Use of licensed H5N1 influenza vaccines in the interpandemic period

Report* of the H5N1 SAGE Working Group to the April 2009 meeting of the Strategic Advisory Group of Experts

* This report has been slightly adjusted from that presented to SAGE members i.e. some confidential information has been removed.
The following authors are acknowledged for their particular contributions to the following chapters: Dr F. Hayden (2.1); Dr Y. Hirota (2.2); Dr T. Uyeki (2.3); United Kingdom Health Protection Agency (2.3A), Dr J. Katz (2.4 and 2.5); Professo P.-H. Lambert (2.6 and 2.7), Dr M. Selgelid (2.8) and the Oliver Wyman consultancy (2.9).
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Supplement: major sources of evidence reviewed are available on the WHO/IVR Internet site at www.who.int/vaccine_research.
**Abbreviations**

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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AEFI</td>
<td>adverse events following immunization</td>
</tr>
<tr>
<td>Al(OH)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>aluminium hydroxide</td>
</tr>
<tr>
<td>Al(PO&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>aluminium phosphate</td>
</tr>
<tr>
<td>ca</td>
<td>cold-adapted</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>ECBS</td>
<td>Expert Committee on Biological Standardization</td>
</tr>
<tr>
<td>EMEA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>GBS</td>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>GMT</td>
<td>geometric mean titre</td>
</tr>
<tr>
<td>HA</td>
<td>haemagglutinin</td>
</tr>
<tr>
<td>HI</td>
<td>haemagglutination inhibition</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HCW</td>
<td>health-care worker</td>
</tr>
<tr>
<td>HPAI</td>
<td>highly pathogenic avian influenza</td>
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<tr>
<td>ILI</td>
<td>influenza-like illness</td>
</tr>
<tr>
<td>LAIV</td>
<td>live attenuated influenza virus</td>
</tr>
<tr>
<td>MN</td>
<td>microneutralization</td>
</tr>
<tr>
<td>NA</td>
<td>neuraminidase</td>
</tr>
<tr>
<td>NIBSC</td>
<td>National Institute for Biological Standards and Control</td>
</tr>
<tr>
<td>PMS</td>
<td>postmarketing surveillance</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life years</td>
</tr>
<tr>
<td>rg</td>
<td>reverse genetics</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>RT-PCR</td>
<td>reverse transcriptase polymerase chain reaction</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAR</td>
<td>Special Administrative Region</td>
</tr>
<tr>
<td>SRH</td>
<td>single radial haemolysis</td>
</tr>
<tr>
<td>TCID&lt;sub&gt;50&lt;/sub&gt;</td>
<td>50% tissue culture infectious dose</td>
</tr>
<tr>
<td>µg</td>
<td>microgram</td>
</tr>
<tr>
<td>URT</td>
<td>upper respiratory tract</td>
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<tr>
<td>VLP</td>
<td>virus-like particle</td>
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1. Executive summary

The WHO Strategic Advisory Group of Experts (SAGE) on immunization identified the need to examine the available evidence with a view to providing an opinion on the use of currently licensed human H5N1 influenza vaccines in the interpandemic (phase 3) period. The SAGE recommendations made at its meeting in April 2009 are based on a thorough review of published and unpublished data conducted over a six-month period by a specially formed SAGE Working Group. The following paragraphs summarize the review and the recommendations made by SAGE.

1.1 Summary of the evidence

Nine parameters were assessed in detail, and areas requiring further research identified for each parameter. The key published literature and other materials that comprised the evidence base can be found on the WHO Internet (www.who.int/vaccine_research).

Five vaccines already licensed for use in the interpandemic period were considered, as well as a number of candidate vaccines submitted for registration, or that are likely to be submitted soon. SAGE noted that the protective potential of these vaccines has been evaluated based on preclinical efficacy data in ferrets and monkeys and on immunogenicity in human clinical trials. H5N1 vaccines were shown to be effective in protecting ferrets from death, illness and pulmonary virus replication (homologous and heterologous clades of H5N1 virus). Limited studies in non-human primates suggest protective efficacy and showed no evidence of disease exacerbation. In clinical trials, most H5N1 vaccines required two doses to meet the three criteria of the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) as defined for seasonal influenza vaccines. Inactivated vaccines combined with oil-in-water adjuvants (MF59, AF03 and AS03) showed encouraging results regarding antigen-sparing, cross-reactivity and effective priming.

About 18 000 people have received one or another H5N1 vaccine, yet data available on the use of each vaccine are still very limited. Available safety data indicate no particular concerns, but licensure of vaccines only requires the assessment of common adverse events and thus rare or longer term adverse events cannot be excluded. SAGE also reviewed preliminary results from a large-scale safety study conducted in Japan using two licensed H5N1 vaccines.

The risk of highly pathogenic avian influenza (HPAI) H5N1 virus infection in specific target groups and in the general population in countries where the virus is enzootic was discussed, as well as cost-benefit and ethical issues. Overall, the risk of HPAI H5N1 virus transmission to humans following exposure to the virus appears to be very low, although this is based on limited epidemiological data to assess the risk among different populations. Notably, each group assessed contains a heterogeneous population with a range of possible exposures to H5N1 virus, making it difficult to ascertain the risk of infection among groups; the key issues are the intensity of exposure to H5N1 virus, potentially modifiable factors such as behaviour or use of protective equipment, and possibly unknown host factors.

The same analysis was carried out for the risk of H5N1 pandemic virus infection, although many unknowns made this exercise difficult. Indeed, no information is available on the likelihood of occurrence of an H5N1 pandemic, nor on the severity of such a potential pandemic.

Finally, current interpandemic H5N1 vaccine production and potential production capacity for pandemic vaccine was reviewed. The study, conducted by a consultant firm, estimates that in the most likely case manufacturers could produce 2.5 billion doses of pandemic vaccine in the 12 months following receipt of the production strain and would require four years to satisfy global demand. The
12-month production capacity is expected to rise to 5 billion doses over the next five years, with a resulting time to meet global demand reduced to 2½ years in the most probable scenario.

1.2 SAGE recommendations

The Working Group recommendations are graded as follows:

- **Strongly recommended:** Persons should not carry out their functions unless they are vaccinated.
- **Recommended:** Persons are encouraged to be vaccinated.
- **May be made available:** Responsible authorities should assess whether licensed human H5N1 influenza vaccines might be made available, without encouraging persons to be vaccinated. This does not imply that vaccine should be provided free of charge.

Vaccination with licensed H5N1 vaccine is strongly recommended for laboratory workers involved in the following activities: large-scale production or manipulation of HPAI H5N1 virus; working with the virus over a long period; working with HPAI H5N1 virus strains that are resistant to licensed antiviral compounds; or working with virus strains with the potential for increased transmissibility in mammalian species. For laboratory personnel working with H5N1 virus, but not involved in these activities, the risks and benefits associated with H5N1 vaccination should be evaluated before it can be made available, and affected staff should be involved in decision-making for vaccination.

Depending on the assumed risk of exposure and type of activities, vaccination is recommended for workers involved in a first response to possible H5N1 outbreaks in animals or humans.

H5N1 vaccination cannot be recommended at present for persons who may only potentially come in contact with infected animals (e.g. farmers). However, vaccine may be made available as a preventive measure to the relatively few persons in contact with poultry in confirmed active outbreak areas, depending on the level of enzooticity, risk of exposure and effectiveness of other prevention measures in place. A careful risk assessment should be undertaken before vaccine is made available.

To date, there are no data indicating that the risk of infection from avian H5N1 influenza virus for essential workers, i.e. workers in critical infrastructure sectors, is higher than for the general population. Therefore, the evidence is insufficient to propose that H5N1 influenza vaccine should be made available, in areas where HPAI virus is enzootic, to essential workers in general on the basis of risk.

In contrast, vaccination is recommended for health-care workers (HCWs) who evaluate or manage suspected or confirmed H5N1 patients in designated outpatient or inpatient referral facilities. These HCWs may be at a higher risk of infection than others, especially if a virus with increased potential for human-to-human transmission emerges. Based on a risk assessment, licensed H5N1 vaccine may be made available to other HCWs in countries where avian H5N1 virus is enzootic and where human cases may continue to emerge and pose the threat of exposure for HCWs. This includes HCWs at the many primary health-care facilities where suspected H5N1 patients may first present for care.

In countries affected by HPAI H5N1 virus, the risk of infection in the general public remains very low. Since one cannot exclude a risk, albeit low, of vaccine-related serious adverse events, and at the present low level of risk of infection, H5N1 vaccination is not recommended currently in the general population, and evidence does not suggest that vaccine should be made available to the general public unless there is judged to be a particular risk.

Regarding the priming or immunizing of essential personnel or the general public against infection with a potential pandemic H5N1 virus, there is currently insufficient scientific evidence to
recommend the use of licensed human H5N1 influenza vaccines – or to propose that such vaccines be made available – for this purpose in the interpandemic period.

**Stockpiled licensed H5N1 vaccine**

In the context of the above recommendations, and without waiting for stockpiled vaccines to approach their expiry date, holders of licensed H5N1 vaccine stockpile are encouraged to gain experience with H5N1 vaccine use, and to expand knowledge on safety, immunogenicity, cross-reactivity, priming potential and duration of immunity in order to inform public health policies. Such experience could be acquired through pilot projects, clinical studies and/or limited vaccination of incremental numbers of persons. Studies might start with persons currently at increased risk (e.g. those in potential contact with infected poultry), or those who would be at increased risk in the event of a pandemic (e.g. HCWs). Additional knowledge could be acquired through pilot projects and/or clinical studies in special population groups (e.g. children, older persons, immunosuppressed and individuals with specific health conditions).

In addition, use of stockpiled vaccine may be considered for specific indications identified above for which vaccination in the interpandemic period is either recommended or strongly recommended.

In the event that such projects or studies are carried out, it will be important to establish post-licensure or postmarketing surveillance procedures that can collect long-term safety data for ongoing risk-benefit analyses.

The results of the above projects and studies should be shared promptly with WHO and the international community in order to allow reconsideration, if and when appropriate, of current recommendations.

The above-mentioned pilot projects and clinical studies are not expected to deplete vaccine doses held in the substantial current and planned stockpiles for use in a pandemic or for other purposes. Therefore, there is no evidence to recommend a change in the size previously recommended by SAGE for the WHO international stockpile, i.e. 50 million doses to complement rapid containment operations in the event of human-to-human transmission of H5N1, and 100 million doses for equitable distribution to low- and middle-income countries to help maintain the services considered most essential.

Following its deliberations and endorsement of the above recommendations, SAGE asked the Working Group to report in November 2009 on the results of a cost-effectiveness study recently initiated; on possible approaches that countries might consider to evaluate the risk of infection in persons who may only potentially come in contact with infected animals in enzootic areas; as well as on potential avenues for low- and middle-income countries to procure vaccine doses that they might decide to make available to specific population groups in enzootic areas during the current (phase 3) interpandemic period.

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1 Meeting of the Strategic Advisory Group on immunization, April 2009 – conclusions and recommendations. WHO Weekly Epidemiological Record, 2009, 84:
2. Summary of the available evidence

2.1 Safety, immunogenicity and efficacy of licensed or soon-to-be licensed H5N1 influenza vaccines

Influenza vaccines are potentially the most efficacious means of mitigating the impact of an influenza pandemic by contributing to containment of an emerging pandemic virus and by potentially reducing the risk of infection by avian viruses in humans during the current interpandemic period. This chapter summarizes the most recent data on registration status, safety, immunogenicity, cross-reactivity, prime-boosting studies, preclinical data and other regulatory issues regarding H5N1 vaccines – licensed, submitted for licensing, or soon to be submitted for licensing – for interpandemic use.

All H5N1 influenza vaccines tested so far have demonstrated a good safety profile with a total number of immunized volunteers of about 18,000. The total reported serious adverse events (SAE) was 20, all unrelated to vaccination. In terms of immunogenicity, only one vaccine meets the three European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) criteria following single dose vaccination; all other vaccines required two doses. However, it is important to note that these criteria were defined for seasonal influenza vaccines and were extrapolated to H5N1 vaccines pending a greater understanding of H5N1 correlates of protection (see Section 2.5).

Egg-derived vaccines combined with oil-in-water adjuvants (MF59, AFO3 and ASO3) have shown encouraging results of antigen-sparing, cross-reactivity and effective priming. More data are needed, especially in the very young and elderly age groups, as priority immunizations are likely to target these and at risk groups in many countries in the event of a pandemic. In order to better predict the potential protective efficacy of prototype pandemic vaccines, especially those using novel technologies and live attenuated vaccines, a fuller understanding of the correlates of protection against H5N1 and other avian subtype viruses is needed. Studies in ferrets and non-human primates should be a priority research area. Significant resources are required for such studies but their results could prove critical in informing future research directions and vaccine policies. Finally, the standardization of established serological assays, as for the first internationally accepted anti-H5 clade 1 antiserum standard, is urgently needed in order to compare vaccine trial outcomes.

2.1.1 Registration status of H5N1 influenza vaccines

As at today, five H5N1 influenza vaccines have received a licence for use in interpandemic period:

- Biken Bk-Pifa and Kitasato vaccines, licensed in Japan in October 2007;
- GlaxoSmithKline (GSK) Prepandrix vaccine, licensed in the European Union, Switzerland, Malaysia and the People’s Republic of China Hong Kong Special Administrative Region (SAR) in May 2008, including a mock-up/pandemic use in the European Union and Australia;
- Omnivest Fluvax H5N1 vaccine, licensed in Hungary in June 2007;
- Sinovac Panflu vaccine, licensed in China in April 2008, including a mock-up/pandemic use.

Three H5N1 influenza candidate vaccines are currently under licence application:

- Denka Seiken and KAKETSUKEN vaccines, submitted for licensing in Japan;

Other H5N1 influenza candidate vaccines have not yet been submitted for licensing:

- Vaccines in phase III trials: GSK Q-Pan is close to submission for licensing in the USA; Novartis Aflunov vaccine;
- Vaccines in phase II trials: Sanofi-Pasteur vaccine derived from Vietnam/1194 strain and AFO3-adjuvanted; Solvay vaccine; and Vabiotech vaccine;
- Vaccines in phase I trials: Nobilon vaccine.

Some H5N1 influenza vaccines have been licensed (or submitted) for mock-up/pandemic use only:
- Baxter Celvapan vaccine, authorized for mock-up/pandemic licensing in 2009;
- The Commonwealth Serum Laboratories (CSL) Panvax vaccine, licensed in Australia in June 2008;
- GSK Daronrix vaccine, licensed in the European Union in March 2007;
- Novartis Focetrix vaccine, licensed in the European Union in 2007;
- Sanofi-Pasteur vaccine derived from Vietnam/1203 strain and non-adjuvanted, licensed in the USA in April 2007;
- Sanofi-Pasteur Emerflu aluminium adjuvanted vaccine, recently rejected for licensing in the European Union but accepted for licensing in Australia (2009).

The registration status and safety data of licensed and soon-to-be licensed H5N1 influenza vaccines are summarized in Table 1.

