Options for the use of human H5N1 influenza vaccines and the WHO H5N1 vaccine stockpile

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TECHNICAL CONSIDERATIONS FOR DEVELOPING OPTIONS FOR USE OF HUMAN H5N1 INFLUENZA VACCINES AND A WHO H5N1 VACCINE STOCKPILE

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Executive summary

Ever since its emergence as a human disease, influenza caused by the H5N1 virus has presented a serious and highly complex public health challenge. In May 1997, the first human case of H5N1 infection was recorded and by the end of the same year 18 further cases had been confirmed. In 2003 and 2004, the virus returned and was found to have spread rapidly in several Asian countries infecting both birds and people. Since February 2003, millions of birds have been infected and 328 human cases have been recorded causing 200 deaths in 12 countries in Africa, Asia and Europe. As an avian pathogen alone, it has had a devastating agricultural and economic impact on the communities it has affected. At present, H5N1 remains primarily an avian virus that causes relatively rare but frequently fatal infections in humans. However, as the virus continues to evolve its greatest threat lies in its potential to develop into a strain that is easily transmissible among people. Should this occur, the virus would then be capable of causing sustained and widespread human-to-human infection, and therefore a human influenza pandemic. Addressing these distinct but interrelated threats has proved to be highly problematic for public health and animal health agencies and authorities.

The development and potentially imminent availability of approved vaccines against human H5N1 influenza therefore marks an important milestone in global efforts to address this threat. As with other influenza vaccines, the development of effective H5N1 vaccines is notable because they are potentially the best way of directly protecting people. Vaccination is potentially the safest and most effective way of preventing or reducing the morbidity and mortality associated with all forms of H5N1. This is true both in the current non-pandemic situation (in which some populations are at elevated risk of infection with avian H5N1 viruses) and in the future should the virus evolve into a human pathogen capable of causing a pandemic.

However, before any new technology can be widely recommended, a number of complex considerations must be taken into account. H5N1 vaccines are a relatively new development and information on their safety, efficacy and the likely degree and duration of their protective effects is relatively limited. Currently, at least 16 different manufacturers have an H5N1 vaccine in relatively advanced development based on a range of approaches (including egg and cell culture grown viruses, live and inactivated antigen, whole and split antigen, and vaccines developed with and without different adjuvants). Additional technologies are also under consideration and development.

Once the safety and efficacy of H5N1 vaccines have been more clearly demonstrated, a number of other issues will also require very careful consideration. For example, difficult decisions will probably need to be taken on who should be vaccinated first (and at what “trigger point”). Another fundamental issue is whether the emphasis of vaccination strategies should be on protecting the most vulnerable individuals from severe disease or death or whether to apply a population perspective and attempt to reduce virus transmissions or to try and protect "essential functions" for the society. Such issues are extremely difficult but once made, then should be clearly communicated and explained to the general population. Regardless, well-coordinated and properly monitored vaccination efforts will be needed.
However in resource-poor countries, existing health infrastructures, resources and vaccine supplies are likely to be inadequate in many of the scenarios outlined in this report. Such logistical shortfalls could seriously undermine efforts to implement effective vaccination campaigns, and to properly monitor their safety and efficacy. In such settings the very personnel needed to maintain the vital infrastructure of a country and to mount a response to the pandemic would themselves be at high risk of infection and severe illness. In order to reduce some of the current inequities in access to H5N1 vaccine the Sixtieth World Health Assembly in its Resolution WHA60.28 requested WHO to create a global stockpile of H5N1 vaccine.

Within 3 years the WHO H5N1 vaccine stockpile could potentially contain at least 50 million doses – enough for 25 million people to receive the two doses likely to be needed to for immunization. Ultimately the size of the stockpile may depend upon the evolving nature of the current H5N1 virus. Based on the consultation described in this report, a stockpile of approximately 100 million doses may be justified given potential uses of the stockpile. In any case, further work will be needed to ensure the best use of this resource including its development, maintenance and access.

To address these and other issues, WHO initiated a series of efforts designed to accelerate understanding of the ways in which human H5N1 influenza vaccines could best be used to deal with the threat posed by avian influenza outbreaks. On 1–3 October 2007 WHO held a scientific consultation review the current data on H5N1 vaccine immunogenicity, safety and other characteristics; consider the current options for the use of such vaccine; and identify options for use of the WHO H5N1 vaccine stockpile.

One of the principal objectives of this consultation was to review the available scientific information and basis for the possible uses of the WHO H5N1 vaccine stockpile in advance of the discussions of the WHO Strategic Advisory Group of Experts (SAGE) in November 2007. The participants included researchers, representatives from WHO Influenza Collaborating Centres, selected country representatives, SAGE members, and the pharmaceutical industry. Observers were also allowed. During an intensive programme of presentations and discussion the following key areas were addressed:

1. Characteristics of candidate human H5N1 influenza vaccines
2. Options for using human H5N1 influenza vaccines
3. Options for using the WHO H5N1 vaccine stockpile

As outlined in section 1 of this report, encouraging scientific data are becoming increasingly available on the following characteristics of candidate human H5N1 influenza vaccines currently under development.

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Vaccine safety

- So far no major or unanticipated safety concerns have been identified related to the use of H5N1 vaccines – but significantly more safety data are needed. There may however be an increase in local reactions associated with some adjuvanted and whole virus vaccines; and additional controlled trials with long-term follow up (especially in children) are required. A crucial consideration is that the perceived risk-benefit ratio and the acceptance of the balance can change considerably depending upon the perceived risk of disease.

Vaccine immunogenicity

- at comparable antigen dose levels, candidate human H5N1 influenza vaccines generally elicit lower immune responses than seasonal human influenza vaccines;
- some candidate human H5N1 influenza vaccines elicit higher antibody titres than others after two doses with a 21-day interval;
- live attenuated influenza vaccines (LAIV) and inactivated whole virus vaccines may be more immunogenic than unadjuvanted split or subunit vaccines; and
- for most human H5N1 split and subunit vaccines, the use of oil-and-water emulsion adjuvants reduces the amount of antigen required to elicit the same level of response as higher doses of the same antigen used without adjuvant.

