

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

WHO scientific consultation

Geneva, Switzerland
1–3 October 2007



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

WHO scientific consultation

Geneva, Switzerland
1–3 October 2007

© World Health Organization 2008

All rights reserved.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either express or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This publication contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization.

Contents

Executive summary	3
1. Characteristics of candidate human H5N1 influenza vaccines	8
1.1. Safety.....	8
1.2. Immunogenicity	10
1.3. Cross-reactivity	11
1.4. Degree and duration of protection.....	12
1.5. Conclusions and priority areas	14
2. Options for using human H5N1 influenza vaccines	15
2.1. To protect people at high risk of contracting zoonotic avian H5N1 influenza.....	15
2.2. To “prime” selected groups or populations in anticipation of a possible H5N1 influenza pandemic	17
2.3. To immunize selected groups or populations in anticipation of a possible H5N1 influenza pandemic	17
2.4. To help contain the initial and localized emergence of a potential H5N1 influenza pandemic	18
2.5. To immunize selected groups or populations following sustained human-to-human transmission of an H5N1 influenza virus.....	19
2.6. Conclusions and priority areas	19
3. Options for using the WHO H5N1 vaccine stockpile	21
3.1. To help contain the initial and localized emergence of a potential H5N1 influenza pandemic	22
3.2. To provide countries least able to obtain H5N1 vaccines with some level of supplies following sustained human-to-human transmission of H5N1 influenza virus	22

Executive summary

Human infections with highly pathogenic avian influenza A (H5N1) viruses present a serious and highly complex public health challenge. In May 1997, the first human case of H5N1 virus infection was identified and by the end of the same year a total of 18 cases had been confirmed. In 2003 and 2004, H5N1 viruses re-emerged and spread rapidly among poultry in several Asian countries with associated human infections. Since February 2003, millions of birds have been infected and more than 360 human cases recorded, with more than 230 deaths in 12 countries in Africa, Asia and Europe. Currently, H5N1 is an avian pathogen that has had a devastating agricultural and economic impact on the communities it has affected. Although it causes infections relatively rarely in people, when they occur, such infections have been frequently fatal. However, H5N1 viruses continue to evolve and could develop into a much greater public health threat if they acquire the ability to cause sustained and widespread human-to-human transmission. Such a transformation could result in the next influenza pandemic. Addressing H5N1 as an agricultural, zoonotic and potential pandemic threat has proved to be complex and problematic for public health and animal health agencies and authorities.

The development and potentially imminent availability of approved human vaccines against H5N1 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 vaccination is potentially the best form of protection by preventing or reducing the chance of severe illness or death in people exposed to the H5N1 virus. This is true both in the current non-pandemic situation (in which some individuals or populations are at elevated risk of zoonotic infection with avian H5N1 viruses) and in the future should H5N1 viruses 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. Human H5N1 vaccines are a relatively new development and information on their safety, immunogenicity, and 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 virus and inactivated virus vaccines, whole and split antigen, and vaccines with and without different adjuvants). Additional technologies are also under consideration and development.

Once the safety and immunogenicity of H5N1 vaccines have been confirmed in larger numbers of persons, a number of other issues will also require very careful consideration to guide development of recommendations on the use of the vaccines during an H5N1 pandemic and possibly in other situations. For example, it will be necessary to decide who should be vaccinated first and at what “trigger point.” Other fundamental issues are whether vaccination strategies should focus on protecting the most vulnerable individuals from severe disease or death or, alternatively, adopt more of a population perspective by either attempting to reduce virus transmission or perhaps by focusing on protecting individuals who perform “essential social functions.” Such decisions are extremely difficult to make and will require clear explanations that are communicated effectively to the general population. Regardless of the approach taken, vaccination efforts will need to be well coordinated and properly monitored.