### 2.1.2 Results of clinical trials

**Egg-derived inactivated vaccines**

The following vaccines were developed as monovalent inactivated vaccine based on the National Institute of Biological Standards and Control (NIBSC) seed virus A/Vietnam/1194/2004/NIBRG-14 (clade 1) and grown in eggs:

- Biken, Kitasato, Denka Seiken and KAKETSUKEN developed whole-virion vaccines containing 15µg of HA antigen adjuvanted with Al(OH)₃. A two-dose regimen 28 days apart using Biken Bk-Pifa vaccine induced seroresponses (microneutralization (MN) ≥1/40) in 85% of adults. Vaccine appeared to be safe with no vaccine-related SAE. Using similar technology, the four vaccines are likely to share similar characteristics of safety and immunogenicity. To date no results are publicly available.

- CSL developed Panvax, a split-virion vaccine (for strict mock-up/pandemic use) containing 30µg of HA antigen adjuvanted with 0.5mg AlPO₄ (aluminium phosphate). A two-dose regimen 21 days apart induced seroresponses (HI≥1/32) in 59% of adults and in 95–100% of children (aged 6 months to 9 years). Cross-reactivity in adults and children to a heterologous clade 2.1 virus (rgA/Indonesia/05/2005) was observed. A homologous booster dose induced seroresponses (MN≥1/20) in 60% of adult subjects six months after two-dose priming. Panvax appeared safe in adults, the elderly and children with no vaccine-related SAE. Infants and young children displayed higher frequencies of systemic reactions than older children.

- GSK developed Prepandrix, a split-virion vaccine containing 3.8µg of HA antigen adjuvanted with Al(OH)₃. A two-dose regimen 21 days apart induced seroresponses (HI≥40) in 94.3% of adults, 83.6% of the elderly and 95.9%–100% in children. Cross-reactivity to clade 2 viruses (A/Anhui/1/2005, A/Indonesia/05/2005 and A/turkey/Turkey/1/2005) was observed. A heterologous booster dose (A/Indonesia/05/2005) induced seroresponses in more than 80% of adults six months after priming with either one or two doses of clade 1 vaccine. Prepandrix appeared safe in adults, the elderly and children with no vaccine-related SAE. The commercial name of the vaccine for its specific mock-up/pandemic use is Pandemrix.

- Microgen developed Orniflu, a subunit vaccine containing 15µg of HA antigen adjuvanted with Al(OH)₃. A two-dose regimen 28 days apart induced seroresponses (MN≥1/40) in 72% of adults. The company developed in parallel IPSIV, an inactivated polymer-subunit vaccine isolated from purified H5N1 avian virions, containing 45µg of HA antigen and aggregated with an N-oxidized polyethylene-piperazine derivative (polyoxidonium, 0.75mg). A two-dose regimen of IPSIV 28 days apart induced seroresponses (MN≥1/40) in 77% of adults. Orniflu and IPSIV appeared to be safe with no vaccine-related SAE.
Table 1. Registration status and safety data for H5N1 influenza vaccines

<table>
<thead>
<tr>
<th>COMPANY - VACCINE</th>
<th>Licensing date</th>
<th>Substrate</th>
<th>Adjuvant</th>
<th>Study Population</th>
<th>Licensing dose (HA content)</th>
<th>Cross reactivity</th>
<th>Safety for licensing dose *</th>
<th>2.3 &gt; Crude cross reacting</th>
<th>% Loc. AE</th>
<th>% Sys. AE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Inactivated WHOLE virion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OUNIENWEST - FLUVIAL H5N1</strong></td>
<td>Licensed in Jun 07 (HeiFlu)</td>
<td>Egg</td>
<td>Alum</td>
<td>12</td>
<td>1 x 6 µg</td>
<td>2</td>
<td>Localised</td>
<td>1%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td><strong>SIFIN - BK FIPA</strong></td>
<td>Licensed in Oct 07 (MLH/W)</td>
<td>Egg</td>
<td>Alum</td>
<td>420</td>
<td>2 x 15 µg</td>
<td>4</td>
<td>Localised</td>
<td>4%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td><strong>KITASATO</strong></td>
<td>Licensed in Oct 07 (MLH/W)</td>
<td>Egg</td>
<td>Alum</td>
<td>420</td>
<td>2 x 15 µg</td>
<td>2</td>
<td>Localised</td>
<td>2%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td><strong>SINOVAQ - PANFLU</strong></td>
<td>Licensed in Apr 08 (SFDA)</td>
<td>Egg</td>
<td>Alum</td>
<td>522</td>
<td>2 x 10 µg</td>
<td>1.2</td>
<td>Localised</td>
<td>34%</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td><strong>KAKETSUKEN</strong></td>
<td>Submitted for license in Apr 08 (MLH/W)</td>
<td>Egg</td>
<td>Alum</td>
<td>450</td>
<td>2 x 15 µg</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DENKA SEIKEN</strong></td>
<td>Submitted for license in Jan 07 (MLH/W)</td>
<td>Egg</td>
<td>Alum</td>
<td>460</td>
<td>2 x 15 µg</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VARIOTHEC</strong></td>
<td>Undergoing phase II trials</td>
<td>PMK cells</td>
<td>-</td>
<td>30</td>
<td>2 x 30 µg</td>
<td>2</td>
<td>Localised</td>
<td>3%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td><strong>BAXTER - CELVAPAN</strong></td>
<td>Licensed in 2009 (EMEA)</td>
<td>Vero cells</td>
<td>-</td>
<td>219</td>
<td>2 x 7.5 µg</td>
<td>1.1</td>
<td>Localised</td>
<td>17%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td><strong>GSK - DARAMIR</strong></td>
<td>Licensed in Mar 07</td>
<td>Egg</td>
<td>Alum</td>
<td>200</td>
<td>2 x 15 µg</td>
<td>1.1</td>
<td>Localised</td>
<td>57%</td>
<td>11%</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COMPANY - VACCINE</th>
<th>Licensing date</th>
<th>Substrate</th>
<th>Adjuvant</th>
<th>Study Population</th>
<th>Licensing dose (HA content)</th>
<th>Cross reactivity</th>
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<th>2.3 &gt; Crude cross reacting</th>
<th>% Loc. AE</th>
<th>% Sys. AE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2. Inactivated SP?LIT virion</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GSK - PREPANDRIX</strong></td>
<td>Licensed in May 08 (EMEA)</td>
<td>Egg</td>
<td>A?505</td>
<td>6577</td>
<td>2 x 3.8 µg</td>
<td>2.1 2 2.2 3</td>
<td>Localised</td>
<td>27%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td><strong>GSK - G PAN</strong></td>
<td>Undergoing Phase III trials</td>
<td>Egg</td>
<td>A?505</td>
<td>n/a</td>
<td>2 x 3.8 µg</td>
<td>2.1 2 2.2 3</td>
<td>Localised</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td><strong>SANOFI PASTEUR - Strain 1194</strong></td>
<td>Undergoing Phase II trials</td>
<td>Egg</td>
<td>AF03</td>
<td>265</td>
<td>2 x 3.75 µg</td>
<td>2.1</td>
<td>Localised</td>
<td>27%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td><strong>CBL - PANVAX</strong></td>
<td>Licensed in Jun 08 (TGA)</td>
<td>Egg</td>
<td>Alum</td>
<td>150</td>
<td>2 x 30 µg</td>
<td>2.1 2 2</td>
<td>Localised</td>
<td>48%</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td><strong>SANOFI PASTEUR - Strain 1203</strong></td>
<td>Licensed in Apr 07 (FDA)</td>
<td>Egg</td>
<td>-</td>
<td>1000</td>
<td>2 x 90 µg</td>
<td>1.1</td>
<td>Localised</td>
<td>57%</td>
<td>35%</td>
<td></td>
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<tr>
<td><strong>SANOFI PASTEUR - EMERFLU</strong></td>
<td>Reacted by EMEA, Accepted by TGA (2009)</td>
<td>Egg</td>
<td>Alum</td>
<td>120</td>
<td>2 x 30 µg</td>
<td>2.1</td>
<td>Localised</td>
<td>23%</td>
<td>90%</td>
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</table>

<table>
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<tr>
<th>COMPANY - VACCINE</th>
<th>Licensing date</th>
<th>Substrate</th>
<th>Adjuvant</th>
<th>Study Population</th>
<th>Licensing dose (HA content)</th>
<th>Cross reactivity</th>
<th>Safety for licensing dose *</th>
<th>2.3 &gt; Crude cross reacting</th>
<th>% Loc. AE</th>
<th>% Sys. AE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3. Inactivated SUBUNIT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td><strong>MICROGEN - OMNIPLU</strong></td>
<td>Submitted for license in 2008</td>
<td>Egg</td>
<td>Alum</td>
<td>480</td>
<td>2 x 15 µg</td>
<td>2.1</td>
<td>Localised</td>
<td>32%</td>
<td>18%</td>
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<tr>
<td><strong>MICROGEN - IPSIV</strong></td>
<td>Undergoing phase II trials</td>
<td>Egg</td>
<td>Polyx</td>
<td>120</td>
<td>2 x 45 µg</td>
<td>2.1</td>
<td>Localised</td>
<td>23%</td>
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<td></td>
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<tr>
<td><strong>NOVARTIS - APLUMO</strong></td>
<td>Withdrawn by EMEA in 2008</td>
<td>Egg</td>
<td>MF59</td>
<td>(4000)</td>
<td>2 x 3.75 µg</td>
<td>2</td>
<td>Localised</td>
<td>59%</td>
<td>n/a</td>
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<tr>
<td><strong>SOLVAY</strong></td>
<td>Undergoing phase II trials</td>
<td>MDCX cells</td>
<td>Alum</td>
<td>400</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>NOVARTIS - PLOSETRA</strong></td>
<td>Licensed in May 07</td>
<td>Egg</td>
<td>MI-59</td>
<td>728</td>
<td>2 x 7.5 µg</td>
<td>2.1</td>
<td>Localised</td>
<td>50%</td>
<td>n/a</td>
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</table>
Novartis developed Aflunov, a subunit candidate vaccine containing 7.5µg of HA antigen adjuvanted with MF59. A two-dose regimen 21 days apart induced seroresponses (HI≥1/40) in 72–87% of adults and more than 87% in children between six months and 18 years. Cross-reactivity to clade 2 heterologous clade 2.2 A/turkey/Turkey/1/2005 was observed. A homologous booster dose induced seroresponses in 90% of adults and 84% of elderly. Moreover, a one-dose booster of Aflunov induced rapid and broadly reactive seroresponses across clade 1 and various clade 2 viruses in subjects primed 6–8 years earlier with two or three doses of a H5N3-derived vaccine (clade 0); results were superior in subjects who had received MF59 adjuvanted priming.\textsuperscript{18} Aflunov appeared safe with no vaccine-related SAE in any of the age groups texted (six months to >65 years).\textsuperscript{17} Withdrawal of the Aflunov file by Novartis from evaluation by the EMEA in June 2008 was related to Good Clinical Practice findings at some phase III clinical trial sites. A replacement trial has since been initiated.

Omninvest developed Fluval H5N1, a whole-virion vaccine containing 6µg of HA antigen adjuvanted with Al(OH)\textsubscript{3}.\textsuperscript{3} Remarkably, a single dose of Fluval H5N1 induced seroresponses (HI≥1/40 using chicken erythrocytes) in 72% of adults and 65% of the elderly. A single dose also induced seroresponses in 75% of a cohort of 12 children aged from 3 to 18 years.\textsuperscript{4} Cross-reactivity to heterologous clade 2 viruses was observed in adults.\textsuperscript{5} Fluval H5N1 appeared safe in adults, the elderly and children with no vaccine-related SAE.\textsuperscript{4,5}

Sanofi-Pasteur developed a split-virion candidate vaccine containing 30µg of HA antigen adjuvanted with Al(OH)\textsubscript{3}. A two-dose regimen 21 days apart induced seroresponses (HI≥1/32) in 67% of adults and in 73–87% of children.\textsuperscript{6} Cross-reactivity to clade 2 viruses (A/Indonesia/05/2005 and A/turkey/Turkey/1/2005) was observed.\textsuperscript{10} A homologous booster dose induced seroresponses in 80% of adults 12 months after two-dose priming and a heterologous booster dose (A/Indonesia/05/2005) in 70% of adults 24 months after two-dose priming. The vaccine appeared safe in adults,\textsuperscript{8} the elderly and children\textsuperscript{9} with no vaccine-related SAE.

Sinovac developed Panflu, a whole-virion vaccine containing 10µg of haemagglutinin (HA) antigen adjuvanted with Al(OH)\textsubscript{3} (aluminium hydroxide). A two-dose regimen 28 days apart induced seroresponses (haemagglutination inhibition (HI)≥1/40) in 78% of adult recipients.\textsuperscript{1} Ongoing studies are determining immunogenicity and safety in the elderly and children. Cross-reactivity to heterologous clade 2 viruses (A/Anhui/1/2005 and A/turkey/Turkey/1/2005) was observed in 70% of vaccinees. A homologous booster of either 5µg or 10µg dose induced seroresponses (HI≥1/40) in more than 78% of adults 12 months after two-dose priming.\textsuperscript{2} Panflu appeared safe in adults with no vaccine-related SAE.

Solvay developed a subunit candidate vaccine containing 15µg to 30µg of HA antigen adjuvanted with Al(OH)\textsubscript{3}. Results of phase I/II involving 400 adult volunteers are not publicly available.

The following vaccines were developed as monovalent inactivated vaccine based on the NIBSC seed virus A/Indonesia/05/2005 (clade 2) and grown in eggs:

GSK developed Q-Pan, a split-virion candidate vaccine containing 3.75µg of HA antigen adjuvanted with AFO3. Q-Pan is similar to Prepandrix vaccine but is derived from clade 2 virus (A/Indonesia/05/2005). Preclinical studies demonstrated protection in ferret models and collection of human data is ongoing.

Sanofi-Pasteur developed a split-virion candidate vaccine adjuvanted with AFO3. A two-vaccine dose regimen 21 days apart containing 2.5µg or 6µg of HA antigen adjuvanted in 2.5% AFO3 induced seroresponses (MN≥1/40) in more than 80% of adults. Cross-reactivity to clade 1 virus (A/Vietnam/1194/2004) was observed in more than 70% of subjects.

The following vaccine was developed as a monovalent inactivated vaccine based on the seed virus A/Vietnam/1203/2004 (clade 1) and grown in eggs:
Sanofi-Pasteur developed a split-virion, non-adjuvanted vaccine containing 90µg HA antigen. A two-dose regimen 28 days apart induced seroresponses (HI≥1/40) in 58% of adults. The vaccine appeared safe in adults with no vaccine-related SAE.

**Cell-derived inactivated vaccines**

Baxter developed Celvapan, a whole-virion vaccine (for mock-up/pandemic use) grown on Vero cells and based on the wild type seed virus A/Vietnam/1203/2004 or A/Indonesia/05/2005, containing 7.5µg of HA antigen without adjuvant. A two-dose regimen 21 days apart induced seroresponses (MN≥1/20) in 55–76% of adults. Cross-reactivity to clade 0 and clade 2 viruses was observed.