Cross-reactivity and protection

- animal data suggest that human H5N1 influenza vaccines produced from viruses from one clade may be cross-reactive against viruses from other clades, and may be protective against challenge with viruses from other clades;
- oil-and-water emulsion adjuvanted vaccines that elicit high levels of antibody against homologous challenge also elicit higher levels of antibody to variants;
- recent developments in areas such as viral clade phylogenetics and antigenic mapping show promise in improving both the selection of vaccine candidates and their likely degree of cross-reactivity with variant strains; and
- cross-reactivity among current H5N1 strains might indicate potential cross-protection against future emerging strains, but such coverage could diminish as H5N1 viruses continue to evolve.

Vaccine efficacy and effectiveness

Vaccine immunogenicity refers to the ability of a vaccine to elicit an immune reaction and this can be measured even in the current period when there are very few human cases. By contrast, vaccine efficacy and effectiveness refer to different approaches used to assess the ability of a vaccine to protect against disease. Both are difficult to measure when very few people are being infected naturally. Ideally, “markers” of immunity should reflect effectiveness in protecting against disease but:

- the relationship between the measurable markers of immune reactions to H5N1 vaccines and protection is not clear – this presents an important scientific obstacle to evaluating these vaccines;
• currently, there are no data from human trials on how well H5N1 vaccines may protect against disease – although data from some animal studies indicate that such vaccines do provide protection;
• in animal models, some candidate human H5N1 influenza vaccines can confer levels of protection against both homologous and heterologous viruses;
• there is no indication of differences in conferred protection between either egg or cell-culture production techniques or between antigen presentation methods; and
• only a few studies have considered duration of protection and cross-reactivity longer than twelve months, with initial results indicating that antibody duration varies depending upon the vaccine strain and method of production used.

The data available so far suggest that human H5N1 vaccines should be safe and effective at protecting against disease. However, confirmation of their effectiveness will require studies in which people are either “challenged” by exposure to H5N1 under experimental conditions or are in a situation in which natural infection is occurring widely. It is also clear that considerable inherent variability in the assay systems used to measure immune responses makes it difficult to directly compare results from different studies.

In sections 2.1–2.5 the scientific and public health rationale is presented for five possible options for using human H5N1 vaccine – three of which relate to non-pandemic periods, while two relate to the early stages of outbreaks with pandemic potential. Careful consideration was given to whether or not the available scientific data and other considerations supported the use of H5N1 vaccines in the following scenarios.

**During the current non-pandemic period**

• to protect people at high risk of contracting zoonotic avian H5N1 influenza;
• to “prime” selected groups or whole populations in anticipation of a possible H5N1 influenza pandemic; and
• to immunize selected groups or whole populations in anticipation of a possible H5N1 influenza pandemic.

**If an H5N1 pandemic appeared imminent or was under way**

• to help contain the initial and localized emergence of a potential H5N1 influenza pandemic; and
• to immunize selected groups or whole populations following sustained human-to-human transmission of H5N1.

It was concluded that all of the options involve complex scientific, ethical and political considerations such as whether and how best to deploy vaccines, and how to target and prioritize access to limited supplies. In many of these areas, current scientific evidence or considerations provide little support on which to base decision-making, but for certain options mathematical modelling may provide valuable insights.

In section 3, the currently considered best options for the use of the WHO H5N1 vaccine stockpile are presented. The use of WHO vaccine stockpiles in other areas of
public health – along with ongoing efforts by a number of countries to establish national H5N1 vaccine stockpiles – may provide a number of important insights. However, the lessons learned may not be directly applicable to the planned H5N1 vaccine stockpile. Given certain assumptions, the two most feasible uses of the WHO H5N1 stockpile at the present time were considered to be:

- to help contain the initial and localized emergence of a potential H5N1 influenza pandemic; and
- to provide countries least able to obtain H5N1 vaccines with some level of supplies following sustained human-to-human transmission of H5N1.

It is intended that this consultation – one in a series of WHO consultations related to H5N1 vaccine that have been under way – will contribute towards the development of robust scientifically informed guidance on how best to use human H5N1 influenza vaccines. Although increasing evidence of the immunogenicity and protective efficacy of candidate human H5N1 influenza vaccines is emerging, there remain numerous uncertainties that will be difficult to resolve ahead of an actual pandemic of H5N1 influenza. Nonetheless, the beginning development of guidance on the H5N1 vaccine stockpile and the vaccine itself will be a key step in facilitating and supporting the increasing efforts now being made by governments, the pharmaceutical industry and other stakeholders in this crucial area.
1. Characteristics of candidate human H5N1 influenza vaccines

1.1: Safety

Q1.1

Are there important safety concerns about current H5N1 vaccines?

Rationale: Human H5N1 vaccines are anticipated to be one of the major pharmaceutical interventions against a pandemic of H5N1 influenza but have not been widely used in human populations.

Evidence: Available data on the safety of H5N1 vaccines are relatively limited. However, no evidence of any additional or unusual safety concerns around the H5N1 antigen was presented. A recent consultation undertaken by the European Centre for Disease Prevention and Control (ECDC) on behalf of the European Commission (EC) identified no serious concerns in the publicly available data or in data disclosed confidentially by industry during the process. This is in line with presentations made at two WHO meetings on the clinical trial results of a range of pandemic candidate vaccines (including H5N1) in November 2005 and May 2006. All the pandemic prototype vaccines tested were not associated with safety issues and were well tolerated in the age groups studied.

There is no indication of any major differences in safety among current human H5N1 vaccines regardless of whether antigen production is based on egg or cell-culture techniques, other than concerns about egg allergy which apply to all vaccines produced in eggs. Additionally current data do not indicate any major safety differences regardless of antigen presentation differences among whole virus, split or subunit vaccines. Initial reports do indicate that whole virus vaccine may be more reactive than split or subunit vaccines in terms of inducing local (or minor systemic) reactions. There are some historical data on the use of whole virus seasonal influenza vaccine in children indicating that such vaccines were more reactogenic than subunit or split-virion vaccines.

Licensed inactivated subunit vaccines for seasonal influenza have been very safe and well-tolerated and pandemic antigens alone are considered unlikely to pose unique risks. However, direct experience with the H5N1 virus as a vaccine antigen is limited and there has been one unexplained episodic association between the use of swine flu vaccine in 1976–77 and an elevated risk of Guillain-Barré Syndrome. However, studies have shown no similarly strong association with any of the formulations used subsequently.