In resource-poor countries, existing health infrastructures, resources and vaccine supplies are likely to be inadequate to address many of the scenarios outlined in this report. Such shortfalls in logistical capacity could seriously undermine efforts to implement effective vaccination campaigns and to properly monitor their safety and efficacy. In such settings the personnel

needed to maintain the vital infrastructure of a country and to mount a response to the pandemic will also be at 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 WHA60.28¹, requested that WHO 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 two doses, which is likely to be needed to achieve protective levels of antibodies. Ultimately the size of the stockpile may reflect the evolving nature of the current H5N1 virus and the danger it poses to people. Based on the results of the consultation described in this report, a stockpile of approximately 100 million doses may be warranted given its potential uses. Further work will be needed to ensure that the best use is made of this stockpile, and to guide its development, maintenance and criteria for access. To address these and other issues, WHO has initiated a series of consultations to accelerate understanding of the ways to use human H5N1 influenza vaccines.

From 1 to 3 October 2007, WHO held a scientific consultation to review the current data on H5N1 vaccine immunogenicity, safety and other characteristics, to consider current general options for the use of such vaccine and to identify options specifically for the use of the WHO H5N1 vaccine stockpile. One of the principal objectives of this consultation was to review the available scientific information as a basis for the possible uses of the WHO H5N1 vaccine stockpile in order to inform the discussions of the WHO Strategic Advisory Group of Experts (SAGE) in November 2007. The participants of the October consultation included researchers, representatives from WHO Influenza Collaborating Centres, selected country representatives, SAGE members, and the pharmaceutical industry. Observers were 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.

Vaccine safety

- So far no major or unanticipated safety concerns have been identified related to the use of H5N1 influenza vaccines in humans – but significantly more safety data are needed. There may be an increase in local reactions associated with some adjuvanted and whole virus vaccines. Additional controlled trials (especially in children) and long-term follow-up studies are therefore required. A crucial consideration regarding use is that the risk-benefit ratio and thus the public's acceptance of using the vaccine may change considerably depending upon whether the perceived risk of disease is considered low or high.

¹ Resolution WHA60.28. In Sixtieth World Health Assembly, Geneva, 23 May 2007. Eleventh plenary meeting, Agenda item 12.1. *Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits*. Geneva, World Health Organization, 2007 (A60/VR/11).

Vaccine immunogenicity

- At comparable antigen dosage levels (based on haemagglutinin content) candidate human H5N1 influenza vaccines generally elicit lower immune responses than seasonal human influenza vaccines;
- some candidate human H5N1 influenza vaccines, based on a schedule of two doses administered 21 days apart, elicit higher antibody titres than others;
- unadjuvanted inactivated whole virus H5N1 vaccines appear to be more immunogenic than unadjuvanted split or subunit vaccines; and
- for most human H5N1 split and subunit vaccines, the use of adjuvants, especially oil-in-water emulsion reduces the amount of antigen required to elicit the same level of response as higher dosages of the same antigen used without adjuvant.

Cross-reactivity and protection

- Animal data suggest that vaccination by human H5N1 influenza vaccines, produced from viruses of one clade, may confer cross-reactivity against H5N1 viruses from other clades, and therefore may confer protection against challenge by H5N1 viruses from other clades;
- 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;
- oil-in-water emulsion adjuvanted vaccines, that elicit high levels of antibody against homologous H5N1 strains, also elicit higher levels of antibody to representative isolates of different clades;
- 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 viruses from other clades.

Vaccine efficacy and effectiveness

Vaccine *immunogenicity* refers to the ability of a vaccine to elicit an immune reaction. 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. Considerations include the following:

- the relationship between the measurable markers of immune responses to H5N1 vaccines and protection is not clear – this presents an important scientific obstacle in evaluating these vaccines;
- currently, there are no data from human trials on how well H5N1 vaccines may protect against disease – although data from animal studies indicate that such vaccines do provide protection against lethal challenge with H5N1 viruses;
- in animal models, some candidate human H5N1 influenza vaccines can confer levels of protection against both homologous and heterologous H5N1 viruses;

- there is no indication that use of either egg or cell-culture production techniques or different antigen presentation methods results in differences in conferred protection;
- only a few studies have considered duration of protection and cross-reactivity longer than twelve months, with initial results indicating that antibody duration may vary depending upon the vaccine strain and method of production used.

The data available so far suggest that human H5N1 influenza vaccines should be safe and effective at protecting against disease. However, confirmation of their efficacy or 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 make a direct comparison between results from different studies.