Studies in children are ongoing. A heterologous booster with A/Indonesia/05/2005 clade 2.1 vaccine induced seroresponses in 90–100% of subjects to both booster and initial strain 12–17 months after two-dose priming, and cross-reactivity to A/Vietnam/1203/2004, A/turkey/Turkey/1/2005 and A/Anhui/1/2005 was also observed in this study. Celvapan was generally well-tolerated with no vaccine-related SAE, even though the previous development of a Vero cell-grown whole-virion seasonal vaccine was abandoned because of excess reactogenicity in about 10% of recipients.

Solovay developed a subunit candidate vaccine grown on MDCK (Madin-Darbin Canine Kidney) epithelial cells using the virus A/Vietnam/1194/2005 adjuvanted with Al(OH)₃. Results of phase I trials have not been made publicly available.

Vabiotech developed a whole virion candidate vaccine grown on PMK (Primary Monkey Kidney) cells using the rgA/Vietnam/1194/2004 virus, containing 30µg of HA antigen without adjuvant. A two-dose regimen 28 days apart induced seroresponses (HI≥1/40) in more than 95% of 30 adults. The vaccine appeared safe with no vaccine-related SAE. Phase II trials involving 300 subjects are ongoing.

**Live attenuated influenza vaccines**

Live attenuated influenza vaccines (LAIV) are attractive pandemic candidate vaccines since they are cheaper and quicker to manufacture than traditional inactivated vaccines, as well as easier to administer (by intranasal spray). Two strains of cold-adapted (ca), temperature-sensitive backbone viruses have been used in most live attenuated candidate vaccines to date: A/Ann Arbor/6/60 (H2N2) and A/Leningrad/134/17/57 (H2N2).

In February 2009, WHO and Nobilon announced a non-exclusive licensure agreement to develop, manufacture, and sell both seasonal and pandemic LAIV using the A/Leningrad backbone and grown in eggs to manufacturers and governments of developing countries.

The National Institute of Allergy and Infectious Diseases, USA, in collaboration with MedImmune and Johns Hopkins University, has been developing a library of A/Ann Arbor/6/60-based LAIV candidate vaccines for several potential pandemic subtypes, including A/Vietnam/1194/2004 and A/Hong Kong/212/2003 H5N1 viruses. Initial human volunteer studies to date have demonstrated disappointing replication ability and immunogenicity.

Microgen developed Ultragrivak, a H5N2 LAIV pandemic vaccine candidate which is a classical reassortant composed of the HA gene from A/Duck/Potsdam/1402-6/86 (H5N2) and the remaining seven genes from the caA/Leningrad/134/17/57 (H2N2) backbone strain. A two-dose regimen induced seroresponses (HI≥40) to H5N1 A/Vietnam/1194/2004 (clade 1) in 51–74% of adults and to H5N1 A/Indonesia/05/2005 (clade 2.1) in 60–73% of adults.

**2.1.3 Preclinical vaccine efficacy studies in ferrets**

For obvious ethical reasons, animal models are necessary to evaluate the protective efficacy of H5N1 virus vaccines at doses and formulations similar to those that have been approved or are awaiting regulatory approval for human use. These include split or subunit vaccines formulated with oil-in-water adjuvants, split vaccine formulated with Al(OH)₃, adjuvant, or non-adjuvanted whole virus vaccine. The ferret is currently the preferred small animal model for influenza vaccine efficacy studies.
because of the natural susceptibility of this host to influenza A viruses and in particular to highly pathogenic avian influenza (HPAI) H5N1 viruses.\textsuperscript{21,22,23} Ferrets also exhibit similar clinical signs of human influenza disease.\textsuperscript{24,25,26} Non-human primates also provide a useful model and have in this context been used to assess whether immunization with certain H5N1 inactivated vaccine formulations may result in exacerbated pulmonary disease following challenge with wild type virus.\textsuperscript{27} In general, the ability of a two-dose vaccine regimen to protect animals from death, illness or viral replication is evaluated for challenge with a high dose (10^5 or 10^6 TCID\textsubscript{50} (50% tissue culture infectious dose) of virus from homologous or heterologous clade. Weight loss was used as the measurement of reduction in illness since it was the most consistently assessed parameter across the different studies. Protection was evaluated typically two to four weeks after administration of the second dose of vaccine, and in some cases as long as two to four months after vaccination.

Initial studies conducted by several manufacturers showed H5N1 vaccines to be highly effective in protecting ferrets from death, illness and pulmonary virus replication following infection with a homologous H5N1 clade virus. H5N1 vaccines also substantially protected ferrets from death and illness due to a heterologous H5N1 clade virus infection. Limited studies suggest that at least certain vaccine formulations also protect non-human primates and result in rapid clearance of homologous clade virus following challenge, with no evidence of exacerbation of pulmonary infection. Future bridging vaccine efficacy studies could be optimized to capture a more detailed measurement of clinical disease and respiratory tract viral titres. Correlation of pre-challenge serum antibody titres with reduction in death, illness and virus replication in individual animals is highly desirable.

2.1.4 Adjuvants used in H5N1 vaccines

Characteristics and safety of adjuvants

AFO3, a novel oil-in-water adjuvant, has been used by Sanofi-Pasteur in recent phase I and II trials with H5N1 vaccine. AFO3 produced a dose related effect on serological responses with the highest concentration leading to highest antibody titres for two different concentrations of antigen. Of note, reactogenicity and adverse event monitoring also demonstrated an adjuvant dose effect on pain at injection site, but overall no important effect of increased adjuvant on systemic adverse events has been seen so far. A number of preclinical studies in non-human primates, mice and ferrets showed that adjuvanted H5N1 vaccines were safe, immunogenic and protective against a viral challenge.

Alum adjuvant (Al(OH)\textsubscript{3} or Al(PO\textsubscript{4})) has been widely used in several vaccine preparations and extensively described for its capacity to trigger significant Th2-type antibody responses and for its good safety profile when used in large-scale vaccination campaigns in adults, the elderly and children.

ASO3, a novel oil-in-water adjuvant, has been used by GSK in a recent phase III trial involving more than 5000 adults receiving H5N1 vaccine. Higher frequencies of local and systemic reactogenicity were noted with the ASO3-adjuvanted vaccine but these were usually mild and no vaccine-related SAE were observed.\textsuperscript{15} Frequencies of adverse events were lower in the elderly than in younger adults. A phase III trial involving over 35 000 elderly (≥65 years) has been undertaken to compare the effectiveness of an ASO3-adjuvanted seasonal vaccine to a non-adjuvanted one.

MF59 is an oil-in-water adjuvant which has been used by Novartis in various vaccine preparations since 1997 and has extensive clinical trial data for over 28 000 participants from a variety of populations including newborns, children, adults with pre-existing health conditions (including HIV), and the elderly.\textsuperscript{28} An MF59 adjuvanted trivalent influenza vaccine has been approved in the European Union and other countries since 1997. More than 40 million doses of this vaccine have been administered to date, and postmarketing surveillance data are available on 27 million of these doses. The rates of adverse events with MF59-adjuvanted vaccines have been similar to those observed in unvaccinated populations and in those receiving conventional, non-adjuvanted influenza vaccine.
Evaluation of H5N1 vaccine adjuvants and mixed vaccine strategies

Following current US policy, optimization of antigen sparing through the use of currently available adjuvants is being evaluated by “mix and match” studies. These involve determining whether stockpiled H5N1 vaccine antigens manufactured by one company can be used safely and effectively with adjuvants from other manufacturers in anticipation of such an approach during an influenza pandemic under Emergency Usage Authorization. A number of preclinical studies in rodents showed that several mixtures (5µg, 10µg or 15µg of split-virion clade 2 vaccine mixed with either MF59 or ASO3 adjuvants) were safe and immunogenic with comparable seroresponses. Phase I clinical trials are planned to start in April 2009.

2.1.5 Data on shelf-life

There are no published data on the precise shelf-life of currently licensed H5N1 vaccines. Classically, up until now stability has usually been demonstrated up to 24 months for antigen and up to 36 months for adjuvant. The main criterion for assessing stability is the retention of HA content in the antigen preparation. Stability studies have been undertaken by several manufacturers in order to prolong shelf-life of the product. Similar studies on stockpiled vaccine that has passed its expiry date would also be useful.

2.1.6 Prime boost strategies related to use of H5N1 vaccines in the interpandemic period

Using vaccines to prime in anticipation of an influenza pandemic presents an opportunity to provide populations with some protection in advance of an emerging pandemic, where a time lag will invariably exist before exact strain-matched vaccine formulations can be produced. The breadth of immune response to heterologous H5 strains, generation of B cell memory, and the speed and magnitude of antibody responses post-boosting are key criteria when assessing the potential usefulness of priming. The potential for oligovalent priming to multiple subtypes presenting a pandemic threat must be explored, as well as the inclusion of adjuvants in vaccine formulations, especially oil-in-water adjuvants, which have been demonstrated to broaden the immune response more effectively to heterologous viruses and increase the persistence of antibodies. Convincing scientific evidence has been reported on prime-boost regimens using homologous or heterologous boosters up to two years after two-dose priming, while long-term studies illustrated effective two-dose priming followed by a boost up to nine years later. 18,29,30

2.1.7 Effects of seasonal vaccines or pre-existing immunity

Because the seasonal H1N1 virus and the H5N1 influenza virus contain the same subtype of neuraminidase, it has been hypothesized that people with immunity to N1, either following seasonal infection or immunization, may be partially protected from H5N1 infections. A variety of scientific reports provide some support to such a hypothesis. 31,32,33,34 However, the effect of prior seasonal influenza vaccination was assessed in adults and children given Panvax split-virion vaccine and 8% of subjects having received seasonal influenza vaccination displayed a 4-fold reduction in MN seroresponses to H5N1 compared to those not given seasonal vaccination. Another study demonstrated the absence of impact of pre-existing H1N1 antibodies on the seroresponses to Sanofi-Pasteur’s vaccine (derived from Vietnam/1194 strain and alum-adjuvanted). Overall, further studies are needed to determine whether prior seasonal vaccine administration lowers the immune response to H5N1 vaccines and which potential factors, e.g. age and vaccine type, might be relevant.

2.1.8 Development of international standards for H5 antibodies

There is an urgent need to instigate standardized protocols and use reference reagents to facilitate meaningful comparisons between vaccine trial results, as influenza HI and MN serological assay results vary considerably from laboratory to laboratory. 35 An effort towards a candidate international H5N1 antibody standard began after the proposal was adopted by the WHO Expert Committee on Biological Standardization in 2006, which established the first International Standard for antibody to
H5N1 clade 1, “07/150”, designating 1000 international units per ampoule. This standard can now be used in serological assays to compare assay methods and vaccine trial outcomes, both future and retrospectively on stored sera. For clade 2 (and other subtypes), similar standards need to be developed as soon as possible.

2.1.9 Evaluation of H5N1 influenza prototype vaccines in clinical trials

The report of the 5th WHO meeting on evaluation of H5N1 influenza prototype vaccines in clinical trials, held on 12–13 February 2009, provides a detailed overview of the latest developments on the safety, immunogenicity and efficacy of H5N1 influenza vaccines.36

References

36. Hayden F et al. Fifth WHO meeting on the evaluation of pandemic influenza vaccines in clinical trials, 12–13 February 2009 (submitted to *Vaccine*).
2.2 Large-scale demonstration trials

2.2.1 Overview

The preliminary results of the large-scale demonstration trial that has recently been completed in Japan are summarized below. Two other studies are ongoing or planned in Japan, one prime-boost study in 200 subjects to assess immune responses, and another in 200 subjects to evaluate cross-reactivity and antibody persistence six months after vaccination. A decision on whether to vaccinate essential personnel in the interpandemic period will depend on the results and analysis of the trials.

Switzerland is at phase A of a large-scale demonstration trial in 2500 volunteers with their stockpiled GSK vaccine. The trial has two principal objectives: (i) to gain experience in organizing a major vaccination campaign in anticipation of an influenza pandemic; and (ii) to assess whether vaccination interferes with daily life. Although not a safety study, safety issues will be reported. The Swiss authorities do not intend to vaccinate before declaration by WHO of phase 4/5 of an influenza interpandemic.

The US Government has initiated a demonstration trial (under IND) of two 90µg doses of the non-adjuvanted Sanofi-Pasteur vaccine to investigate, in particular, cross-reactivity, which may be broadened in 2010 to include more at-risk groups.

Preliminary results of a proposed study in the Netherlands on the GSK vaccine in 100 adults to evaluate the reactogenicity and immunogenicity of the vaccine and explore the kinetics of antibody responses might be available in early 2010.

2.2.2 Preliminary results from the large-scale demonstration study in Japan

In 2008–2009, a large-scale safety study was conducted in Japan using two licensed H5N1 vaccines, one based on A/Indonesia/5/05 strain (Biken) and the other on A/Anhui/1/2005 strain (Kitasato). Both were egg-derived, whole-virion, alum adjuvanted vaccine containing 15µg haemagglutinin, 0.15mg aluminium hydrochloride, and 4–5µg thimerosal per 0.5mL. Two doses were administered intramuscularly. Preliminary results are provided below.

All 5561 study subjects were healthy volunteers aged 20 years or older (mean age: 40.4) working either for hospitals designated by the Law of Infectious Diseases (the hospitals), quarantine stations, immigration offices, etc. and were vaccinated at the hospitals. Health-care workers (HCWs) at the hospitals represented 97% of the study subjects. The 64 participating hospitals were randomized into either the Indonesia (2726 persons) or Anhui (2835 persons) vaccine by hospital, not by individual. There was no placebo arm. A survey was performed on local and systemic reactions for seven days after each dose and on any other adverse events for 50 days after the first dose.

The proportions of persons with fever (≥37.5°C) were 2.2% and 0.7% after the first and second dose, respectively. The reactions reported between the first and second doses (in average figures) were as follows:

Local reactions: redness 21%, swelling 13%, feverish 13%, itching 15% and severe pain 0.7%.
Systemic reactions: headache 13%, malaise 22% and rhinorrhea 6.0%.

These reactions were more frequent in younger age groups, but no particular difference was identified between the two vaccine strains.

Eight subjects were hospitalized within 30 days after vaccination: five after the first dose (three A/Indonesia/5/05 and two A/Anhui/1/2005 cases), and three after the second dose (one Indonesia and two Anhui cases). All hospitalized cases recovered fully, and an investigation is underway to ascertain whether the adverse events were related to vaccination.
2.3 Epidemiological trends for risk assessment in different groups

2.3.1 Background

This assessment of the risk of human infection with highly pathogenic avian influenza A (H5N1) virus considered the available evidence to date among the following groups: cullers; essential personnel; health-care workers (HCWs); laboratory workers; poultry workers and farmers; public health personnel; and the general public. The sources of data included published WHO H5N1 surveillance summary data and articles published in scientific journals. To date, 10 H5N1 virus clades have been identified, and strains in clades 0, 1, 2 and 7 have infected humans, including 3 subclades of clade 2. For the purposes of this assessment, all clades of H5N1 virus strains were assumed to pose an equivalent risk of transmission to humans; although this may not be valid, no comparative data are currently available.