Because H5 antigen appears to be generally less immunogenic than the haemagglutinin of seasonal influenza A viruses, most human H5N1 influenza vaccines developed to date are adjuvanted. Such “potentiated” immune responses inherently increase the level of uncertainty surrounding the risk of rare unanticipated

2 [www.ecdc.eu.int/Health_topics/Pandemic_Influenza/Guidance.html](http://www.ecdc.eu.int/Health_topics/Pandemic_Influenza/Guidance.html)
adverse affects. Novel adjuvants can provide a potent and potentially antigen non-specific immune and inflammatory stimulation although the precise ways in which this effect is produced are not fully understood. The presence of adjuvant may also increase the frequency of local reactions (for example, redness, soreness or swelling at the injection site) and this has been observed with some newer oil-and-water emulsion adjuvants. It is unclear if these are correlated with any risk of rare adverse effects but no major safety signals have been reported to date.

There is also no current evidence of an increased risk of autoimmune conditions associated with such adjuvanted vaccines. However there have only been limited controlled studies with long-term follow up or in children.

There are only very limited reports of transmission of a live attenuated vaccine virus from a vaccinated individual to another person. One concern that was discussed was the possibility that a live attenuated vaccine based upon an H5N1 virus used in a non-pandemic situation could undergo genetic reassortment with a seasonal human virus resulting in the creation of a hybrid virus. Although the overall probability of such an event is considered to be low there remains an element of risk. It was considered that the use of a live attenuated H5N1 vaccine during a non-pandemic period would not be prudent.

**Current considerations:** At present and based on the limited amount of safety data available, there is no evidence of an unacceptable adverse event profile for any of the human H5N1 vaccines thus far evaluated.

Clinical trials involving human H5N1 vaccines offer important opportunities to capture essential safety data. However, the amount of data produced by such trials is limited, and continuing efforts to confirm H5N1 vaccine safety after licensure and widespread administration is essential. If the decision is made to use H5N1 vaccines then monitoring their safety profile will be essential to ensure that any adverse events are identified rapidly so appropriate responses can be taken. Any proposal to use the current human H5N1 vaccines in a non-pandemic period where H5N1 is predominantly a zoonotic disease should also incorporate effective post-marketing surveillance.

Even if human H5N1 vaccines were shown to be safe in extensive clinical trials and were supported by large safety databases, it can be anticipated that additional safety signals will become apparent with widespread use. Vaccine administration on the scale anticipated for a human pandemic H5N1 vaccine will likely lead to the reporting of adverse events, which might be real or perceived, and possibly reports of vaccine failures. Coincidental adverse events unrelated to the use of vaccines will almost inevitably occur, and possibly at levels sufficient to raise concerns about their use.

The acceptability of adverse events will depend largely upon when the vaccine is used, and the associated perception of benefit versus risk in the area of deployment. For example, a severity and/or frequency of adverse events considered as unacceptable when there is little or no disease may well become more acceptable as disease levels escalate. As a result, the assessment of risk-benefit is a crucial aspect of determining the acceptability of human H5N1 vaccine deployment, and such assessments may well vary depending upon location and disease situation.
An increased frequency of local reactions and/or minor systemic reactions may occur with adjuvanted or whole virus vaccines compared to non-adjuvanted vaccines. However, different adjuvants might exhibit different adverse-event profiles, and it must not be assumed that all adjuvants will behave in the same way.

Use of live attenuated influenza vaccines based upon a pandemic H5 virus may be beneficial if an H5 pandemic develops. Live attenuated vaccines have certain advantages in a pandemic scenario in that they can be effective at lower antigen doses than some other types of vaccine, and may also be sufficiently immunogenic to provide significant efficacy following a single inoculation. However, in light of current knowledge, the use of a live attenuated vaccine based on the H5N1 virus in a non-pandemic period when H5N1 viruses are not in wide circulation may not be prudent. More studies are needed to guide usage of this type of H5N1 vaccine.

1.2: Immunogenicity

**Q1.2**

**Are current H5N1 vaccines immunogenic?**

**Rationale:** In a period when human H5N1 infections occur infrequently, it is difficult to demonstrate the effectiveness or efficacy of vaccine against disease. In this situation, demonstrating the capacity of candidate human H5N1 influenza vaccines to stimulate the immune system is vitally important.

**Evidence:** Clinical trials indicate that human H5N1 influenza vaccines differ from seasonal human influenza vaccines in that they generally elicit lower levels of immune response at comparable antigen dose levels in both human and animal models.

Based on current methods for assessing immunogenicity, the use of certain adjuvants appears to reduce the amount of antigen required to elicit the same immune response as higher doses of the same antigen used without adjuvant. Aluminium-containing adjuvants appear to provide less of this “antigen sparing” effect than oil-and-water emulsion adjuvants but further study is required. Without any adjuvant, split and subunit vaccines are likely to require very high levels of antigen per dose (up to 90µg). However this falls to 30µg or more with alum; and potentially even smaller amounts with newer oil-and-water emulsion adjuvants (7.5µg with MF-59 and 3.8µg with AS). The use of effective adjuvants in split and subunit vaccines appears essential to keep the required amounts of antigen at the levels required for the bulk production of vaccine doses. There have been no direct head-to-head comparisons of adjuvanted and non-adjuvanted vaccines from different companies enabling direct cross-comparison. Limited data are available which indicate increased immunogenicity in one vaccine adjuvanted with an oil-and-water emulsion (MF-59).

Although the data are limited, adjuvanted vaccines that elicit higher titres of antibodies than non-adjuvanted vaccines against homologous challenge also appear to
elicit higher titres of antibodies to viruses that are variants to the virus in the vaccine. The use of adjuvants here may not only increase the level of antibody produced but also broaden the response to provide a heterologous response (of currently unknown clinical significance) against non-homologous H5N1 viruses. The effect may depend upon the adjuvant used, with oil-and-water emulsion adjuvants stimulating higher responses than alum against variant H5N1 strains. MF-59 is an oil-and-water emulsion adjuvant licensed for use in seasonal influenza vaccine in Europe. It has been tested in vaccines containing either H5 or H9 antigens, and has demonstrated an improved immune response with increased cross-reactivity to antigenic variants. Preliminary data in humans also indicate that immunological priming at 16 months or earlier with a different H5N1 variant or preparation of human H5N1 vaccine can lead to a more vigorous antibody response – once again this effect was more robust when using adjuvanted vaccine. These limited observations are supported by animal data.