In **section 2**, the scientific and public health rationale for five possible general options for using human H5N1 influenza vaccine is presented – three of which relate to non-pandemic periods, while two relate to the early stages of outbreaks with pandemic potential. Careful consideration was given as to whether the available scientific data and other considerations supported the use of H5N1 vaccines in the following scenarios.

During the current non-pandemic period when H5N1 infections of people are zoonotic and the identity of the next pandemic influenza virus is unknown

- to protect people at high risk of contracting zoonotic avian H5N1 influenza;
- to “prime” the immune systems of people in selected groups or populations in anticipation of a possible H5N1 influenza pandemic; and
- to fully immunize people in selected groups or 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 people in selected groups or populations following sustained human-to-human transmission of an H5N1 influenza virus.

It was concluded that all of the options involve complex scientific, ethical and political considerations. Moreover, for many options, the existing scientific evidence and considerations provide little support on which to base decision-making, but for certain options mathematical modelling may provide valuable insights.

In **section 3**, the preferred options, based on current understanding, for the use of the WHO H5N1 vaccine stockpile are presented. Previous experience within WHO in developing and managing vaccine stockpiles that have been established for other diseases – along with ongoing efforts by a number of countries to establish national H5N1 vaccine stockpiles – may provide some important insights although specific lessons learned of relevance to other diseases may not be applicable to an H5N1 vaccine stockpile. Given certain assumptions, the two most feasible uses of this stockpile at the present time were considered to be:

- to help contain the initial and localized emergence of a potential H5N1 influenza pandemic if such an event is identified early enough; and
- to provide countries that are least able to obtain H5N1 vaccines with some level of supplies if sustained human-to-human transmission of an H5N1 influenza virus starts.

Although there is increasing evidence of the immunogenicity and likely protective efficacy of candidate human H5N1 influenza vaccines, there remain numerous uncertainties that will be difficult to resolve ahead of an actual pandemic of H5N1 influenza. Nonetheless, beginning the process of developing general guidance on the use of the H5N1 vaccine and specific guidance on the use of the WHO vaccine stockpile, will be a key step in facilitating and supporting increasing efforts 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 related to H5N1 vaccines was presented. A recent consultation² 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. None of the pandemic prototype vaccines tested were associated with additional 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 potential allergic reactions to eggs which apply generally to all vaccines produced in eggs. Additionally current data do not indicate any major safety differences among whole virus, split or subunit vaccines, despite antigen presentation differences. Initial reports do indicate that whole virus vaccines may be more reactive than split or subunit vaccines in terms of inducing local (or minor systemic) reactions. Historical data indicate that whole virus influenza vaccines in children were more reactogenic than subunit or split-virion vaccines.

Licensed inactivated subunit vaccines for seasonal influenza have been very safe and well-tolerated; vaccines based on a new antigen from a pandemic influenza virus 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 clear association between the use of swine influenza vaccine (H1N1 subtype) in 1976–77 with an elevated risk of Guillain-Barré Syndrome. However, studies have shown no similarly strong association with any formulation used subsequently.

Because H5 haemagglutinin appears to be generally less immunogenic than the haemagglutinin of seasonal influenza A viruses, most human H5N1 influenza vaccines developed to date contain an adjuvant. Use of such adjuvants to “potentiate” immune responses inherently increases the level of uncertainty surrounding the risk of rare unanticipated adverse effects. Novel adjuvants can provide a potent nonspecific immune and inflammatory stimulation in addition to the stimulation of the specific virus antigen in the vaccine, although the precise ways in which an adjuvant produces this effect is not fully understood. The presence of adjuvant may 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-in-water emulsion adjuvants. It

² www.ecdc.eu.int/Health_topics/Pandemic_Influenza/Guidance.html

is unclear if these are correlated with any increased risk of rare adverse effects, but no major safety signals have been reported to date.

There is 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 and limited studies in children.

One concern that was discussed was the possibility that use of a live-attenuated vaccine based upon an H5N1 virus in a non-pandemic situation could result in genetic reassortment between the vaccine virus and a seasonal human virus. This potentially could lead to the creation of a hybrid virus. The overall probability of such an event was considered to be low but not zero. It was therefore considered prudent to avoid using live attenuated H5N1 vaccines during a non-pandemic period. There are only very limited reports of transmission of a live-attenuated seasonal influenza vaccine virus from a vaccinated child to another person.