The risk to an individual in any of the defined groups depends upon specific exposures to H5N1 virus which may occur within or outside an occupational setting, and the behaviour and exposure is more relevant than the person’s occupation. The intensity or dose of H5N1 virus exposure (repeated exposures, level of viral concentration, duration) and route of exposure may influence whether infection occurs. Some protective factors might reduce the risk of infection following exposure to H5N1 virus, e.g. use of appropriate personal protective equipment, antiviral chemoprophylaxis, hand-washing, H5N1 vaccination. Lastly, it should be noted that there could be undefined susceptibility or protective host factors (e.g. age, immunologic, genetic) that might modify the risk of H5N1 virus infection following exposure to H5N1 virus.

2.3.2 Surveillance

Most surveillance for suspect H5N1 cases worldwide is based upon case-finding for hospitalized patients with acute respiratory disease who had recent contact with diseased poultry or with a probable or confirmed H5N1 patient, although the source populations and case definitions vary from country to country. Only a few reports with H5N1 surveillance data have been published. Among ill persons suspected to have H5N1 virus infection, collection of respiratory specimens for H5N1 testing by RT-PCR has yielded variable frequencies of confirmed H5N1 patients. In Thailand, testing of 11,957 clinical respiratory specimens from 5027 suspected H5N1 patients during 2004–2006 yielded 25 confirmed H5N1 cases (0.5%). During 2005–2006, testing of respiratory specimens from 598 suspected H5N1 patients in Indonesia yielded 54 confirmed H5N1 cases (9%).

2.3.3 H5N1 risk factors

Descriptive epidemiological (field investigations) and analytical (case-control) studies have consistently identified direct contact with sick or dead poultry as the primary risk factor for illness resulting from H5N1 virus infection of humans. In addition, having close, but not direct contact with sick or dead poultry, and having sick or dead poultry in the household are identified H5N1 risk factors. One case-control study conducted in 1998 in Hong Kong SAR reported visiting a live poultry market stall the week prior to illness onset as the only significant risk factor for H5N1 illness. A retrospective case-control study in China identified three independent H5N1 risk factors – direct contact with sick or dead poultry, close contact with sick or dead poultry, and visiting a live poultry market. However, in approximately 20% of cases in Indonesia, the source of H5N1 virus exposure could not be determined.

2.3.4 Human-to-human transmission

The assessment of human-to-human H5N1 virus transmission is based upon the findings of epidemiological investigations, with supportive virological data. To date, rare episodes of limited,
non-sustained human-to-human transmission of H5N1 virus have been documented in several countries,\textsuperscript{10,13} including two instances of third generation transmission among blood-related family members.\textsuperscript{12,13} One sero-survey conducted among 91 household, social and HCW contacts of two H5N1 patients found no evidence of H5N1 neutralizing antibodies.\textsuperscript{11}

2.3.5 Overall risk

From 1997 through to 8 April 2009, 437 human cases of infection with H5N1 virus had been identified from 15 countries, resulting in 264 deaths (60% mortality).\textsuperscript{14} The risk of H5N1 virus transmission to humans following exposure to H5N1 virus appears to be very low, but likely depends upon many factors, and epidemiological data to assess the risk among different populations are very limited. Among the risk groups considered in this assessment for SAGE, the highest number of H5N1 cases has occurred among poultry workers and backyard poultry farmers and their household members in rural areas. Only a few H5N1 cases have occurred among cullers or HCWs, and none have been identified among animal health or public health laboratory workers/researchers or essential personnel. For the purposes of this assessment, the risk groups are presented in the order of highest to lowest risk, based on available evidence. Table 2 summarizes the results of sero-epidemiological studies included in the assessment.

2.3.6 Risk groups

Exposure to H5N1 virus could be considered unprotected (no personal protective equipment used), partially protected (some, but inadequate use of personal protective equipment, or breach in protection) or fully protected (appropriate level of personal protective equipment used without breach in protection). For cullers, HCWs, laboratory workers and public health personnel, the risk of H5N1 virus infection from exposure might be reduced if an individual had previously received H5N1 vaccination, and/or was taking antiviral medication for chemoprophylaxis and the H5N1 virus strain was susceptible to that antiviral drug.

(i) Poultry workers and farmers

For this assessment, a poultry worker or poultry farmer is defined as any person who works with live poultry potentially infected with H5N1 virus. These individuals might be exposed to H5N1 virus through the following activities: raising poultry; collecting or transporting poultry or poultry products for sale; selling live poultry or poultry products; or slaughtering live poultry or handling poultry products for sale. The location of these activities might include rural or semi-rural areas where small numbers of poultry are raised for eating or income – backyard poultry raising; medium-to-large commercial poultry farms; or wet poultry markets. Such persons might also participate in culling activities. Exposure to H5N1 virus-infected poultry includes direct or close contact with well-appearing, sick, and dead domestic poultry, and to faecally contaminated environments. The exposure dose or intensity of exposure to H5N1 virus will vary depending upon the number of infected birds and whether repeated exposures have occurred. No H5N1 vaccination programmes are known to have been implemented among poultry workers or farmers.

**Surveillance:** Limited epidemiological data are available, but H5N1 cases have been identified among poultry workers and farmers in several countries. In the published literature, such cases have been documented in China (4 poultry workers without backyard poultry contact),\textsuperscript{7} Indonesia (3 farmers, 2 market workers),\textsuperscript{3} Thailand,\textsuperscript{16} and Viet Nam (3 backyard farmers).\textsuperscript{15}

**Epidemiological studies:** Eleven cross-sectional sero-epidemiological studies, conducted mostly during 2004–2006, suggest that the risk of H5N1 virus infection among exposed poultry workers and farmers in Cambodia, China, Hong Kong SAR, Indonesia, Israel, Nigeria, Thailand and Viet Nam is low, but that transmission occurred. The study populations ranged in size from N = 8 to N = 1525. The study designs were heterogeneous and most had no comparison groups. Additionally, the serological testing methods varied among the studies, including kind of testing – hemagglutination inhibition antibody versus neutralizing antibody detection, and cut-off titres to determine a
seropositive result – and cannot all be compared directly. One study among 231 occupationally exposed persons (raised, slaughtered, sold chickens and ducks) and 983 without occupational exposure in Guangdong, China during 2004 was excluded from this assessment because the serological data are uninterpretable.

Table 2. Published sero-epidemiological studies of H5N1 virus neutralizing antibodies, 1997–2009

<table>
<thead>
<tr>
<th>Study population</th>
<th>H5N1 virus</th>
<th>Country</th>
<th>Year</th>
<th>Outcome</th>
<th>Ref. No.</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poultry workers (N = 1525)</td>
<td>Clade 0</td>
<td>Hong Kong SAR</td>
<td>1997</td>
<td>~10% seropositive</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Poultry market workers</td>
<td>Clade 0</td>
<td>Viet Nam</td>
<td>2001</td>
<td>≤1% seropositive</td>
<td>18</td>
<td>Details and denominator not provided</td>
</tr>
<tr>
<td>(N = 110)</td>
<td>Clade 2.3.4</td>
<td>China</td>
<td>2006</td>
<td>1 (0.9%) seropositive</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Poultry market workers (N = 87)</td>
<td>Clade 2.1</td>
<td>Indonesia</td>
<td>2005</td>
<td>All seronegative</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Rural poultry farmers (N = 322)</td>
<td>Clade 1</td>
<td>Thailand</td>
<td>2004</td>
<td>All seronegative</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Rural villagers, incl. farmers (N = 901)</td>
<td>Clade 1</td>
<td>Thailand</td>
<td>2005</td>
<td>All seronegative</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Rural villagers, incl. farmers (N = 351)</td>
<td>Clade 1</td>
<td>Cambodia</td>
<td>2005</td>
<td>All seronegative</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Poultry workers (N = 295)</td>
<td>Clade 2.2</td>
<td>Nigeria</td>
<td>2006</td>
<td>All seronegative</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Poultry workers (N = 8)</td>
<td>Clade 2.2</td>
<td>Israel</td>
<td>2006</td>
<td>All seronegative</td>
<td>24</td>
<td>Had received oseltamivir chemoprophylaxis</td>
</tr>
<tr>
<td>Rural villagers, incl. farmers (N = 674)</td>
<td>Clade 1</td>
<td>Cambodia</td>
<td>2006</td>
<td>7 (1%) seropositive</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Rural villagers, incl. farmers (N = 841)</td>
<td>Clade 2.1</td>
<td>Indonesia</td>
<td>2005</td>
<td>All seronegative</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Health care workers (N = 217)</td>
<td>Clade 0</td>
<td>Hong Kong SAR</td>
<td>1997</td>
<td>8/217 (3.7%) seropositive</td>
<td>29</td>
<td>2 HCWs had evidence of seroconversion after patient contact</td>
</tr>
<tr>
<td>Health care workers (N = 87)</td>
<td>Clade 1</td>
<td>Viet Nam</td>
<td>2004</td>
<td>All seronegative</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Health care workers (N = 42)</td>
<td>Clade 1</td>
<td>Viet Nam</td>
<td>2004</td>
<td>All seronegative</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Health care workers (N = 25)</td>
<td>Clade 1</td>
<td>Thailand</td>
<td>2004</td>
<td>All seronegative</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Government cullers (N = 293)</td>
<td>Clade 0</td>
<td>Hong Kong SAR</td>
<td>1997</td>
<td>9 (3%) seropositive</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Animal laboratory workers (N = 25)</td>
<td>Clade 2.2</td>
<td>Nigeria</td>
<td>2006</td>
<td>All seronegative</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Contacts of 2 H5N1 patients (N = 91)</td>
<td>Clade 2.3.4</td>
<td>China</td>
<td>2007</td>
<td>All seronegative</td>
<td>11</td>
<td>Included household, social and HCW contacts (son-to-father transmission)</td>
</tr>
</tbody>
</table>

(ii) Health-care workers

A HCW is defined here as a person providing medical care to a patient potentially infected or confirmed to be infected with H5N1 virus. These HCWs might be exposed to H5N1 virus through the following activities: caring for an H5N1 patient; examining an H5N1 patient; touching clothing or surfaces contaminated with body fluids containing H5N1 virus (e.g. respiratory droplets from coughing, diarrhoea); collecting clinical specimens from an H5N1 patient; suctioning the patient; intubating the patient; or administering aerosolized medications. The intensity of the exposure to H5N1 virus will depend on the clinical status of the H5N1 virus-infected patient (severity/level of H5N1 viral shedding, symptoms, mechanically ventilated), repeated exposures, duration of exposure, and whether infection control measures were observed and personal protective equipment used appropriately.
**Surveillance:** One case of patient-to-HCW transmission was reported in Viet Nam in an unprotected nurse.\(^28\)

**Epidemiological studies:** Limited sero-epidemiological data suggest that the risk of H5N1 virus transmission from patient-to-HCW is low, but has occurred. Four sero-epidemiologic studies have been published, including one from 1997 (clade 0) and 3 from 2004 (clade 1).\(^29\)-\(^32\) No published data are available among HCWs since 2004.

**(iii) Cullers**
For this assessment, a culler is defined as any person involved in containment activities related to killing or disposal of wild birds or domestic poultry potentially or known to be infected with H5N1 virus. Cullers might be exposed to H5N1 virus through the following activities: killing of well-appearing or sick birds infected with H5N1 virus; disposal of dead birds infected with H5N1 virus; or disinfection of surfaces contaminated by birds infected with H5N1 virus. The exposure dose or intensity of exposure to H5N1 virus will vary depending on the number of infected birds and whether repeated exposures have occurred. Culling activities might occur in rural areas in backyard poultry farms, commercial poultry farms, urban or rural wet poultry markets, wetlands where dead wild birds are found, or in other environments. No H5N1 vaccination programmes are known to have been implemented among cullers.

**Surveillance:** Of the confirmed H5N1 cases, only one has occurred among cullers.\(^12\) This individual was a 25-year old livestock production officer involved with culling and disposal of poultry in Pakistan in October 2007 who was infected with clade 2.2 H5N1 virus. The individual was not using protective equipment.

**Epidemiological studies:** No epidemiological data are available on the risk of H5N1 virus infection among cullers since 1997, and the evidence is therefore insufficient to determine the risk of H5N1 virus infection among this group. Only one study assessed the risk of H5N1 virus infection among government workers who participated in the culling and disposal of poultry during the 1997 outbreak in Hong Kong SAR (N = 293); 9 (3%) were seropositive for H5N1 neutralizing antibodies, and 1/229 with paired sera had evidence of seroconversion.\(^17\)

**(iv) Laboratory workers**
A laboratory worker is defined as any person potentially exposed to an H5N1 virus-infected patient or animal, to a clinical specimen from an H5N1 patient, or to a specimen from an H5N1 virus-infected animal, or to live H5N1 virus.\(^*\) Laboratory workers might be exposed to H5N1 virus through the following activities: collecting specimens from H5N1 patients or infected animals; processing specimens in a laboratory; performing H5N1 testing on clinical or autopsy specimens, including conducting virus isolation or serological testing using live H5N1 virus; performing research with live H5N1 virus, including in vitro work or with animals experimentally infected with H5N1 virus; or large-scale production or manipulation of H5N1 virus. The exposure dose or intensity of exposure will vary depending upon the H5N1 patient’s clinical status, the quantity of virus in clinical specimens, the kind of clinical specimens, the concentration of virus used in experimental research, the level of infection control containment in the laboratory setting, and the behaviour of the individual laboratory worker during exposure to H5N1 virus.

**Surveillance:** Of the confirmed H5N1 cases since 1997, none have occurred in animal or public health laboratory workers to date, but the available evidence is insufficient to determine the risk of H5N1 virus infection for persons working in these settings.

**Epidemiological studies:** No studies have been published on laboratory workers exposed to clinical specimens from H5N1 virus-infected patients or to H5N1 virus, and only one small H5N1 sero-epidemiological investigation has been conducted among animal laboratory workers. This study found

\(^*\) Exposure to H5N1 viral RNA is not considered an exposure to H5N1 virus because viral RNA is non-infectious.
no evidence of H5N1 neutralizing antibodies among 25 Nigerian laboratory workers who were exposed to specimens from suspected or confirmed clade 2.2 H5N1 virus-infected poultry in 2006. 23

(v) General public
The risk of H5N1 virus infection among the general public depends upon the definition of “general population” and whether a population is exposed to H5N1 virus, e.g. to H5N1 virus-infected animals or contaminated environments. In countries or areas without documented or suspected H5N1 virus-infected animals, the risk to the general population should be zero. The risk among the general population in urban areas with H5N1 virus-infected animals (e.g. wet poultry markets) or in rural communities with backyard poultry infected with H5N1 virus may be low, but greater than zero, and depends on specific exposure to H5N1 virus and potentially on unknown host factors. Age may be a factor since most H5N1 cases have occurred among children and young adults. Clusters of cases among blood-related family members3,4,10-13,25,33 suggest the possibility of an elevated risk of H5N1 virus infection in some individuals compared to the general population, although this needs further investigation.