In addition to stimulating the antibody response, some adjuvanted human H5N1 influenza vaccines may simulate cell-mediated immunity. A number of factors in cell-mediated immunity are increased (including CD4+ cell; IFN; and IL-2 measures) with a constant increase across the range of antigen doses tested.

Finally, there is some limited evidence that live attenuated vaccines and inactivated whole viruses may be more immunogenic than split or subunit vaccines. Data from one non-adjuvanted whole virus vaccine (using a wild-type H5N1 strain grown in cell culture) indicate that 2 doses at 7.5µg per dose will be needed. Other whole virus vaccines formulated with aluminium-based adjuvants also appear promising. However further studies are needed to determine the precise contribution of the adjuvant in such cases. It may be that the envelope and/or internal components of whole virus vaccines contribute to vaccine immunogenicity in the same way as some of the synthetic adjuvants, as suggested by studies in mice. However this has not been conclusively proven, or demonstrated in humans.

Current considerations: Broadly speaking, it appears that the use of certain adjuvants in human H5N1 influenza vaccines can lead to a greater immunogenic response than that observed with the same vaccine used without adjuvant. It cannot be assumed however that all adjuvants have the same effect. Different adjuvants appear to confer differing degrees of immunogenicity, particularly when comparing the newer oil-and-water emulsion adjuvants with alum.

There is wide variability in the serological assays used to assess H5N1 vaccines. As a result, there are currently no agreed upon criteria or benchmarks to assess the immunogenicity of human H5N1 influenza vaccines. This lack of standardization in assay procedures is highlighted here as a priority issue. The European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP) criteria\(^3\) for human seasonal influenza vaccines have been used in Europe to assess

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human H5N1 and pandemic vaccines but these may not be the most appropriate criteria.

1.3: Cross-reactivity

Q1.3

Are current H5N1 vaccines broadly cross-reactive against non-homologous H5N1 viruses?

**Rationale:** Like all influenza viruses, H5N1 has undergone evolutionary genetic changes, and these have resulted in antigenically heterogeneous and distinct clades, sub-clades and strains. Currently ten clades have been identified and it is anticipated that further evolution and divergence will occur among these viruses. In this situation, the availability of H5N1 vaccines capable of inducing cross-reactive – and more importantly cross-protective - immunity against both currently circulating and future emerging strains would be highly beneficial.

**Evidence:** Ten distinct clades of H5N1 virus have so far been recognized (0–9) based upon ongoing phylogenetic analyses of the publicly available sequences of the haemagglutinin (HA) gene of H5N1 viruses isolated from humans and animals. Sequences within a clade differ by less than 1.5%, while sequence differences of 1.5% or greater will place strains in different clades. The classification of viruses into clades is based upon genetic analyses, with the differences tending to reflect antigenic variations. However, it is important to note that antigenicity is evaluated separately (for example, with hemagglutinin inhibition (HI) panel testing and antigenic cartography) and that genetic changes identified through sequencing do not necessarily indicate or predict the degree of antigenic change. Clade 2 viruses are the most divergent, with five sub-clades (2.1–2.5) of which two (2.1 and 2.3) are further delineated into more than one lineage. Viruses from clade 1 and from sub-clades 2.1, 2.2 and 2.3 have caused recognized human infection, and are used in a number of current candidate vaccines.

Ideally several vaccine candidate strains should be made available for each antigenically relevant clade to improve the likelihood that one of the candidates will be both immunogenic and protective but also optimal from a manufacturing perspective. Animal viruses have been used as candidates if an appropriate human isolate is not available. The timely sharing of new H5N1 viruses with WHO and their rapid analysis are vitally important in ensuring that vaccine candidate strains are as up to date as possible.

Animal model studies have shown cross-reactivity when animals vaccinated against clade 1 strains were challenged with clade 2 and 3 viruses. Current data indicate that adjuvanted human H5N1 vaccines elicit greater cross-reactive responses than non-

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adjuvanted vaccines (with the possible exception of whole virus vaccines) both within and across clades. There is no indication in the currently available data of any significant differences in cross-reactivity among current human H5N1 vaccines in terms of antigen production based on either egg or cell-culture techniques or means of antigen presentation. There are no data yet available on differences between live and inactivated H5N1 vaccines in terms of cross-reactivity.

There are convincing data in the ferret animal model indicating that some degree of cross-protection is possible and that human H5N1 vaccines produced using virus from one clade might be protective against challenge by a virus from a different sub-clade or clade. Preliminary studies in humans also indicate some degree of cross-neutralization.

Cross-reactivity between the N1 components of seasonal influenza H1N1 vaccination and any H5N1 challenge virus, or between other viral proteins of variant H5N1 strains has not been conclusively demonstrated either in the field, in animal models or in human clinical trials.

**Current considerations:** It is anticipated that if H5N1 evolves into a pandemic strain, then any H5N1 vaccine stockpiled now during this non-pandemic period will not be a perfect match. Furthermore, even if there is a relatively close match between stockpiled H5N1 vaccines and any H5N1 virus that initiates a pandemic, the pandemic virus will continue to evolve. In this situation, adjuvanted (or whole virus) vaccines may possibly confer some heterologous cross-reactivity and cross-protection.

A high degree of cross-reactivity among vaccines made from current clades could indicate potential cross-reactivity with future drifted strains. However, there is no certainty about the degree to which H5N1 vaccine made with current viruses will be able to provide protection against future H5N1 viruses. It is likely that cross-reactivity will decrease as the antigenic distance increases due to the process of viral evolution between current and future H5N1 strains.

Some strains do appear to elicit higher antibody responses than others, and those that do often elicit response against variants. The data suggesting that cross-protective antibodies can be generated is encouraging, but once again the effect may not be maintained as H5N1 viruses continue to drift.

Finally, the degree to which laboratory-demonstrated cross-reactivity may translate into cross-protection is uncertain. This will only become clearer once data from further animal-protection studies become available, and more widely divergent viruses are used and the results correlated with cross-immunity.