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 data produced by such trials are limited, and continuing efforts to confirm H5N1 vaccine safety after licensure and widespread administration are essential. If the decision is made to use H5N1 vaccines, then monitoring their safety profile will be key to ensure that any important or unexpected 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, when human H5N1 influenza virus infections remain predominantly zoonotic, should also incorporate effective post-marketing surveillance for both safety and effectiveness.

Even if human H5N1 vaccines were shown to be safe in extensive clinical trials and in analysis of large safety databases, it can be anticipated that additional safety signals may 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, some of which might be real and others of which might be only perceived, as well as 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 the risk of adverse events, in the area where vaccine is deployed, will depend largely upon when the vaccine is used and the associated perception of benefit. For example, the level of risk of adverse events which would be considered unacceptable when there is little or no disease, may well become more acceptable as disease levels rise, particularly if disease is associated with serious morbidity or death. 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.

If an H5 pandemic develops, use of live attenuated influenza vaccines, based upon a pandemic H5 virus, may be beneficial. Live attenuated vaccines have certain advantages in a pandemic scenario. They might, for example, be produced more efficiently, and might also be more immunogenic following a single application, than some other types of vaccine. 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 to protect against development of disease. In this situation, assessing the capacity of candidate human H5N1 influenza vaccines to stimulate the immune system is vitally important.

Evidence: Clinical trials indicate that H5N1 influenza vaccines differ from seasonal human influenza vaccines in that the H5N1 vaccines generally elicit lower levels of immune response at comparable antigen dosage 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 dosages of the same antigen used without adjuvant. The ability of some adjuvants to reduce the amount of antigen needed has been termed "antigen sparing". Aluminium-containing adjuvants provide less of this "antigen sparing" effect than oil-in-water emulsion adjuvants. Without adjuvant, split and subunit influenza H5N1 virus vaccines are likely to require very high levels of HA antigen per dose (up to 90 µg). There are indications that this may be reduced modestly through the use of aluminium-based adjuvants (to around 30 µg); and potentially even smaller HA antigen amounts appear to be immunogenic when used with newer oil-in-water emulsion adjuvants (e.g., 7.5 µg with MF-59 and 3.8 µg with AS). The use of effective adjuvants in split and subunit vaccines appears essential to minimize the amounts of antigen required to elicit an immune response. There have been no human trials involving direct head-to-head comparisons of adjuvanted and non-adjuvanted vaccines from different companies; such trials would enable direct cross-comparison.

Although data are limited, adjuvanted vaccines that elicit higher titres of antibodies against homologous challenge than non-adjuvanted vaccines, also appear to elicit higher titres of antibodies against other H5N1 strains than the one used in the vaccine. In other words, the use of adjuvants here may also broaden the heterologous response, which is a theoretical advantage, although the actual degree of clinical significance has not been established. The effect may depend upon the adjuvant used, with oil-in-water emulsion adjuvants stimulating higher responses than aluminium-based adjuvants against variant H5N1 strains. MF-59 is an oil-in-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 profile with increased cross-reactivity to antigenic variants. Preliminary data in humans also indicate that when two doses of one H5N1 vaccine are used, administration of a third dose of a heterologous H5N1 vaccine 16 months or more can boost existing antibody levels. Once again this effect was more robust when an adjuvanted vaccine was used. These limited observations of vaccination in people 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 dosages tested. The possible clinical significance of these immunologic observations is unknown.

Finally, available evidence indicates that inactivated whole H5N1 virus vaccines 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 of 7.5 µg per dose are immunogenic. Other whole virus vaccines formulated with aluminium-based adjuvants also appear promising; further studies are needed to determine the precise contribution of the adjuvant. The envelope and/or internal components of whole virus vaccines may contribute to vaccine immunogenicity in the same way as some 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 if the same vaccine does not contain an adjuvant. However, different adjuvants appear to confer differing degrees of immunogenicity, particularly when comparing the newer oil-in-water emulsion adjuvants with aluminium-based adjuvants.