(vi) Public health personnel
No H5N1 cases have been identified among public health personnel, and no epidemiological data are available to assess the risk of H5N1 virus infection in this population. For this assessment, public health personnel are defined as public health workers who have participated in investigations of persons suspected or confirmed to be infected with H5N1 virus. Public health personnel could be exposed to H5N1 virus through the following activities: exposure to suspected H5N1 cases; examination of H5N1 patients; collection of specimens from H5N1 patients; collection of animal specimens or environmental samples containing H5N1 virus; visiting settings contaminated with H5N1 virus (wet poultry markets, backyard poultry farms, patient’s homes); visiting clinics and hospitals, or other activities.

(vii) Essential personnel
To date, no H5N1 cases have been identified among essential personnel and there are no data to assess the risk of H5N1 virus infection among this population. In general, the risk of H5N1 virus infection depends upon the risk of exposure to H5N1 virus, which might occur during performance of activities related to essential personnel work, or outside of such duties. Agreement on how “essential personnel” should be defined is needed.

2.3.7 Conclusions
Overall, the risk of H5N1 virus transmission to humans following exposure to H5N1 virus appears to be very low to date, but most likely depends upon many factors, and epidemiological data to assess the risk among different populations are very limited. Notably, each group assessed contains a heterogeneous population with a range of possible exposures to H5N1 virus, making it difficult to ascertain their risk of infection. The key issues are the intensity of exposure to H5N1 virus, modifiable factors such as behaviour or use of protective equipment, and possibly unknown host factors. Data suggest that blood-related family members of a confirmed H5N1 case could be at higher risk of H5N1 virus infection than other exposed individuals, but this remains unproven.

The risk of H5N1 virus transmission to exposed poultry workers and farmers is low, but higher than in other groups, due to exposure to sick or dead H5N1 virus-infected poultry. The risk of patient-to-HCW transmission appears to be very low, and can be reduced with use of appropriate personal protective equipment and implementation of infection control measures. The risk of H5N1 virus transmission to cullers appears to be low, but one confirmed H5N1 case was identified and a low frequency of H5N1 neutralizing antibodies detected among cullers in one cross-sectional sero-survey. Since no H5N1 cases have been identified among animal and public health laboratory workers exposed to specimens containing H5N1 virus or researchers working with live H5N1 virus, the risk of H5N1 virus transmission to this population appears to be very low, but data are insufficient to quantify any risk. The risk to the general public cannot be determined, but is likely to be very low in
countries where H5N1 virus strains are circulating among poultry. However, the risk to the general public depends upon the urban versus rural setting, and specific exposures to H5N1 virus. No cases have been identified among public health personnel or essential workers, but no epidemiological data are available to assess the risk in these groups.

2.3.8 Need for additional data

Available data are lacking to estimate the current risk of H5N1 virus transmission among different populations and occupational groups worldwide. Detailed epidemiological data are needed to inform the risk of H5N1 virus infection among people living in countries experiencing H5N1 poultry outbreaks. Since H5N1 virus strains continue to circulate and evolve among poultry in many countries, detailed epidemiological assessments will be needed in the future since the risk of H5N1 virus transmission to exposed groups may change.

References


2.3(A) The risk of infection to health-care workers compared to non-healthcare workers

Preliminary work was carried out by the UK Health Protection Agency two to three years ago to assess whether health-care workers (HCWs) have experienced increased levels of infection during pandemic, epidemic and seasonal influenza using a number of possible markers for illness; ranging from mortality, hospitalization and illness data and sickness absence data as a proxy for illness. The literature search that was carried out identified a limited number of studies going back to 1918. There is limited information available on the mortality and morbidity of influenza in HCWs compared to non-HCWs and the majority of the studies relating to HCW experience of influenza-like illness (ILI) is more contemporary and relates to sickness absence.

Preliminary analysis of existing studies

Pandemic influenza

Data on mortality in the 1918 pandemic suggest that rates among HCWs were not substantially higher than among non-HCWs and may even be lower (though this may be confounded by a “healthy worker effect” if HCWs are compared to the general population. Data on absenteeism from 1918 were not found. Data from the 1957 pandemic were limited, but suggest that while rates for all causes in HCWs may be high, up to 20% at the peak, this is not substantially higher than that reported by other industries. While more extensive data on non-HCWs were available for 1968, there were no suitable data on HCWs.

Seasonal influenza

During seasonal influenza, typical absenteeism rates in HCWs due to influenza across the flu season were less than 10%. Peak incidence due to influenza is likely to be less than 5%.

Non-HCWs in seasonal influenza: absenteeism in workplaces varies considerably across the reports documented. Reported absenteeism due to ILI varies from 5–26%, typically being around 10%. However, national measures of absenteeism tend to be lower, of the order of 1–5%.

During seasonal influenza, the excess absenteeism rate across the flu season due to influenza for both HCWs and non-HCWs tends to be in the range of 5–10%. Based on the current preliminary analysis it appears that rates of absenteeism among HCWs and non-HCWs were not consistently different for seasonal or pandemic influenza.

It must be stressed that these preliminary conclusions are based on an initial appraisal of the available studies and these may change following further analysis.

Current work plan

The original literature search is being repeated and widened to include additional terms and search engines. The potential role of confounding factors such as vaccination of HCWs will be explored. The possibility of using UK mortality data relating to the 1918, 1957 and 1968 pandemics is being explored to identify whether there was an excess of deaths in HCWs.
2.4 Pathogenesis and transmission

2.4.1 Overview

Multiple molecular determinants affect influenza virus virulence and transmission. The constellation of genes and gene mutations that contribute to these traits are both virus and host dependent. Although enhanced virulence is not a requirement of a pandemic strain, efficient transmissibility among humans is essential, and remains a key trait lacking in contemporary H5N1 viruses. Although the factors allowing an influenza virus to acquire pandemic capability are poorly understood, the accumulation of human host-specific adaptive mutations is critical. Because influenza viruses have a segmented genome, they have the unique capability of undergoing gene reassortment to generate entirely novel viruses. If a virus with a novel haemagglutinin (HA) is generated from this process that has the ability to cause disease and spread efficiently among humans that lack immunity to the novel HA, a pandemic could occur. The H2N2 pandemic in 1957 arose when a circulating human influenza virus acquired the H2, N2 and PB1 genes from an avian influenza virus. Similarly, the H3N2 pandemic in 1968 occurred after a circulating human influenza virus acquired the H3 and PB1 genes from an avian influenza virus.1 Previous pandemic viruses crossed the species barrier after acquiring mutations that changed the binding preference of the HA from avian-like, to human-like.2-5 Although highly pathogenic avian influenza (HPAI) H5N1 viruses continue to cause limited human infections, whether they are capable of acquiring genetic changes necessary for efficient and sustained transmission among humans, either through genetic reassortment or acquisition of key point mutations, or both, remains unknown.

Much of our current knowledge on the molecular basis of the pathogenicity and transmissibility of HPAI H5N1 viruses in mammals is derived from studies in animal models.6-11 Such models have been used widely to identify general molecular determinants that contribute to enhanced virulence as well as mechanism of spread of influenza viruses in humans. Here we first review the current knowledge on the molecular basis of pathogenicity and transmissibility of HPAI H5N1 viruses in animal models and then discuss the properties of HPAI H5N1 viruses isolated from confirmed H5N1 virus-infected cases.

2.4.2 Genetic determinants of pathogenicity of HPAI H5N1 viruses in mammalian models

Surface glycoproteins

The HA molecule, the major surface glycoprotein and the target of neutralizing antibody, mediates the attachment to and entry into host cells through binding to sialic acid (SA) residues on host cell glycoproteins and glycolipids. Human and avian influenza viruses differ in their preferred binding to SA moieties and this is the basis of influenza virus host range and tissue tropism within a host. Avian influenza viruses preferentially recognize SA in an α2,3 linkage to galactose, whereas human influenza viruses preferentially recognize SA in an α2,6 linkage to galactose, the major glycans found on avian gut epithelia and human respiratory tract epithelia, respectively. The importance of this receptor binding preference will be discussed in more detail below.

Cleavage of the HA glycoprotein of influenza virus into HA1 and HA2 by host cell proteases, is an essential step for virus fusion during infection and is a prerequisite for infectivity. The amino acids around the HA cleavage site determine the susceptibility of the HA to host proteases and has been identified as a determinant of tissue tropism for influenza viruses (reviewed in [12]). Avian influenza viruses are considered to be of either high or low pathogenicity (HPAI or LPAI) based on their intravenous pathogenicity index in experimentally inoculated chickens.13 LPAI and human influenza viruses have a cleavage site that is cleaved by host trypsin-like proteases that limit the virus to tissues of the intestinal or respiratory epithelium, respectively. On the other hand, HPAI, including H5N1
viruses, possess additional basic amino acids within the HA cleavage site that make the HA susceptible to a wider range of proteases that are ubiquitous in multiple tissue and organ types, which allows these viruses to replicate systemically. Removal of the multibasic amino acid motif changes the virulence of H5N1 viruses from a fatal systemic infection to a localized non-pathogenic infection in mice.\textsuperscript{14} However, in mammalian models, the presence of the multibasic cleavage site in the HA of HPAI H5N1 viruses does not uniformly confer high virulence, indicating that while the multibasic cleavage site is critical for virulence, it is not sufficient, and that additional virulence determinants are involved.\textsuperscript{14-16} Removal of the multibasic cleavage site of HPAI H5N1 viruses together with the introductions of base substitutions to stabilize the removal of multiple basic amino acids is considered to be a critical step to attenuate H5N1 vaccine reassortant strains.\textsuperscript{17} This process also increases the safety of the reassortants for humans, reducing environmental risks for avian species and enhances growth characteristics of the reassortant in embryonated eggs.

The second glycoprotein on the viral surface is the neuraminidase (NA) which functions as a sialadase to release the progeny virions from the host cell and promote the spread of the virus within a tissue. A functional balance between the HA receptor affinity and the NA sialidase activity is required for efficient viral replication, but this optimal balance may differ between hosts and in vivo versus in vitro systems. With few exceptions, HPAI H5N1 viruses that have circulated in birds since 1996 have a 19-20 amino acid deletion in the stalk region of the NA, a common feature of HPAI viruses in terrestrial poultry which accompanies the acquisition of additional glycosylation sites in the HA.\textsuperscript{18-20} Compared to H5N1 viruses with a long stalk NA, viruses with a short stalk NA showed increased virulence in mice, which was further enhanced in viruses lacking glycosylation at key sites on the HA.\textsuperscript{21} Further studies are needed to better understand the contribution of the NA in H5N1 virulence in mammals.

The polymerase complex
Influenza virus replication is controlled by the viral RNA-dependent RNA polymerase complex responsible for the synthesis of viral and message sense RNA. In general, a high virulence phenotype has been associated with increased levels of virus replication both in vitro and in vivo. The polymerase complex is composed of the PA, PB1 and PB2 proteins and the nucleoprotein (NP) which is associated with the RNA segments. The polymerase complex has been identified as a virulence determinant of H5N1 viruses, although phenotypes vary among animal models. In the PB2 protein, a Lys at amino acid 627 confers enhanced viral replication in mammalian epithelial cells, in particular at lower temperatures, similar to those of the upper respiratory tract of humans.\textsuperscript{22,23} The presence of a Lys at 627 or an Asn at 701 in the PB2 protein confers high virulence for H5N1 viruses in inbred mice, but not in ferrets.\textsuperscript{14-16,24} Additional studies have also implicated the polymerase complex in HPAI virus virulence and virus adaptation to mammalian hosts,\textsuperscript{25,26} and identified efficient polymerase activity as a virulence marker. In a study that generated 63 possible hybrid H5 and N1 bearing viruses that could emerge through reassortment between an avian H5N1 virus and a contemporary human H3N2 virus, hybrid viruses that possessed the PB1 gene in addition to the H5 HA and N1 NA, exhibited the highest virulence in mice.\textsuperscript{27} However, in this case, this enhanced virulence did not appear to be directly related to in vitro polymerase complex activity. The PB1 gene also encodes a recently identified protein, PB1-F2, which is derived from an alternate open reading frame and has been shown to contribute to virulence in mice.\textsuperscript{28,29} PB1-F2 promotes apoptosis, particularly in monocytes, which may contribute to modulation of the host immune response.\textsuperscript{28-33} A serine at residue 66 of PB1-F2 was associated with high virulence of the 1997 H5N1 viruses in mice.\textsuperscript{33} However, this mutation is not found in more contemporary HPAI H5N1 viruses, including those which exhibit high virulence in animal models. Further studies are needed to assess the role of PB1-F2 in virulence of H5N1 viruses, and influenza viruses in general.

The NS1 protein
The NS1 protein of influenza viruses is a multi-functional protein that acts as a virulence determinant by disrupting the type I interferon response of hosts and preventing an antiviral state in infected cells from being achieved.\textsuperscript{34,35} H5N1 viruses isolated in 1997 were resistant to the effects of type I interferon and TNF\textalpha in a porcine model; a glutamic acid at position 92 of the NS1 was required for
the inhibitory effect. NS1 has also been found to contribute to high virulence of 2003 HPAI H5N1 viruses for mice, although in this case a serine at residue 42 was implicated in undermining the host antiviral response. H5N1 viruses also possess a four amino acid motif at the carboxy-terminal of NS1 which is a protein-protein recognition module (PDZ ligand) that organizes cell signaling. This motif has also been associated with enhanced virulence in mice.

In summary, HPAI H5N1 virus virulence is dictated by multiple determinants encoded on multiple gene segments. One caveat common to some of the above mentioned studies is that molecular determinants are evaluated on a virus backbone other than an H5N1 virus and so the exact contribution of the gene product or mutation for virulence of H5N1 virus is unclear. Furthermore, most determinants have been revealed through studies in only one animal model, most commonly in mice, and validation of their role in virulence is needed in other, outbred models.

2.4.3 Genetic determinants of transmissibility of HPAI H5N1 viruses in mammalian models

Transmissibility of influenza viruses among humans is a complex and polygenic trait. The genetic changes necessary for H5N1 influenza viruses to adapt to humans and acquire efficient and sustained transmissibility are not known. Genetic changes in one or both major surface glycoproteins as well as one or more internal proteins are likely to be required. It remains unclear whether the H5N1 viruses are capable of acquiring stable genetic changes necessary for pandemicity.