### 1.4: Degree and duration of protection

**Q1.4**

*Are current H5N1 vaccines effective in protecting against disease – if so how long is the protective effect likely to last?*
**Rationale:** Although influenza vaccines may deliver a variety of desirable outcomes – including reduced virus transmission which would be highly beneficial at the population level – the most important outcomes would be the protection of vaccinated individuals against severe disease, hospitalization and premature death.

**Evidence:** In animal models, current evidence indicates that some human H5N1 influenza vaccines can confer levels of homologous and heterologous protection. No corresponding data are yet available from human studies.

Based on limited data from animal studies, the use of some live attenuated H5N1 vaccines has shown promising initial results indicating some protection against challenge in vaccinated animals. Only a few studies have considered the duration of antibodies for longer than twelve months, and initial data indicate that this duration varies depending upon the vaccine strain used.

There is currently little direct evidence concerning the effectiveness of H5N1 vaccines at preventing disease, and no available evidence to indicate any differences in terms of antigen production based on either egg or cell-culture techniques or on antigen presentation with whole virus, split or subunit vaccines. There are promising indications of immunogenicity and cross-reactivity that suggest that adjuvanted human H5N1 vaccines may be more effective at preventing disease than non-adjuvanted vaccines.

Adjuvants may also impact on the duration of the immune memory. However currently available data do not cover periods longer than 16 months. In addition, currently formulated H5N1 inactivated influenza vaccines require at least two doses given 21 days apart to provide seroprotection for an individual.

**Current considerations:** The level of protection offered by H5N1 vaccination is likely to depend upon the specific H5N1 vaccine antigen used, the rate of genetic drift occurring among circulating H5N1 viruses, and the duration of antibody response. In an immunologically naïve population, a single inoculation with human H5N1 influenza vaccine is likely to have only a priming effect that will probably be insufficient, without a boosting dose, to stimulate a full protective response.

Although significant progress has recently been made, the interpretation and comparison of clinical trial data are impeded by current gaps in the knowledge regarding what constitutes acceptable correlates of protection. There is therefore a need for the development of well-validated immunological markers of effectiveness for H5N1 vaccines.

Because currently available data on the duration of protection do not cover periods longer than 16 months studies conducted over longer timeframes will be required to document the duration of protection afforded by current human H5N1 influenza vaccines.

1.5: Conclusions and priority areas
More research is needed to resolve many of the outstanding scientific issues relating to the characteristics of human H5N1 influenza vaccines. For example, in the absence of widespread disease, human clinical trials can still be conducted to determine the duration of the antibody response to current H5N1 vaccines as well as their ability to foster cross-reactive antibody production in humans. Other important issues include determining the lowest dose levels of antigen required to induce an immune response. A fuller exploration of the dose-response relationship might lead to the conclusion that even lower doses of antigen induce measurable levels of antibody (as indicated in recent data from Sanofi Pasteur). It is also not known if there would be greater benefit -- from a population perspective -- in offering lower quantities of antigen to many people (for example, by the use of a single dose) than could be achieved by offering higher amounts of antigen to fewer people. Similarly, robust data from animal-challenge models on “priming” the immune system with one vaccine dose before challenge with a live virus could provide useful insights. It is anticipated that the standard licensed schedule will be 2 doses with an interval of not less than 21 days but more data on single-dose priming regimens would increase the range of implementation options. There is also a pressing need to investigate immune responses following the use of abbreviated immunization schedules – evidence of adequate responses after closely spaced innoculations would significantly improve the utility of immunization as an intervention to block viral transmission.

The interpretation and comparison of clinical trial data are impeded by a lack of consistency and comparability in the assay methods used. At present there is considerable inherent variability in the HI and neutralization-antibody assay systems used to measure immunogenicity and comparing the results of different clinical trials is difficult. Addressing these issues would allow for direct trial-to-trial comparison of the immunogenicity and other characteristics of different vaccines, including those of non-adjuvanted and differently adjuvanted vaccines from different companies.

In the ongoing trials of candidate human H5N1 influenza vaccines, the degree to which immunological measures of immunogenicity can be considered to be markers of vaccine efficacy or effectiveness (i.e., protection) is still not clear. Vaccine effectiveness itself can be considered in different ways, including the extent to which vaccination:

- of an individual can reduce the severity of illness even if infection occurs ("therapeutic benefit");
- within a population can reduce the infectiousness of individuals (for example, through reduced viral shedding) and dampen the spread (or transmission) of the virus through the population ("epidemiological benefit");
- of an individual will prevent infection (potentially both therapeutic and epidemiological benefit);

Nevertheless, the available data on human H5N1 influenza vaccines are encouraging, and in the near future an increasing number of these vaccines are expected to be submitted for regulatory approval. Moreover, the development of a WHO stockpile of H5N1 vaccines is expected to take place over the next three years providing an opportunity for developing countries to gain access to these vaccines. Such
developments are welcome and important, and underscore the need for health authorities to begin planning now for how such vaccines might optimally be used.

2. Options for using human H5N1 influenza vaccines

Numerous considerations must be taken into account when assessing the current range of possible options for the use of human H5N1 influenza vaccines. At all stages of a pandemic, any proposed use of an H5N1 vaccine should reflect an acceptable balance between the perceived benefits and risks. The perceived balance itself or the acceptance may vary considerably depending upon whether H5N1-related disease is common or infrequent. For example, during non-pandemic periods, the perceived benefit-risk balance may be very different in countries in which there have been no human H5N1 cases compared with countries where there have been many such cases. During periods in which a pandemic is considered either imminent or under way, then the level of perceived benefit is likely to be high in most countries.

Regardless of how or when H5N1 vaccines are used, the use of a stepwise targeted approach aimed at benefiting individual, regional and global health while at the same time collecting valuable safety and effectiveness data would be prudent.

Current possible options for the use of human H5N1 influenza vaccines include:

During the current non-pandemic period

2.1: To protect people at high risk of contracting zoonotic avian H5N1 influenza.
2.2: To "prime" selected groups or whole populations in anticipation of a possible H5N1 influenza pandemic.
2.3: To immunize selected groups or whole populations in anticipation of a possible H5N1 influenza pandemic.

If an H5N1 pandemic appeared imminent or was under way

2.4: To help contain the initial and localized emergence of a potential H5N1 influenza pandemic.
2.5: To immunize selected groups or whole populations following sustained human-to-human transmission of H5N1.