There is currently wide variability in the serological assays used to assess immunogenicity, and no agreed-upon immunological criteria or benchmarks for assessing the response to human H5N1 influenza vaccines. This lack of standardization in assay procedures is highlighted here as a priority issue. The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) criteria³ for human seasonal influenza vaccines have been used in Europe to assess human H5N1 and pandemic vaccines, but these may not be the most appropriate criteria for use at the global level.

1.3. Cross-reactivity

Q1.3 Are current H5N1 vaccines broadly cross-reactive against non-homologous H5N1 viruses?

Rationale: H5N1 viruses have continued to undergo evolutionary genetic changes, and these have resulted in antigenically heterogeneous and distinct clades, sub-clades and strains. Currently ten clades have been identified. It is anticipated that further evolution and divergence will occur among these viruses and therefore 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

³ EMA/CPMP/BWP/214/96. Committee for Proprietary Medicinal Products (CPMP). *Note for guidance on harmonisation of requirements for influenza vaccines*. 12 March 1997.

www.emea.europa.eu/pdfs/human/bwp/021496en.pdf

EMA/CPMP/VEG/4717/03. Committee for Proprietary Medicinal Products (CPMP). *Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application*. 05 April 2004.

www.emea.europa.eu/pdfs/human/vwp/471703en.pdf

EMA/CHMP/VWP/263499/2006. Committee for Human Medicinal Products (CHMP). *Guideline on dossier structure and content of Marketing Authorisation applications for influenza vaccine derived from strains with a pandemic potential for use outside of the core dossier context*. 24 July 2006.

www.emea.europa.eu/pdfs/human/vwp/26349906en.pdf – All accessed 12 April 2007.

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 the antigenicity of influenza viruses is evaluated separately (for example, with hemagglutination inhibition (HI) panel testing and antigenic cartography) from genetic changes. 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 several viruses from each clade to improve the likelihood that at least one of the candidates will be both immunogenic and protective, as well as optimal from a manufacturing perspective. Influenza H5N1 viruses isolated from animals have been used as vaccine candidates when an appropriate human isolate has not been 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 demonstrated the ability of H5N1 influenza vaccines to induce protective levels of antibodies against homologous viruses, as well as cross-reactive immunity to antigenically distinct H5N1 viruses. There are convincing data from mouse and ferret animal models 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-reactivity in post-vaccination serum samples to viruses representing different clades. Current data indicate that oil-in water adjuvanted human H5N1 influenza vaccines elicit greater cross-reactive responses than non-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 influenza vaccines based on antigen production in either egg or cell-culture techniques or means of antigen presentation. There are no data yet available on differences between live-attenuated and inactivated H5N1 vaccines in terms of cross-reactivity.

Current considerations: It is anticipated that if H5N1 evolves into a pandemic strain, then any H5N1 vaccine stockpiled now during this non-pandemic period may not be a perfect antigenic match. Furthermore, any pandemic virus will continue to evolve during the course of the pandemic and later. 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 H5N1 virus clades could indicate potential cross-reactivity with future antigenically 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 between current and future H5N1 strains increases due to viral evolution.

Some H5N1 strains 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 in humans is uncertain. This will only become clearer once additional data from studies become available, more widely divergent viruses are used and the results are 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 vaccination against influenza may deliver a variety of desirable outcomes – including potentially reduced virus transmission in populations with high vaccination levels – 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 protection against homologous and heterologous viruses. No corresponding protection 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. However, the replication and associated immunogenicity of intranasal live-attenuated H5N1 vaccines have been quite variable in humans to date.

Only a few human studies have considered the duration of H5N1 antibody detectability for longer than twelve months, and initial data indicate that this duration varies depending upon the vaccine strain used. Adjuvants may also affect the duration of the immune memory. However, currently available data do not go beyond 16 months. In addition, currently formulated H5N1 inactivated influenza vaccines require at least two doses, given 21 days apart, to provide reliable rates of sero-response.

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 immune response. In an immunologically naive population, a single inoculation with human H5N1 influenza vaccine is likely to provide insufficient protection against H5N1 infection.