The HA protein
Mutations in the HA that enable binding to human-like α2,6 SA and concomitant reduction in affinity for avian-like α2,3 SA are considered to be an essential adaption required for efficient transmission of influenza viruses among humans. Such changes are likely to result in higher efficiency replication in α2,6 SA-rich respiratory epithelium of the human upper airways, potentially augmenting viral spread from infected persons during coughing or sneezing. Through the use of glycan array technology it is now possible to measure the relative binding of viral HA to α2,6 SA- and α2,3 SA-bearing glycans. A number of reports have identified mutations in the clade 1 H5 HA which confer some modest affinity for α2,6 SA. However, overall binding remained predominantly avian α2,3 SA specific. These included two key changes that switched HA binding specificity from avian-like to human-like in the previous H2N2 and H3N2 pandemic strains (Gln226Leu and Gly228Ser). However, on the H5 HA these changes had only modest effects in increasing HA binding to α2,6 SA and decreasing binding to α2,3 SA. A different set of mutations (Glu190Asp, Gly225Asp) that were found to switch receptor specificity for H1N1 viruses, completely abolished binding to both α2,3 SA and α2,6 SA when introduced to the H5 HA. Interestingly, a more recent study by Stevens et al. focusing on clade 2 H5N1 viruses, has identified two naturally occurring mutations on the H5 HA, residue 193Arg and the loss of the glycosylation site at 158, that together with the H3 receptor switching mutations (Gln226Leu and Gly228Ser) enhance binding to human-like receptors. Contemporary clade 2.2 viruses possess these mutations. Since chickens possess both avian- and human-like receptors in the trachea and intestine, continuing circulation of H5N1 viruses in this species may provide a means for emergence of an H5N1 virus with receptor/binding properties that favour infectivity and transmissibility in humans.

The PB2 gene
Recent transmission studies in guinea pigs and ferrets have identified a role for the PB2 gene in influenza virus transmissibility. Van Hoeven et al. demonstrated that the PB2 gene, together with the HA and NA of the 1918 H1N1 pandemic virus were sufficient for airborne transmission of an avian influenza virus in the ferret transmission model. Viruses which transmitted through the air in the ferret model also exhibited increased efficiency in replication in epithelial cells at a lower temperature (33°C), similar to that found in mammalian airways. Steel et al., found that the 627Lys residue in PB2 was associated with transmission of H5N1 virus by direct contact in guinea pigs, but that mutation to a 627Glu residue reduced transmission substantially. However, introduction of an asparagine at residue 701 together with 627Glu residue in PB2, restored the direct contact
transmission phenotype. It should be noted that it has not yet been possible to generate an H5N1 virus that transmits efficiently through the air in animal models. Nevertheless, these new studies suggest a previously unrecognized role for the PB2 gene in transmission of influenza viruses.

Avian H5N1 – human H3N2 reassortment
Reassortment between an HPAI H5N1 virus and a circulating human influenza virus is one way in which a pandemic H5N1 virus could emerge. To evaluate the potential for such an event, several studies have used reverse genetics to generate in cell culture, viruses that contain the surface glycoproteins of H5N1 viruses and one or more internal proteins of a human H3N2 virus. Viruses that possessed the 1997 H5 and N1 genes and four or six internal genes from a human H3N2 virus were generated but exhibited reduced replication in ferrets, compared with either parental virus and no airborne transmission. In another study, 63 reassortant combinations derived from a clade 1 2004 HPAI H5N1 virus and 2003 human H3N2 virus were generated and approximately 50% of these viruses replicated efficiently in vitro, indicating a high degree of compatibility between avian and human virus genes, although the capacity for transmission was not evaluated in this study. In a parallel study, ferrets were co-infected with the same HPAI H5N1 clade 1 2004 and human 2003 H3N2 viruses (Jackson et al., submitted for publication). Taken together, these studies confirm that reassortment between H5N1 and human H3N2 viruses can occur, and that continued exposure of humans and animals to H5N1 viruses, in the context of seasonal influenza virus circulation, increases the risk for the generation of an H5 reassortant that may acquire pandemic potential.

2.4.4 Molecular features of HPAI H5N1 viruses isolated from humans
Despite widespread exposure to HPAI H5N1 infected poultry, human HPAI H5N1 virus disease remains rare. Since late 2003, the overall fatality rate among over 400 human cases is approximately 60%, although case-fatality proportions vary by region.

Genetic diversity among H5N1 viruses in avian species
HPAI H5N1 viruses are now enzootic among wild birds and domestic poultry in three continents. Clade 0 viruses have not circulated widely in poultry since 1997. However, since then, the HPAI H5N1 virus lineage has undergone extensive genetic reassortment with viruses from different sources to produce numerous genotypes and develop the multiple clades and subclades that exist in birds today. It is important to note that the evolution of the H5 HA in avian hosts is different from the evolution typically observed for human HA genes. While human HA exhibits limited diversity at any one time because of extinction of previous clades or lineages, H5 genes of multiple clades and lineages co-evolve and co-circulate in different regions and avian species.

Molecular features of HPAI H5N1 viruses isolated from humans
To date, the genes from all H5N1 viruses isolated from humans are wholly avian in origin and retain the multibasic amino acid cleavage site motif characteristic of HPAI H5N1 viruses circulating in avian species. Although there is some variation in the cleavage site motif due to geographic differences, there has been no association with disease severity among humans. The HA of H5N1 viruses isolated from humans retain the avian-like α2,3 SA sialic acid receptor binding preference, similar to H5N1 viruses isolated from avian species. Occasional human isolates that exhibit modest enhancement of human-like α2,6 SA sialic acid receptor binding have been reported, but the associated point mutations in HA have not become established in H5N1 viruses isolated from either birds or humans. As noted above, clade 2.2 viruses possess mutations at residues 158 and 193, that have been implicated in the overall transition to human-like receptor binding preference which is considered to be essential for transmission among humans. Nevertheless, these viruses presently retain avian-like receptor binding properties. Where one or more H5N1 viruses have been isolated and characterized from human disease clusters, there are no obvious mutations in HA to suggest human adaptation (CDC unpublished data). All H5N1 viruses isolated from humans to date possess a 19–20 amino acid deletion in the stalk region of the NA. The consequences of this deletion for virulence or transmissibility in humans is not known.
The majority of H5N1 human isolates possess the 627Lys residue in PB2 which has been associated with mammalian adaptation, replication at lower temperatures similar to that of human upper airways, and virulence in mice (see above). Some human H5N1 viruses that possessed the 627Glu in PB2 have a 701Asn residue, which has also been implicated in virulence in mice and direct contact transmission in guinea pigs. However, these mutations do not correlate generally with differences in mortality among humans. A recent study determined that for a small number of H5N1 virus-infected patients, viruses in original clinical material were heterogeneous with respect to mutations in PB2, suggesting that selection of mutations may occur upon laboratory isolation of viruses. Although clade 1 and clade 2.1 H5N1 viruses isolated from birds possessed a 627Glu in PB2, considered to be the avian-like residue, a larger proportion of clade 2.2 viruses isolated from birds possess 627Lys substitution in PB2. PB2 genes with either 627Glu or 627Lys have been detected in viruses isolated from human-to-human transmission cases. Further studies are necessary to determine whether these mutations are indeed markers for H5N1 virus adaptation in humans.

Most H5N1 viruses including those isolated from humans contain the four amino acid motif at the carboxy-terminal of NS1 which is associated with virulence in mice. At this time, the importance of this and other sequence variations in the NS1 gene of H5N1 viruses isolated from humans is not known.

2.4.5 Resistance to antiviral drugs

Recent experiences with global circulation of aminoadamantane-resistant A/H3N2 and oseltamivir-resistant A/H1N1 viruses highlight that the widespread transmission of a drug-resistant pandemic influenza A virus might render some current antiviral stockpiles ineffective.

2.4.6 Gaps in knowledge

Clearly, information on the key genetic changes that could enable H5N1 viruses to transmit in a sustained manner among humans is lacking. As HPAI H5N1 viruses continue to evolve in avian species, it is important to characterize and compare properties of H5N1 viruses from both human and avian sources on an ongoing basis. Several risk assessment tools, including glycan array technology, tissue-binding arrays, and animal models should be used in combination to continue to monitor for changes in H5N1 virus receptor binding and transmission properties in circulating H5N1 viruses. Further research on genetic and biologic properties of transmissible influenza viruses compared with poorly transmissible avian H5N1 viruses, is needed to understand not only their genetic properties, but also precise receptor usage in human tissues, locations within respiratory tract and consequences for transmission. Studies of virulence are also important as they will contribute to our understanding of whether genetic changes required for human adaptation of H5N1 viruses will also modify their ability to induce severe and fatal human disease. Furthermore, such studies can lead to improved therapeutic strategies for H5N1 virus infected patients.

References


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2.5 Correlates of protection

Virus-specific neutralizing antibodies directed against the influenza virus haemagglutinin (HA) are the major mediator of protection against subsequent infection with influenza viruses. The haemagglutination-inhibition (HI) assay is commonly used to measure serum antibody responses and is considered a surrogate for the detection of neutralizing antibodies in serum from infected or vaccinated humans. An HI titre of 1:32 to 1:40 is often reported as a “protective titre” but actually represent a titre at which approximately 50% of individuals in a population would be protected from infection with or disease from seasonal influenza viruses. Since quality as well as quantity of antibody is important, there is no absolute titre at which protection from infection is guaranteed. Because of their increased sensitivity compared with traditional HI assays, neutralization assays have been used to detect HA-specific antibodies to H5N1 viruses or vaccines. However, currently there is no known “protective titre” equivalent for antibody detected by neutralization assays. Licensure of H5N1 vaccines has been based on immunogenicity and protective (HI titre) correlates developed for seasonal influenza virus vaccines. It is not known whether the so-called protective HI titres provide a comparable level of protection in a human population against HPAI H5N1 viruses.

Influenza virus infection or vaccination induces various humoral and cellular responses in addition to neutralizing or HI antibodies, many of which likely also contribute to effective protection from influenza virus infection or disease in humans. The degree to which these immune mediators are important for protection against seasonal viruses, or avian HPAI viruses with pandemic potential remains to be determined. These other humoral and cellular responses induced by infection, and in some cases, vaccination are described briefly below.

Antibodies that do not neutralize viral infectivity, but target other, more conserved, regions of the HA molecule may also play a role in protection. Such antibodies may act by blocking fusion or target epitopes on virus-infected cells through antibody-dependent cellular cytotoxicity. However, the extent to which such non-neutralizing anti-HA antibodies are induced by influenza vaccines, and in particular H5N1 vaccines, is not known. Antibodies to the neuraminidase (NA) can block the enzymatic function of the protein which is important for the successful release of progeny virus from the infected cell. Therefore, although anti-NA antibodies cannot prevent virus infection, they contribute to reducing viral load and disease severity. Compared with anti-HA antibodies, NA-specific antibodies are induced in a smaller proportion of inactivated or live attenuated influenza vaccine recipients. However, improved assays to quantify NA-specific antibody titres are needed to further our understanding of this immune correlate. Antibodies directed against the ectodomain of the transmembrane M2 protein of influenza A viruses have been shown to reduce the severity of influenza infection in mice. M2 antibodies can be detected in human serum following influenza A infection, but evidence for a protective role in humans is lacking. Furthermore because there is likely to be very little, if any, M2 protein in split, subunit and even whole virus vaccines, anti-M2 antibodies are unlikely to be induced by such vaccines. Local (nasal wash) IgA has also been shown to correlate with protection, particularly after vaccination with LAIV. The IgA induced post-vaccination is predominately of the secretory polymeric IgAI subclass. However, split or whole virus or subunit vaccines that are administered intramuscularly generally are inefficient in inducing mucosal antibody responses.

The cellular arm of the immune response also plays an important role in the induction of protective immunity to influenza. However, there is general uncertainty as to the extent to which T cell-mediated immunity directly contributes to the resolution of viral infections in humans. CD4+ T helper cells have an indirect role by producing cytokines that regulate both antibody and other T cell responses, but do not have a direct antiviral effector role in protection. Most influenza virus proteins contain epitopes recognized by CD4+ T helper cells, which are induced or recalled following vaccination. In contrast to CD4+ T cells, CD8+ cytotoxic T cells have a direct antiviral effector function in the recognition and destruction of virus-infected cells through the release of cytolytic molecules, or other interactions that induce apoptosis. Limited studies have demonstrated a role for CD8+ cytotoxic T cells in enhanced
resolution of virus shedding during influenza infection in humans in the absence of detectable serum neutralizing antibody responses. In a recent study, cell-mediated immune responses were found to complement antibody titres in the evaluation of seasonal influenza vaccination effectiveness in the elderly. Taken together, the available evidence suggests that CD8+ cytotoxic T cells may play a significant role in protection against influenza virus infections in humans under certain circumstances. Epitopes recognized by CD8+ T cells are generally found on internal proteins of influenza that are more highly conserved between subtypes, including H5N1 viruses, and therefore are a target for more broadly cross-reactive vaccines. However, optimal induction of CD8+ T cells will require newer vaccine delivery approaches, such as the use of live attenuated or novel viral vector vaccines.

References

2.6 Assessment of risks in different groups for adverse events following immunization

2.6.1 Overview

Safety issues may be related either to the influenza-related component of the vaccine (influenza proteins, contaminants) or to additional vaccine components (e.g. adjuvant).

Although about 18 000 people have now received one or another H5N1 vaccine, data available for each vaccine are still very limited. The likelihood of detecting serious adverse events (SAE) in studies of H5N1 vaccines can be estimated from the data compiled to date.

The analysis indicates that the individual vaccine trial sizes studied to date provide confidence only in excluding high frequencies of related SAE. In the same way, it is also possible to determine the risk of an SAE according to various categories of adjuvant and formulation. Even when the increased sample gained by combining studies of related vaccines, the ability to exclude related SAE at 95% level of confidence is modest, with upper boundaries of event rates ranging from 1 in 579 (split/subunit + alum) to 1 in 3896 (oil-in-water adjuvants).

Therefore, although it can generally be said that whereas available safety data do not indicate particular concerns, this only allows the assessment of common adverse effects and does not exclude rare or longer term adverse events. Safety considerations for non-adjuvanted H5N1 vaccines are very similar to those related to annually modified influenza vaccines.

2.6.2 Influenza vaccine-related potential safety issues

Rare SAE have been previously recorded with influenza vaccines. The main risk previously identified is the post-vaccination occurrence of Guillain-Barré syndrome (GBS). GBS occurred in about 1/100 000 following the use of a Swine Influenza (swine flu) vaccine in 1976–1977. The neurological adverse event was considered causally related to this vaccination. Today this risk cannot be predicted from preclinical and initial clinical studies. It can only be detected through appropriate postmarketing surveillance. However, GBS is often associated with the occurrence of anti-ganglioside antibodies that can affect the neural node function. Some influenza vaccines (egg grown), including the swine flu vaccine, were recently shown to induce anti-ganglioside antibodies in mice. It was hypothesized that egg contamination with minute amounts (undetectable) of Campylobacter jejuni might be the cause of the anti-ganglioside response. It may be useful to establish whether sera from recipients of the H5N1 vaccines do contain anti-ganglioside antibodies.