One of the purposes of the consultation was to review the currently available scientific data relating to the above range of possible options. In addition, assessment of the potential benefits will need to be weighed against the risks, and decisions such as who should receive vaccine first will need to be considered. It was generally thought that while scientific evidence has some bearing on discussions of how to target vaccine
use and prioritization, such decisions inherently will depend primarily upon other considerations, including ethical and political considerations.

2.1: To protect people at high risk of contracting zoonotic avian H5N1 influenza

**Q2.1**

**During the current non-pandemic period, could human H5N1 influenza vaccines be used to protect people at high risk of contracting zoonotic avian H5N1?**

**Rationale:** In some countries, human illness and deaths caused by avian H5N1 are occurring or have occurred, primarily following exposure to infected poultry. In some of these affected countries there is potential interest in conducting H5N1 vaccination of selected individuals or groups considered to be at high risk of infection or exposure to H5N1.

**Evidence:** Most reported human H5N1 cases have been zoonotic. However, limited and non-sustained human-to-human transmission, though rare, is believed to have occurred or cannot be excluded in some of the clusters investigated to date. Most clusters have occurred among blood-related family members – typically involving 2–3 cases, with the largest recorded cluster being 8 (7 confirmed and 1 probable). However in these cases, exposure to a common source of H5N1 is extremely difficult to rule out.

Following observational and analytic studies, the primary risk factors for humans to become infected by H5N1 appear to be direct contact with sick or dead poultry in a variety of settings – although other indirect or environmental exposures may also be important. Limited cross-sectional seroprevalence studies suggest that the frequency of asymptomatic or mild H5N1 virus infections is low among rural villagers exposed to sick or dead poultry in Cambodia and Thailand; poultry workers in Nigeria; and poultry market workers in China although one study following the 1997 outbreak in Hong Kong found a seroprevalence of about 10% in poultry workers. A small number of clinically mild H5N1 cases have also been identified in children. Such seroprevalence studies can be difficult to conduct in part because microneutralization assays for H5N1 antibody are not routinely performed by many laboratories.

Limited cross-sectional seroprevalence studies among health care workers in Thailand, and northern and southern Viet Nam found no evidence of transmission from patient to health care worker, but in a small number of cases nosocomial transmission appears to have occurred.

**Current considerations:** In some countries, those considered to be at high risk of exposure to avian influenza are commercial poultry workers and veterinarians. In other countries however the demarcation between commercial and domestic exposure to H5N1 is not clear and broad segments of the population could be considered to be at risk of exposure to H5N1-infected birds. The definition of groups at high risk will be situation-dependent. These could include certain specific groups (for example, poultry market workers, butchers, responders to avian and human H5N1 outbreaks,
and laboratory staff handling specimens) as well as broader population groups (for example, those raising backyard poultry, visiting wet markets in affected regions or living in repeatedly affected communities). It is also possible that the identified risk factors or epidemiological profiles may change as H5N1 viruses evolve.

If human H5N1 influenza vaccines were used to immunize individuals and groups thought to be at high risk of either infection or exposure, the advantages would include a strong likelihood of a good match between the H5N1 vaccine and circulating H5N1 virus strains, and the ability to conduct immunization programmes in an orderly manner. The drawbacks of this approach may include difficulties in identifying at-risk populations, and potentially insufficient quantities of vaccine to vaccinate the entire target populations. Vaccinated individuals will still be expected to acquire acute respiratory infections caused by other pathogens, potentially leading to confusion and concerns that the vaccine is not effective. Furthermore, any H5N1 vaccine used may have reduced immunity against future evolving (“drifted”) virus strains. The current rarity of human cases will also reduce perceptions of the potential benefits and the occurrence of any adverse effects (whether real or perceived) are likely to further impact negatively on perceptions of the risk-benefit equation. In addition, vaccination efforts would not be expected to reduce the continued use of other disease-control measures, including surveillance, testing of suspected cases, antiviral treatment of cases, antiviral chemoprophylaxis of case contacts, use of PPE, culling, and poultry H5 vaccination.

2.2: To “prime” selected groups or whole populations in anticipation of a possible H5N1 influenza pandemic

**Q2.2**

*During the current non-pandemic period, could human H5N1 influenza vaccines be used to immunologically “prime” selected groups or whole populations in anticipation of a possible H5N1 influenza pandemic?*

**Rationale:** This option is based upon the idea that vaccinating individuals with a single dose of vaccine during a non-pandemic period might “prime” their immune system so that the likelihood of disease is lower should they be exposed to natural H5N1 infection in the future.

**Evidence:** There are currently very little scientific data to support or not support the use of H5N1 vaccines in this way. As a result, there is a large degree of uncertainty concerning the likely benefits of vaccinating groups or populations with a single priming dose of H5N1 vaccine in anticipation of an H5N1 influenza pandemic. In addition, there are no data to indicate the degree to which disease levels might be reduced. There is also no certainty that the next pandemic will be caused by H5N1. Even if this was the case and populations had been primed, there would still be a need to administer a second dose using an H5N1 pandemic vaccine.

**Current considerations:** Priming is theoretically an effective approach if the right vaccine were to be used. However, the uncertainties are considerable. From both a
scientific and public-health perspective, there are insufficient data to provide strong
and clear guidance in this area. Crucially however there is no certainty that the next
pandemic will be related to H5N1. Current indications are that single priming doses of
candidate H5N1 vaccines do not produce antibody levels sufficient for licensing.
Should this be overcome many of the advantages and disadvantages of the approach
would be similar to those described above for vaccinating those at risk of contracting
zoonotic avian influenza in the current non-pandemic situation.

2.3: To immunize selected groups or whole populations in anticipation of a
possible H5N1 influenza pandemic

Q2.3

During the current non-pandemic period, could human H5N1 influenza vaccine
be used to immunize selected or whole populations in anticipation of a possible
H5N1 influenza pandemic?

Rationale: This option is similar to the concept of “priming” groups or populations
during a non-pandemic period with exception that a full vaccination dosing schedule
would be used to induce immunity for “pre-protection” against future infection with
H5N1.