Although significant progress has recently been made, the interpretation and comparison of human H5N1 vaccine immunogenicity data are impeded by current gaps in the knowledge regarding acceptable correlates of protection. There is 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 time frames 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, much of which can be conducted during this non-pandemic period, 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 responses following use of current H5N1 vaccines, as well as their ability to foster cross-reactive antibody production in humans. Other important issues include determining the lowest dosage levels of antigen required to induce an immune response, including in children and elderly subjects. It is also not known in a pandemic situation if there would be greater benefit – from a population perspective – in vaccinating larger numbers of people with vaccines containing lower quantities of antigen than vaccinating fewer people with vaccine containing higher amounts of antigen. Data from animal-challenge models on “priming” the immune system with one vaccine dose before challenge with a live virus could also provide useful insights. Based on current understanding, it is anticipated that the standard licensed schedule will be 2 doses of vaccine separated by not less than 21 days. There is a pressing need to investigate whether more closely spaced inoculations could provide adequate immunization of people against pandemic influenza. In addition, more data on single-dose priming regimens might increase the options.

The interpretation and comparison of clinical trial data are impeded by limited consistency and comparability in the antibody assay methods used. At present, there is some inherent variability in the HI and neutralization-antibody assay systems used to measure immunogenicity, as well as reagents that are utilized in these tests, and consequently, comparing the results of different clinical trials is difficult. Addressing these issues would improve the ability to directly compare the immunogenicity testing results and other characteristics of different vaccines, including findings from 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 can be considered to be markers of vaccine efficacy or effectiveness (i.e. protection) is not precisely known. Vaccine efficacy or effectiveness itself can be measured in different ways, including the extent to which:

- vaccination of an individual will prevent infection (potentially having both individual and epidemiological benefit);
- vaccination of an individual can reduce the severity of illness;
- vaccination within a population can reduce the infectiousness of individuals (for example, through reduced viral shedding) and dampen the transmission of the virus through the population (epidemiological benefit).

Nevertheless, the available data on the safety and immunogenicity of 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 improve their 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 possible options for the use of human H5N1 influenza vaccines. Any proposed use of an H5N1 vaccine should reflect an acceptable balance between the perceived benefits and risks, recognizing that the acceptable balance and the perceived benefit-risk ratio may vary considerably depending upon whether H5N1-related disease is common or infrequent. For example, during non-pandemic periods, the perceived benefit-risk ratio 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. By contrast, if a pandemic is considered either imminent or under way, then the perceived benefit of vaccination is likely to be considered high in most countries. Regardless of how or when H5N1 vaccines are used, the use of a stepwise targeted approach that also includes the collection of 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 groups of people considered to be at high risk of contracting zoonotic avian H5N1 influenza.
- 2.2: To “prime” selected groups or populations in anticipation of a possible H5N1 influenza pandemic.
- 2.3: To fully immunize selected groups or 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 populations following sustained human-to-human transmission of H5N1.

One purpose of the consultation was to review the currently available scientific data relating to the above range of possible options. Each option has potential benefits that need to be weighed against potential risks. Moreover, before any option can be acted upon, additional decisions will be needed such as who should receive vaccine first. While scientific evidence will have some bearing on such discussions, these decisions will inherently depend primarily upon ethical, political and other 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 infections by H5N1 have been zoonotic. However, in some of the clusters investigated to date, limited and non-sustained human-to-human transmission, though rare, is believed to have occurred and cannot be excluded. 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). In investigations of such clusters, identification of specific exposures and routes of transmission for each case can be difficult to determine with certainty.

Observational and analytic studies indicate that the primary risk factors for humans to become infected by H5N1 are 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. However, one study conducted following the 1997 outbreak in, Hong Kong (China, Hong Kong Special Administrative Region) found a seroprevalence of about 10% in poultry workers. A small number of clinically mild H5N1 cases have also been identified in children. Seroprevalence studies can be difficult to conduct, in part because micro-neutralization assays for H5N1 antibody, which are considered to be the gold standard for measuring such antibodies, 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 workers. However, in a small number of cases, nosocomial transmission from patient to health care workers, and particularly to family members providing care, appears to have occurred.