It is possible to use statistical power calculation to estimate the population size required to detect an elevated risk of GBS in the case of mass H5N1 vaccine administration. Assuming that the risk of GBS associated with an H5N1 vaccine might be similar to that of the 1978 swine flu vaccine (attributable rate of 8.8 cases per million vaccinees within six weeks of vaccination) and a GBS background rate of 0.7 to 4.6 cases per million, an indicative vaccinated population size of between approx. 409 000 to 970 000 would be required to demonstrate that the adverse event rate in vaccinated individuals is greater than the background rate. However, in the absence of randomization the strength of the evidence would be relatively low.

Cases of vasculitis have also been described following annual influenza vaccination but there was no demonstrated evidence of a causality relationship.

Oculo-respiratory syndrome, a new influenza vaccine associated adverse event, was identified in the year 2000. Its definition requires the presence of bilateral red eyes or respiratory symptoms or facial
oedema occurring 2–24 hours following immunization and lasting 48 hours. It appeared to be associated with the presence of large aggregates in the vaccine lot.

Other rare but severe adverse events that may occur include acute anaphylaxis.\(^1\) Theoretically, immune hypersensitisation towards subsequent wild-type virus infection, as described after use of formalin-inactivated RSV and measles vaccines, might occur but this has not been observed with influenza vaccines to date. Furthermore the possible immune mediated complications cannot all be deduced from animal experiments and for some of the known complications that might arise, no in vitro correlates have yet been defined.\(^3\)

The risk of coincidental SAE may be the most relevant risk in large-scale vaccination of adult populations. The frequency of related allegations can be reduced if appropriate public information is provided before vaccination. In addition, where feasible, assessing the background incidence of some immune-mediated diseases in the targeted population before vaccination would also be useful.

2.6.3 Adjuvant-related potential safety issues

The addition of adjuvants to avian influenza vaccines may raise other safety issues. The main concern expressed by regulatory agencies is the theoretical risk that some adjuvants may overstimulate the immune system and trigger or enhance some chronic immunological diseases. However, there is a high degree of confidence that aluminium-based adjuvants are unlikely to trigger long-term immune-mediated adverse effects or enhance pre-existing autoimmune diseases. This is based on the extensive data base obtained with other vaccines. Although it appears unlikely from available evidence, one cannot exclude that some of the new adjuvanted H5N1 formulations would occasionally enhance undesirable responses. A definitive answer to this question cannot be expected from prelicensure clinical trials. Post-marketing surveillance will be essential for that matter.

2.6.4 Risk of H5N1 vaccines in different age groups and special populations

So far, safety data related to vaccine use in children and in older adults are limited. These data do not indicate an increased safety risk in children over 3 years of age nor in adults over 65. Data are still missing for infants, pregnant women, and immunocompromised individuals.

References


2.7 Postmarketing surveillance for vaccines from the WHO international stockpile

2.7.1 General comment

It is important to underscore that better knowledge of the safety profile of H5N1 influenza vaccines in the WHO stockpile can only come with more widespread use, and such information will accumulate gradually. Use of the vaccines in the interpandemic period would provide an important opportunity to collect safety and immunogenicity data. Incentives to develop, build and improve existing vaccine postmarketing surveillance (PMS) systems would benefit national immunization programmes in general, as well as allowing the testing of new systems for PMS to be utilized during a pandemic.

2.7.2 Current context

The WHO stockpile will most likely have several different H5N1 vaccines from different manufacturers and will be delivered in a two-dose schedule. PMS activities for H5N1 vaccine is required in both the interpandemic and pandemic period. Because the two periods present two different paradigms, there must necessarily be some differences in how PMS is conducted. Nonetheless, building a PMS system in the interpandemic phase is indispensable for the efficient functioning of this system in an eventual pandemic.

The conditions of use during the interpandemic period may be more like those encountered during phase IV trials, or at least allow vaccine administration and the identification and treatment of any subsequent adverse events following immunization (AEFI) in relatively controlled settings. Therefore the choice of PMS strategy could rely more on active surveillance where the population has been selected and will depend on trained AEFI reporters and/or stimulated self-reporting. Surveillance under these conditions is less likely to rely exclusively on passive surveillance.

In a pandemic period, it is also possible that more than one vaccine is in use in a single country, and that different products may even be used for the two doses. Pending programmatic decisions, these vaccines may be administered concurrently with other vaccines (i.e. pneumococcal, vaccines relevant for occupational health protection). Effective PMS should be designed to address such circumstances.

There are many determinants of functional PMS and careful consideration of realities and needs should be undertaken by national authorities. Introduction of new vaccines, or scaling up of vaccination programmes and uptake of underutilized vaccines in the absence of adequate PMS and risk management strategies may have a deleterious effect on public perception of vaccine safety and acceptability of overall immunization programme.

2.7.3 The evidence

Clinical trials with vaccines involve relatively small numbers of healthy subjects, mainly detecting common AEFI. Prelicensure trials are not designed to address rare adverse events, potential safety issues within population subgroups and rarely address vaccine-vaccine reactions. Based on currently available data from animal and limited human clinical trials, there is no evidence of any identifiable major safety concerns related to current H5N1 or other vaccines against novel human influenza viruses.

It is anticipated that the future range of H5N1 vaccines will be extremely heterogeneous in formulation, antigen presentation and substrate used for manufacturing. Therefore, the safety profiles may differ significantly between new products. Similarly these new vaccines will have different safety profiles to those of the licensed seasonal influenza vaccines. As with any new pharmacological
product, these novel vaccines will need specific, long term follow-up of their safety profile, and careful risk-benefit analysis.

2.7.4 Limitations

The lack of data on vaccine use allows provision of only generic recommendations regarding PMS at this point in time.

In most of the countries that would be accessing the WHO H5N1 vaccine stockpile, PMS of vaccines is currently designed to capture data primarily through the public health sector. Most PMS systems in resource-poor settings focus on infant populations, programmatic errors, and the prime reporters in this system are vaccinators. Therefore, only a limited set of AEFI is captured, mainly immediate and systemic reactions, while those occurring at more distant points in time from immunization, with rare occurrence or diagnosed by the curative sector, are less likely to be reported. In addition, PMS requires input from systems monitoring disease occurrence, vaccine use and occasional seroprevalence surveys.

Safety profiles pertinent to specific population subgroups will depend on their inclusion into target cohorts for immunization during interpandemic period.

2.7.5 The aim and principles of postmarketing surveillance

During the **interpandemic period**, enhanced routine PMS activities need to be carried out. The focus of the PMS system will be on safety, since efficacy/efficiency data will be difficult, if nearly impossible, to obtain. Apart from gaining a better understanding of the vaccine safety profile, the opportunity should be seized to collect good quality data and identify elements that influence vaccine safety reporting. The immunization strategy and choice of target groups will have a direct impact on the structure of the PMS system designed for the occasion. Key activities of the PMS system should include:

- establish baseline studies to determine background incidence of conditions of interest and/or rates of risk factors for comparison purposes;
- establish a robust and efficient mechanism for the reporting of AEFI that links seamlessly to global networks for analysis and communication of these events;
- develop registries of vaccinated subjects to monitor vaccine doses administered and permit the collection and analysis of data necessary for case-control and cohort studies to determine safety (and estimate effectiveness in pandemic situations);
- enhance rapid detection of potential signals;
- assign roles and train staff in the public and private sector to carry out functions required of them in the interpandemic and pandemic phases.

Immunization during interpandemic period provides an opportunity to prepare, test, adjust, and modify PMS for a pandemic period when the vaccine will be in widespread use. In designing an appropriate system, the specifics of the target groups to be immunized need to be considered as in many countries the first groups to be immunized may be able to self-report based on their professional affiliation, e.g. health-care workers and government staff. Options for reporting methods need to be based on reliable and available resources.

In a **pandemic period**, prioritization of activities regarding PMS will be required. The focus will be on collection of essential, minimal data feasible under pandemic conditions. Timeliness will be of utmost importance and rapid cycle monitoring and analysis should be performed giving an update on the vaccine(s) and subsequent outcomes every week. Only adverse events of special interest should be reported and followed. If feasible, predefined cohorts of vaccine recipients may be followed more intensely.
Protocols should be developed beforehand which should include study populations, case definitions, endpoints and analysis planning. Countries should assess what systems are already in place and determine what will be needed for the local situation. It will be important to determine feasible and realistic PMS systems for different scenarios and ensure that the systems will be flexible enough to allow for changes as the situation unfolds. Authorities should be committed to implement a national PMS strategy and to devise a plan of action for PMS in connection with the use of vaccines from the WHO H5N1 vaccine stockpile.

2.7.6 WHO support

In line with request of World Health Assembly resolution 61.50 (WHA/61/2008/REC/1) to provide guidelines and technical support to Member States in order to establish integrated surveillance of AEFI, a guidance document on PMS for H5N1 influenza vaccine from the WHO stockpile is currently being devised by WHO. The document is intended for senior level, national decision-makers of potential stockpile recipient countries. In view of the need for advance planning, this document will provide a basic set of recommendations for planning and implementation of PMS that can be applied to any existing system. The document will need to be updated as new evidence on the safety profile of products in the stockpile, or details of their potential use become available. Technical assistance is being provided to national regulatory authorities of countries with no or limited experience with influenza vaccine research and development, that are new entrants to influenza vaccine production.
2.8 Ethical considerations on H5N1 vaccination in the interpandemic period

2.8.1 Considerations related to a recommendation on the interpandemic use of licensed human H5N1 influenza vaccine (see 3.1, 3.2 and 3.4)

Logically, the human population can be divided into three groups:

1. those for whom, based on available evidence, expected health benefits of H5N1 vaccine (for protection against current strains of H5N1 and/or a later/related pandemic strain of the virus) outweigh risks for those individuals;
2. those for whom, based on available evidence, it is an open question whether or not expected health risks of H5N1 vaccine outweigh benefits (of protection against current strains of H5N1 and/or a later/related pandemic strain of the virus) for those individuals, or vice versa; and/or those for whom risks and benefits are expected/ascertained to be equal; and
3. those for whom, based on available evidence, expected health risks of H5N1 vaccine outweigh benefits (of protection against current strains of H5N1 and/or a later/related pandemic strain of the virus) for those individuals.

This does not imply that there are individuals who actually fall into each of these groups. Even assuming that members of some groups—e.g. surveillance workers exposed to dead and/or infected birds, farmers and poultry handlers, health workers treating patients infected with H5N1, and laboratory personnel working with H5N1—face higher relative risk of infection with current strains of H5N1, and despite the likelihood that some groups would be at higher relative risk of infection and/or death from a pandemic strain of a related virus in the event that such a pandemic arises, it is logically possible that all individuals fall into group 2 (and that groups 1 and 3 contain no members).

Assignment of individuals to groups 1 and 3 is largely (though not entirely—because questions about whether risks outweigh benefits, or vice versa, involve value judgments, while there are multiple different reasonable risk-taking strategies) a scientific matter requiring empirical evidence, i.e. statistics/probabilities demonstrating that either vaccination or non-vaccination is expected to promote health benefits for the persons/groups in question. To date, SAGE has made no such empirical case regarding any particular at-risk group. The paper on “H5N1 vaccination in selected groups against avian virus”, for example, does not demonstrate that, based on available evidence, benefits of vaccination outweigh risks for members of groups at higher levels of relative risk. In addition, the review of “Current risk of human infection with highly pathogenic avian influenza A (H5N1) virus” indicates that it is (currently) impossible to quantify the actual risks of infection with H5N1 for those groups that would appear to face higher relative risks; moreover, the analysis indicates that risks are, in any case, likely to be low, even for those groups that face higher relative risks.

Additional obstacles to assigning individuals into groups 1 and 3 relate to the fact that, although previous (limited) studies indicate that numerous current H5N1 vaccines are relatively safe and may provide (some) protection against H5N1 infection in humans, and plausibly some protection against a future related pandemic strain of the virus (e.g. via priming), it will be impossible to know whether they do not increase risks of rare vaccine-associated diseases (such as Guillain-Barré syndrome) until many more people are vaccinated. And the likelihood that a human pandemic strain of influenza will result from H5N1 is, meanwhile, uncertain. Both (i) the risks and (protective) benefits of current H5N1 vaccines for humans and (ii) the likelihood of a human pandemic resulting from H5N1, are largely unknown.
When and if additional evidence—or further analysis of existing evidence—enables assignment of individuals to groups 1 and 3, it would *prima facie* be appropriate to *recommend* vaccination of those in group 1 and to *recommend against* vaccination of those in group 3.

Meanwhile, it appears that everyone (except those excluded on medical grounds) may fall into group 2 (merely as a result of the fact that there is so much uncertainty). Insofar as the health of the individuals in question is the main concern, there would apparently be no (scientific) grounds for either recommending for or against vaccination of those in group 2. Other things being equal, from an ethical standpoint it appears that these people should be provided with available information about the risks and benefits of vaccination—and the risks/dangers of infection with H5N1 and/or a potential related pandemic strain of the virus—and make their own decisions based on their own risk-taking strategies, i.e. they should be *offered* the vaccine without encouragement one way or the other, and vaccination should be based on voluntary informed consent.

If supplies of vaccine are limited, however, and likely to be untowardly depleted if the vaccine is offered to everyone in group 2, then it should perhaps not be offered to everyone in this group, i.e. as opposed to just those who are at greater risk (of infection) (e.g. laboratory workers, surveillance workers). Even if everyone falls into group 2, it may still be true that some individuals face higher relative risks than others. Health systems would furthermore likely want to maintain some supply of vaccine for when/if a pandemic actually arises. Suppose that a country determines that it should save X doses of its current supply in reserve for such an eventuality, i.e. to be used for outbreak containment and protection of essential service providers. It may then be appropriate for that country to offer surplus doses first to those determined to face the highest level of relative risk, then to those at the next highest level of relative risk, and so on until either everyone who wants to become vaccinated is vaccinated or no further surplus beyond X doses remains.

This analysis assumes that prioritization (during the interpandemic period) should be based on relative risk. Insofar as H5N1 vaccine would be important for protection against a related pandemic strain of the virus, social function—e.g. provision of essential services—may provide additional grounds for prioritization when H5N1 vaccine is offered to the population during the interpandemic period. An alternative option, therefore, would be a more complex tiered allocation scheme whereby prioritization is a function of relative risk and/or the importance of the social role played by essential service providers and so on.

There are numerous reasons why such a strategy would be ethically appropriate. Assuming that the health of potentially vaccinated individuals is the most important consideration, WHO should not make recommendations for or against vaccination of people in group 2. Given the definition of group 2, such recommendations could not be justified—and if things turned out badly, WHO and/or Member States following WHO recommendations would be responsible for any harm that results. Criticism analogous to that following the 1976 Swine Flu vaccination programme would then be expected—and (at least in this case) appropriate. In the absence of empirical evidence to the contrary, it would be most appropriate to allow/encourage individuals to make their own informed decisions based on their own risk-taking strategies. If harm then results from vaccination or non-vaccination, individuals themselves would be the responsible parties. WHO and Member States following WHO guidance would not be subject to legitimate criticism because WHO and Member States following WHO guidance would, by hypothesis, have had no grounds for encouraging individuals to take other actions.

