. WHO Technical Report, Series No. 924, 2004. Accessed 17 May 2007 http://www.who.int/biologicals/publications/trs/areas/vaccines/clinical_evaluation/035-101.pdf

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 $\geq 25mm^2$ 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 ≥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 $\geq 25mm^2$, 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 $\geq 25mm^2$.
– 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):

	Adults 18–60 yrs	**Adults ≥60 yrs**
Seroconversion rate	≥40%	≥30%
Seroprotection rate	≥70%	≥60%
Mean geometric increase	≥2.5	≥2.0

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

References

- EMEA/CPMP/BWP/214/96. Committee for Proprietary Medicinal Products (CPMP) Note for guidance on harmonisation of requirements for influenza vaccines. 12 March 1997. Accessed 12 April 2007. http://www.emea.europa.eu/pdfs/human/bwp/021496en.pdf
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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 Gijsens 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			Personal		
	Specific	Non-specific	Non-personal	Specific	Non-specific	Non-personal
Dr Patrick Celis						
Dr Martine Denis	GSK employee					
Dr John Edmunds						
Dr Nedret Emiroglou						
Dr Johan Giesecke						
Dr Antoon Gijsens						
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 Maeurer						
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	

APPENDIX 6: REFERENCES

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