Current considerations: In some countries, those considered to be at high risk of exposure to avian influenza are unprotected persons exposed to infected poultry. In these countries, the number of people exposed, in either commercial or domestic settings, may be large. 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 live poultry markets in affected regions, or living in communities that are repeatedly affected). It is also possible that the identified risk factors or epidemiological profiles may change as H5N1 viruses evolve.

Using H5N1 influenza vaccines to immunize individuals and groups thought to be at high risk of either infection from, or exposure to, infected poultry, would have the advantage of providing protection to people from zoonotic H5N1 infections with a strong likelihood of a good match between the H5N1 vaccine and circulating H5N1 virus strains. It would also enable immunization programmes to be conducted in an orderly manner. The drawbacks may include difficulties in identifying at-risk populations, the possibility of insufficient supplies to vaccinate entire target populations, and the potential of adverse behaviour (failure to follow risk-reduction practices) in those immunized. It will still be anticipated that vaccinated individuals will acquire acute respiratory infections caused by other pathogens on a sporadic basis, potentially leading to confusion and concerns that the vaccine is not effective. Furthermore, no H5N1 vaccine is likely to be 100% protective and any H5N1 vaccine may become less protective as H5N1 strains evolve (“drift”) over time. The current rarity of human cases will also reduce perceptions of the potential benefits while the occurrence of any adverse effects (whether real or perceived) are likely to negatively affect the perceived risk-benefit ratio. In addition, vaccination efforts should

not be used as a reason for relaxing continuation 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 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 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, and 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 the H5N1 influenza virus subtype. 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 vaccines 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, there is no certainty that the next pandemic will be related to the H5N1 virus. Current indications are that single priming doses of candidate H5N1 vaccines do not produce antibody levels sufficient for licensing. Studies are needed to assess whether single doses might have a substantial priming effect, when second doses are given many months or longer afterwards. Should studies support the use of H5N1 vaccine for priming, many of the potential advantages and disadvantages 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 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 groups or 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 influenza virus.

Evidence: There are currently some scientific data relevant to this option but none of these data address the fundamental issue that the influenza virus that will cause the next pandemic cannot

be predicted. For example, current studies indicate that H5N1 vaccines are immunogenic although their effectiveness in providing protection has not been well documented. 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 might provide more protection than administration of a more effective vaccine that was available only after an H5N1 pandemic had started. Assuming widespread population coverage (of the order of approximately 80%) and low vaccine efficacy (25%) this would lead to an effective population coverage of 20%. At this level (and even lower), vaccination in advance of the first wave of a pandemic could significantly reduce the number of expected disease cases. Where there are insufficient numbers of doses for the whole population, another option might be to prioritize children for vaccination in an attempt to reduce virus transmission – assuming there is a sufficient supply of vaccine to vaccinate the target paediatric population.

Current considerations: A number of the considerations of immunizing groups or populations during a non-pandemic period are similar to those described above for priming approaches. As with priming, the potential benefits and drawbacks must be considered with the understanding that the next influenza pandemic could be caused by virus that is completely unrelated to the H5N1 influenza virus subtype.

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: Attempts to rapidly contain the first emergence of a potential H5N1 influenza pandemic will require a multiple, combined approach including intensified surveillance, use of anti-viral drugs in treatment and for chemoprophylaxis of at-risk individuals, quarantine of exposed persons, isolation of infected persons, and social distancing within a well-defined area to try to prevent the further spread of H5N1 infections beyond the initial outbreak area. The development of human H5N1 influenza vaccines offers additional option and could potentially be used in the area surrounding the local outbreak area, to "dampen" the possibility of virus spread. In this way, H5N1 vaccines could be used as an adjunct to other immediate containment efforts.

Evidence: There are currently limited scientific data to support or not support the use of H5N1 vaccines in this way. Theoretical indications from mathematical modelling studies suggest that the extensive use of vaccination could potentially help to decrease the spread of the virus. These 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 sufficient early warning that an outbreak of H5N1 influenza is due to a virus that is 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 and providing regional awareness and training workshops in the implementation of a containment effort in coordination with national authorities. However, a containment effort would be feasible only in

settings where the number of localized cases are still limited, 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. As their availability becomes imminent, the situation is changing, and there is now considerable interest in adding vaccination to the list of other available interventions. Efforts to use H5N1 vaccines in a containment operations must be well coordinated and properly aligned with other available approaches and used with the understanding that the full effects of immunization could take some weeks to be realised.