Evidence: There are currently very little scientific data to support or not support the
use of H5N1 vaccines in this way. From a population perspective, theoretical
indications from mathematical modelling studies suggest that H5N1 vaccine – even if
poorly matched and of low efficacy – used in advance of the first wave of an
emerging H5N1 pandemic would be more effective than vaccine of much higher
efficacy but available only after the pandemic had started. Assuming widespread
population coverage (of the order of approximately 80%) and low vaccine efficacy
(25%) this would lead to an effective coverage of 20%. At this level of effective
coverage (and even lower) vaccination in advance of the first wave of a pandemic
could have a significant impact on the number of eventual cases if as expected the \( R_0 \)
is low. Where there are insufficient numbers of doses for the whole population it
potentially may be more "efficient" to target vaccination at children in terms of trying
to reduce virus transmission -- if there is sufficient supply of available vaccine to
vaccinate the target pediatric population.

Current considerations: A number of the disadvantages of immunizing groups or
populations during a non-pandemic period are similar to those described above for
priming approaches. As with priming, there is no certainty that the next pandemic will
be related to H5N1.

2.4: To help contain the initial and localized emergence of a potential H5N1
influenza pandemic

Q2.4
In the event that a localized outbreak appears to signal the start of a potential H5N1 influenza pandemic, could human H5N1 influenza vaccines be used in the containment effort?

**Rationale:** Any attempt to contain the first emergence of a potential H5N1 influenza pandemic will involve multiple combined approaches such as intensified surveillance accompanied by the use of antiviral drugs, quarantine, isolation, and community distancing within a well-defined area to try and prevent the further spread of H5N1 infections outside of the area of the first local outbreak. Human H5N1 influenza vaccine could potentially be used in the area surrounding the immediate outbreak area to decrease the number of people who would be susceptible to H5N1 infection.

**Evidence:** There are currently very little scientific data to support or not support the use of H5N1 vaccines in this way. Once again there are theoretical indications from mathematical modelling studies which suggest that the extensive use of vaccination could potentially help to decrease the spread of the virus. Such studies suggest that there may be advantages in using human H5N1 influenza vaccines to complement other urgent measures as long as vaccination was timely and implemented efficiently.

**Current considerations:** If there is sufficiently early warning of an H5N1 influenza outbreak caused by a virus capable of sustained human-to-human transmission then theoretically, there may be a relatively limited “window of opportunity” to stop the spread of the virus before it spreads nationally or internationally. WHO has been developing protocols to implement such a containment effort in coordination with national authorities. Such an effort is only likely to be feasible where there are limited numbers of localized cases because of early warning, where adequate logistical support is available and where the national government is supported by international assistance.

Until recently, draft protocols developed by WHO for conducting such operations did not take into account the possible use of human H5N1 influenza vaccines. With their potentially imminent availability, the situation is changing and there is now much interest in adding vaccination to the list of available interventions. These include non-pharmaceutical public health measures (such as social distancing) and the use of antiviral drugs. Efforts to use H5N1 vaccines in a containment attempt must be well coordinated and properly aligned with other available approaches.

2.5: To immunize selected groups or whole populations following sustained human-to-human transmission of H5N1

**Q2.5**

In the event of sustained human-to-human transmission of H5N1, could stockpiled human H5N1 influenza vaccines be used to help protect selected groups or whole populations?
Rationale: If an H5N1 virus acquires the capacity for sustained person-to-person transmission, and its spread can not be contained, it is highly likely that an H5N1 pandemic will be imminent. At this point, the purpose of vaccinating people would be to protect groups or whole populations against severe disease, hospitalization and premature death.

Evidence: As outlined in section 1 of this report, there are scientific data indicating that current human H5N1 influenza vaccines can stimulate the immune system, with animal studies indicating that such vaccines can provide protection against disease. Moreover, the current data do not indicate any significant new safety concerns – although much more safety data are needed. However, none of the vaccines currently under development have been shown to effectively protect humans against disease caused by H5N1. In the current epidemiological situation – where human H5N1 influenza cases remain infrequent and occur sporadically or in small clusters – mounting the types of vaccine trials needed to demonstrate effectiveness is extremely difficult.

Current considerations: In a situation where an H5N1 influenza pandemic is considered imminent or under way, a very large number of infections and cases of illness can be expected, with the number of deaths depending upon the degree of pathogenicity of the pandemic virus. In contrast to perceptions of vaccination during non-pandemic periods, it is anticipated that the benefit-to-risk ratio in a pandemic situation would be considered very high but vaccine availability in the immediate term could be limited in most countries.

2.6: Conclusions and priority areas

The effectiveness of any of the above options for the use of human H5N1 influenza vaccine will depend upon a number of factors in addition to the properties of the vaccine. These include issues such as the timing of vaccination and which population groups to target for greatest impact. At the same time, there is also likely to be a need to prioritize vaccine access, for example to those at greatest risk or for protecting people performing "essential services."

There is evidence to indicate that children and young adults can play an important role in spreading seasonal human influenza. However, there are some important differences between seasonal and pandemic influenza and it cannot be assumed that the transmission patterns will be sufficient similar to extrapolate from one situation to the other. In addition, while some groups (such as children) might be “early spreaders” in some populations this might not hold true in other settings where social mixing and other demographic patterns differ. As societies change and evolve, the effect of the selective vaccination of specific age and other groups might have only limited impact Nonetheless, if use of human H5N1 vaccines are guided by population disease control considerations, in addition to protection of individuals from severe disease or death, then vaccinating certain groups could have beneficial secondary

4 The term “target” is used in this document to describe the strategic selection of particular groups (or locations) to achieve specific immunological goals.

5 The term “prioritize” is used in this document to describe the determining of the sequence in which particular groups would receive vaccine where supplies were limited.
effects for protection of other population groups. Alternatively, directly vaccinating older or other particularly vulnerable population groups may reduce severe disease outcomes more effectively. Such considerations are very complex and have not been resolved.