2.5. To immunize selected groups or populations following sustained human-to-human transmission of an H5N1 influenza virus

Q2.5 In the event of sustained human-to-human transmission of an H5N1 influenza virus, could stockpiled human H5N1 influenza vaccines be used to help protect selected groups or populations?

Rationale: If an H5N1 virus acquires the capacity for sustained human-to-human transmission, and its spread can not be contained, it is highly likely that an H5N1 pandemic will ensue. At this point, the purpose of vaccinating people would be to protect groups or 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 suggesting that such vaccines can provide protection in people 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 directly demonstrated in humans trials that they effectively protect humans against disease caused by H5N1 influenza virus. 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 directly is extremely difficult.

Current considerations: In an H5N1 influenza pandemic, a very large number of infections and cases of illness is possible with the number of deaths depending in part upon the pathogenicity of the pandemic virus. In such a situation, it is anticipated that most countries would perceive the benefit-to-risk ratio for vaccination to be very high, but that vaccine availability in the immediate term would be limited in most countries unless steps are taken before a pandemic to improve the capacity to produce vaccine and increase access to such a vaccine.

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 and available supply of the vaccine. These include issues such as the timing of vaccination and which population groups to

target⁴ for greatest impact. At the same time, there is also likely to be a need to prioritize⁵ vaccine access, for example to protect those at greatest risk, or those responsible for carrying out “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 transmission patterns will be sufficiently similar to allow simple extrapolation 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 the use of human H5N1 vaccines is guided by population disease-control considerations, then vaccinating certain groups could have beneficial secondary effects in protecting others. Alternatively, directly vaccinating older or other particularly vulnerable population groups, may reduce severe disease outcomes more effectively. Such considerations are highly complex.

Even as scientific knowledge of human H5N1 influenza vaccines and understanding of the epidemiology of H5N1 virus infections and pandemics of influenza increase, it is unlikely that such information will be sufficient by itself to provide guidance on how to prioritize access to H5N1 vaccines. This issue will require very careful consideration, and decisions will inevitably reflect the prevailing ethical, social and political environment in each setting – considerations that went far beyond the scope of this consultation.

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.

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 create national stockpiles. In May 2007, the Sixtieth World Health Assembly, in its Resolution WHA60.28⁶, 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.⁷ 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 supply replacement cycles for stockpiles. In addition, other issues such as the liability implications for any countries that might host or use the WHO international stockpile and stockpiles of supporting materials such as syringes 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.

Once recommendations have been developed on the basis of 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. To address these issues, WHO convened a second consultation from 17

⁶ Resolution WHA60.28. In Sixtieth World Health Assembly, Geneva, 23 May 2007. Eleventh plenary meeting, Agenda item 12.1. *Pandemic influenza preparedness: sharing of influenza viruses and access to vaccines and other benefits*. Geneva, World Health Organization, 2007 (A60/VR/11).

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.

to 19 October, to discuss the technical specifications required for an international H5N1 vaccine stockpile. The outcomes of those deliberations will be reported upon separately.

At the consultation held from 1 to 3 October, experience in using other WHO vaccine stockpiles was reviewed. Speakers stressed, however, 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 a 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 coordinate 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 mobilize vaccine supplies quickly enough to support such an operation, will be a critical component in their successful use in containment operations.

Current considerations: It is unlikely that a potential pandemic could be successfully contained through the use of vaccination alone. 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 considerable 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 addition to the effects of other control actions, by reducing the ability of the virus to spread through the populations immediately surrounding the containment zone. Preliminary models suggest that optimal benefit would be achieved if several million people could be vaccinated, but further modelling using different assumptions will be needed to refine the estimates.

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

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. These vaccines, once made available to these countries, could be used in a number of ways, including the protection of critical infrastructure personnel, as defined by the national authority concerned.

Current considerations: Efforts are under way to improve access to H5N1 vaccines so that if an H5N1 influenza pandemic were to 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 how such vaccines would best be used.