Even as scientific knowledge of H5N1 vaccines and the understanding of the epidemiology of H5N1 infections and pandemics of influenza increases, it is unlikely that this type of information will be enough to provide guidance on how to prioritize who should receive H5N1 vaccines first. This issue will require very careful consideration, and decisions inherently will reflect the prevailing ethical, social and political environment in each setting – considerations that went far beyond the capacity of this consultation to address.
3. Options for using the WHO H5N1 vaccine stockpile

In March 2007, the participants of a High Level Meeting held in Jakarta, Indonesia called upon WHO to create a global stockpile of human H5N1 influenza vaccine. In April 2007 the WHO Strategic Advisory Group of Experts (SAGE) recommended to the Director General that there was sufficient evidence for WHO to create such a stockpile for use in countries without influenza vaccine production capacity and no ability to purchase national stockpiles. In May 2007, the Sixtieth World Health Assembly in its Resolution WHA60.28 called for the Director General:

... to establish, in close consultation with Member States, an international stockpile of vaccines for H5N1 or other influenza viruses of pandemic potential as appropriate, for use in countries in need in a timely manner and according to sound public-health principles, with transparent rules and procedures, informed by expert guidance and evidence, for operation, prioritization, release of stocks, management and oversight;

At the Pacific Health Summit held in June 2007 in Seattle, Washington, USA, GlaxoSmithKline Biologicals (GSK) announced that it would deliver 50 million doses of H5N1 adjuvanted human influenza vaccine over 3 years to support the WHO stockpile initiative. Assuming 2 doses per person, this amount could vaccinate 25 million people in the world's poorest countries. Omninvest of Hungary, Baxter and Sanofi Pasteur have subsequently indicated their willingness to make H5N1 vaccine available for stockpiling.

At this time, a physical WHO stockpile of H5N1 vaccine does not exist, and its development will depend upon several factors, including discussions with manufacturers on the terms and conditions of their donation, as well as on technical issues such as obtaining further information on the stability of vaccines. Data from ongoing studies into the stability of GSK H5N1 vaccine are preliminary but current indications are that it will have a stability profile at least equivalent to seasonal vaccine. It will be incumbent on all producers providing vaccine for stockpiling to undertake extended stability testing for the purpose of identifying the longevity of both antigen and adjuvant (if presented separately). This will be essential in establishing the turnover cycles for stockpiles. In addition, other issues such as the liability implications for any countries that might host or use the WHO international stockpile must be investigated.

Although development of the WHO H5N1 vaccine stockpile is under way, many of the specific issues related to its use are yet to be resolved. The most fundamental of these decisions is how the stockpile is to be used. This will then inform other issues such as its potential size, location(s), the triggers for release of vaccine, and stockpile management and governance processes.

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7 Stability studies for the seasonal influenza Fluarix vaccine show that it is stable under these following conditions: 2 weeks at 25°C, followed by 12 months at 2–8°C; or 4 weeks at 30°C.
Once recommendations have been developed in line with currently available scientific and other evidence, further issues such as liability, access protocols and logistical demands can be resolved. It is already apparent that the logistical challenges both of maintaining and deploying a WHO H5N1 vaccine stockpile are likely to be considerable and these in themselves may limit its envisaged uses. On 17–19 October, WHO therefore convened a second consultation to discuss the technical specifications required of an international H5N1 vaccine stockpile and the outcomes of those deliberations will be reported upon separately.

At the 1–3 October consultation, experience in using other WHO vaccine stockpiles was reviewed but speakers highlighted that some of the “lessons learned” may not be directly applicable to the planned H5N1 vaccine stockpile, and cautioned against extrapolating more than is prudent. As first step, two major options for the use of the WHO H5N1 vaccine stockpile were discussed:

3.1: To help contain the initial and localized emergence of a potential H5N1 influenza pandemic

**Rationale:** WHO has been planning how it would conduct an operation to try and contain a potential pandemic of influenza should the first outbreak be identified early enough to make the attempt feasible. The success of such an operation will depend upon the early detection and reporting of the first outbreak, and the implementation of multiple combined containment strategies. Recently, the potential use of human H5N1 vaccines has been discussed as part of such containment strategies. If such vaccines are used in any attempt to stop a pandemic, then the capacity to very rapidly mobilize vaccine supplies will be a critical component in their successful use in containment operations.

**Current considerations:** Vaccination alone is unlikely to be useful in containing a potential pandemic. Vaccination, with some exceptions, is not normally used to “contain” outbreaks of seasonal influenza. Full immunity is likely to require two doses of vaccine and to take 3 weeks to develop after the first vaccination. Moreover, the degree of antigenic match between stockpiled vaccine and a potential H5N1 influenza pandemic virus cannot be known. There will also be large logistical challenges in vaccinating large numbers (possibly millions of people) over a relatively short period of time.

Nevertheless, even with these considerations, mathematical modelling approaches suggest that under certain conditions, vaccination could make a significant contribution by reducing the ability of the virus to spread through the populations surrounding the immediate containment zone. Preliminary models suggest that optimal benefit would be achieved if several million people could be vaccinated, but further modelling will be needed to refine the estimates under different assumptions.

3.2: To provide countries least able to obtain H5N1 vaccines with some level of supplies following sustained human-to-human transmission of H5N1

**Rationale:** If efforts to contain the emergence of a potential influenza pandemic have failed or have not been attempted and an H5N1 pandemic appears imminent, a global surge in vaccine demand is anticipated. In this situation, poorer and developing
countries will be least likely to obtain vaccines unless there are dedicated supplies. Such vaccines, once made available to these countries, could be used in a number of ways, including the protection of critical infrastructure personnel. That however is a decision that will ultimately be taken by each national authority.

**Current considerations:** Efforts are under way to improve access to H5N1 vaccines so that if an H5N1 influenza pandemic did emerge, supplies of H5N1 vaccine will be more readily and widely available. Although such efforts will take time to implement, once a WHO stockpile is available, H5N1 vaccines could be made available to poorer and developing countries relatively rapidly. Eligibility criteria for receiving stockpiled H5N1 vaccines in this situation require definition, and recipient countries would need to decide upon how such vaccines would best be used.

As discussions proceed, guidance will be needed on how a WHO stockpile of limited size could best be used. Such guidance will help to establish the target size of the stockpile, and will facilitate discussions on issues such as the potential “triggers” for release of vaccine. Decisions such as whether or not to reserve a portion of the WHO H5N1 vaccine stockpile for containment efforts in eligible countries – and if so how much – are also now required. Equally important will be the decisions made on reserving stockpiled H5N1 vaccine for GAVI-eligible countries – and the basis upon which apportioning decisions are to be made.