Another benefit of this strategy is that it is autonomy promoting. If informed individuals want to face risks of vaccination to protect against possible infection (from current H5N1 and/or a potential pandemic strain), then unless they fall into group 3, there is no good reason—aside from resource constraints—to deprive them of the opportunity to do so. It would be a shame to allow vaccine stockpiles to go to waste if there are people who want to be vaccinated, and if there is no good reason

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* In this discussion, “offer” means to offer or make available, without necessarily implying free of charge.
why they should not be vaccinated (especially given the plausibility of a pandemic, or, especially in the case of (relatively) high-risk groups, the plausibility of infection with current H5N1). In addition to promoting autonomy, a benefit of (gradually) providing vaccine to those who want it is that this will provide more information about the safety and efficacy of the vaccine, and perhaps enable the eventual assignment of persons to groups 1 and 3.

The strategy described above takes resource constraints into consideration by prioritizing according to need—i.e. relative risk—and/or the importance of essential providers’ social function when vaccination offers are made. While this would appear to be fair—and while the rationale behind such a policy should be transparent (i.e. well communicated/explained to the public)—some may complain if surplus vaccine supplies (beyond the X doses held in reserve) are not sufficient to vaccinate all who wish to be vaccinated. Considerations of equity should thus perhaps motivate States offering H5N1 to some members of group 2 to acquire supplies adequate to meet total population (at least with regard to groups 1 and 2) demand. Though H5N1 vaccine supplies are limited at present, it has been estimated that it would be possible to produce enough H5N1 vaccine for the entire global population within four or five years.

While it may be appropriate to offer H5N1 to those at the highest levels of relative risk of infection with current strains of H5N1 and/or essential service providers, on the other hand, provision of such vaccine to members of the general public may not be good use of limited health-care resources (given the especially low risk of infection with H5N1 for ordinary members of the public, and uncertainty about the likelihood of a related pandemic strain arising). It is, therefore, by no means obvious that countries would be ethically obligated, based on grounds of equity/justice, to (eventually) offer H5N1 to everyone in group 2 if they offer it to those at highest relative risk. Given the definition of group 2, the estimated/expected cost-effectiveness of vaccinating members of group 2 would be extremely low (i.e. because there is zero expected benefit from vaccinating such people).

Another reason for offering the vaccine to some but not all members of group 2 runs as follows: given the uncertainty involved, there are risks associated with making the vaccine available to everyone (potentially a very large number of people) who would want it. One might argue that there must be a particular reason (beyond individual caprice) for allowing individuals to expose themselves to such risks. This may provide grounds for offering the vaccine to those at elevated risk of infection with H5N1 (and possibly essential service providers) but not to members of the general public (for whom such risks are virtually zero). On the other hand, it may be argued that given the plausibility of a pandemic with a related strain of influenza against which current H5N1 vaccine would offer some protection, there are risks—even for ordinary members of the public—associated with remaining unvaccinated. Despite differences in relative risk of infection, the defining characteristic of all members of group 2 is that there is no reason to be confident that they would likely benefit or be harmed from vaccination.

Note that the above analysis is primarily based on individual risk-benefit considerations. Factoring overall public health into the equation would complicate the analysis, and the public health consequences of alternative vaccination strategies presumably involve even greater uncertainty. In the short-term, however, there may be special public health reasons for recommending vaccination to those at greatest risk of infection with (human-to-human) transmissible strains, e.g. laboratory workers involved with genetically engineered strains, health workers treating patients in clusters, and so on.

A rigorous ethical analysis based on public health considerations would start by identifying another way of logically dividing the population into three groups:

1*. those for whom, based on available evidence, their H5N1 vaccination during the interpandemic period is expected to have public health benefits overall;
2*. those for whom, based on available evidence, it is an open question whether their H5N1 vaccination during the interpandemic period is expected to have public health benefits or harms overall; and/or those for whom there is reason to believe their vaccination would have zero (positive or negative) net effect on public health; and

3*. those for whom, based on available evidence, their H5N1 vaccination during the interpandemic period is expected to have public health harm overall.

As in the earlier three-group division, it is logically possible (and perhaps likely given available evidence) that almost everyone currently falls into group 2*. If some individuals can be assigned to group 1*, this would not necessarily imply that vaccination of such people should be recommended, because this partly depends on which of the earlier groups (1, 2, or 3) they would fall into. Prima facie, vaccination should be recommended for anyone who both falls into group 1* and groups 1 or 2. It is not clear what should be done if there are individuals who fall into both group 1* and group 3. In such a case a difficult ethical question would arise: how great would the expected public health benefit need to be in order for the expected harm to the individual in question be justified? Answering such a question was beyond the scope/mandate of the H5N1 working group, although the importance of this kind of question to vaccination policy more generally is noted.

2.8.2 Considerations related to the use of stockpiled H5N1 influenza vaccines approaching their expiry date during the interpandemic period

For reasons outlined above, assuming everyone falls into group 2 (and 2*), expiring vaccine could be offered first to those at the highest level of (relative) risk, then to those at the next highest level of (relative) risk and so on until there is no more expiring vaccine left or no one else that (once properly informed) wants it. Another option would be to take both relative risk and the social importance of essential service providers into account when dividing the population into tiers. There may be no good reasons (except perhaps those associated with the expense of using the vaccine if it is unlikely to provide anything of value) for disposing of the vaccine if (i) there are informed people who (without being irrational or misinformed or excluded on medical/scientific grounds) want to be vaccinated with it; (ii) its use will provide valuable information; and (iii) there are reasons to believe it is (relatively) safe and would provide protection against a plausible threat of existing H5N1 (especially for those at highest risk of infection with current H5N1) and/or a pandemic from a related strain (even for ordinary people).

References

1. Osterhaus A. H5N1 vaccination in selected groups against avian virus. Background paper prepared for the SAGE Working Group on H5N1 Vaccines.

2.9 H5N1 and pandemic vaccine production capacity

2.9.1 Background and methodology

Over the past two years, substantial progress has been made around increasing the production capacity of seasonal, H5N1, and potential pandemic vaccine. New and expanded facilities have been announced, including in the developing world; antigen per dose requirements have been reduced due to the use of novel adjuvants; production yields have improved; and progress has been made with new technologies.

A study was therefore undertaken to provide a new set of estimates regarding the global capacity to produce real-time pandemic influenza vaccine at the point of a pandemic and H5N1 vaccine in the interpandemic period. The study was carried out from August to December 2008 by Oliver Wyman in collaboration with WHO and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA). To complete the estimates, interviews were conducted with 17 current and emerging influenza vaccine manufacturers, the Developing Countries Vaccine Manufacturers Network (DCVMN), IFPMA and other industry experts. This was supplemented by extensive secondary research to create capacity estimates for 44 current and planned facilities in 24 countries, focused on both inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV) technologies (see www.oliverwyman.com/ow/pdf_files/InfluenzaVaccineSupplyDemandMar09.pdf for details of the study methodology, assumptions and findings).

2.9.2 Real-time pandemic influenza vaccine capacity estimates

Two scenarios were created to provide a range of estimates for real-time pandemic influenza vaccine production capacity. In the “base case”, or most likely situation, it was assumed that manufacturers would rationalize some of their influenza vaccine capacity when the US-sponsored cell facilities come online – as is considered likely by the manufacturers. It was further assumed that manufacturers would only be able to provide vaccine at a dosage corresponding to their licensed mock-up vaccines and that the pandemic vaccine yield would be half of that achieved for seasonal influenza vaccines. In contrast, the “best case” scenario assumed that seasonal influenza vaccine capacity would not be rationalized, that manufacturers could produce vaccines at dosages corresponding to their most recent successful trials, and that pandemic yields would be equivalent to seasonal yields.

As shown in Figure 1 below, in the base case manufacturers could produce 2.5 billion doses of pandemic vaccine in the 12 months following receipt of the production strain and would require four years to satisfy global demand. This represents a 300% increase over previous estimates driven primarily by advances in dosage-sparing technologies and yields, but is still far short of global need. In the best case, 7.7 billion doses could be produced in the first 12 months, requiring 18 months to satisfy global demand. In both cases, vaccine would not be available for nearly three months after receipt of the production strain due to the technical lead time required to manufacture the vaccine. The 12-month production capacity is expected to rise to 5–14.5 billion doses over the next five years. The resulting time to meet global demand would be reduced to between 2 years and six months (in the base case) and 1 year (in the best case).

* Weighted average antigen per dose ranges from 9.2µg in 2009 to 5.4µg in 2014 in the most likely case and 5.0µg in 2009 to 5.5µg in 2014 in the best case.

** H5N1 vaccine yields have varied from 1/3 to 1/1 of seasonal vaccine yields, driven by the individual strain. In the base (most likely) case a conservative estimate was used to account for uncertainty in the pandemic strain.

*** To this timing should be added 3–4 weeks from a pandemic declaration to create reference strain – remaining two weeks of pathogenicity testing will occur after strain release.
2.9.3 H5N1 vaccine capacity in the interpandemic period

Estimates were also developed around the capacity to produce H5N1 vaccine in the interpandemic period. These estimates represent the surplus capacity in the interpandemic period after projected demand for seasonal influenza vaccine and for H5N1 vaccine for high-likelihood country stockpiles are served. Two scenarios, “high surplus capacity” and “low surplus capacity” were developed based on different assumptions around the demand for seasonal vaccine and stockpiled H5N1 vaccine.

In both scenarios, it was assumed that some seasonal vaccine capacity would be rationalized when the US-sponsored cell facilities come online, that dosages would correspond to those licensed by the manufacturers, and that H5N1 vaccine yields would be equivalent to those achieved for seasonal vaccines.

As shown in Figure 2 below, considerable surplus capacity exists in the interpandemic period – enough to produce 2.5 billion annual doses of H5N1 vaccine. This surplus capacity is expected to rise further over the next five years to between 2.6 and 5.4 billion doses per year.

Figure 2. H5N1 vaccine production capacity in the interpandemic period

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LAIV included in best case represents ~10M doses per month (~1% of total pandemic capacity) in 2009 and ~20M doses per month (~1% of total pandemic capacity) in 2014. LAIV pandemic capacity constrained by filling capacity at manufacturers; recombinant excluded.

Seasonal demand estimated using the Macroepidemiology of Influenza Vaccination (MIV) Study Group. Additional research was conducted to provide 2006 and 2007 estimates for key countries. H5N1 stockpile demand estimated through interviews with major existing stockpile holders.
3. SAGE recommendations

SAGE sought to determine whether the evidence summarized in Section 2 was sufficient to be able to recommend the use of licensed human H5N1 vaccines in the interpandemic period among different professional and general population groups. The second area assessed related to whether specific target groups might be primed or immunized against a potential pandemic H5N1 virus. The third and final issues concerned the size and use of stockpiled H5N1 influenza vaccine.

The SAGE recommendations outlined below are of a generic nature. It is underlined that the recommendations concern the use of currently licensed human H5N1 influenza vaccines in the interpandemic (phase 3) period, and do not apply to vaccination during later phases or a pandemic event. It is further underlined that recommendations 3.1 and 3.2 on the potential use of vaccine are independent of the possible use of vaccine from existing or planned stockpiles, addressed in recommendation 3.3.

The following important considerations apply to all recommendations.

- Each of the licensed inactivated H5N1 influenza vaccines has its own specific characteristics. Where vaccination is recommended or vaccine made available to a given population group, it is preferable to use a licensed H5N1 vaccine that is a close antigenic and genetic match with the highly pathogenic avian influenza (HPAI) H5N1 viruses manipulated in experimental settings or circulating in the geographical location, and/or H5N1 vaccine formulations that have been shown to induce enhanced cross-clade antibody responses.

- Licensure of H5N1 vaccines has been based on immunogenicity and so-called protective (haemagglutination inhibition (HI) titre) correlates developed for seasonal influenza vaccines. It is currently not known whether these titres would provide a comparable level of protection against H5N1 influenza.

- The safety profile of licensed vaccines is based on the local and systemic adverse events evaluated in the clinical trials required for licensing. Other rare but severe adverse events cannot be excluded since they can only be identified after use of the vaccines in much larger population groups. Data should be gathered for any group vaccinated with licensed H5N1 vaccine on safety, immunogenicity, cross-reactivity, priming potential and duration of immunity. Such data should be shared promptly with WHO and the international community in order to build upon the global experience with H5N1 vaccine use.

- In any use of human H5N1 influenza vaccine during the interpandemic period, thorough monitoring of both safety and immunogenicity is of paramount importance. Vaccinated individuals, for example, should have sequential serum samples (e.g. every 6 months) collected for subsequent analyses of durability of H5N1 neutralizing antibody levels and of evidence for antibody rises related to intercurrent H5N1 exposures.

- Risk-benefit analyses, and cost-benefit analyses when possible, should be carried out for each risk group and for each of the respective vaccines before deciding to vaccinate. The SAGE recommendations are based on a risk-benefit evaluation. The initial results of a cost-benefit analysis should be available by end 2009.

- The use of seasonal influenza vaccine is encouraged in all countries and especially for groups at risk of HPAI H5N1 infection to reduce the theoretical possibility of reassortant viruses with H5 HA and some mixture of remaining avian and human virus genes fostering human-to-human transmissibility of a novel virus. In addition to reducing the risk of seasonal influenza and its complications, seasonal vaccine should reduce cases of acute influenza illness due to seasonal virus in the context of an H5N1 exposure, which could lead to unnecessary investigation and public health responses.
Finally, it is emphasized that vaccination is complementary to, and does not replace other containment and protective measures that should be in place.\(^1\) Such measures include personal protective equipment and prophylactic or post-exposure use of currently licensed antiviral drugs, although the latter are not currently a long-term option because of potential side-effects, drug resistance and cost-effectiveness issues.

SAGE recommendations are graded as follows and summarized in Table 3:

- **Strongly recommended:** Persons should not carry out their functions unless they are vaccinated.
- **Recommended:** Persons are encouraged to be vaccinated.
- **May be made available:** Responsible authorities should assess whether licensed human H5N1 influenza vaccines might be made available, without encouraging persons to be vaccinated. This does not imply that vaccine should be provided free of charge.

### 3.1 Is the evidence sufficient to recommend the interpandemic use of licensed human H5N1 influenza vaccine to immunize against H5N1 avian influenza?

#### 3.1.1 Higher risk groups

**Laboratory personnel: at risk of being exposed to HPAI H5N1 virus.** This group includes medical and veterinary laboratory workers involved in experimental studies with HPAI H5N1 virus, animal and human diagnostic testing of samples that might contain HPAI H5N1, and in the small- or large-scale growth of HPAI H5N1 virus for vaccine production and other purposes. To date, no human cases have been identified among personnel working with HPAI H5N1 virus or specimens containing HPAI H5N1 virus in animal or public health laboratories and the available evidence is insufficient to quantify the risk of H5N1 virus infection in this population. However, depending on the type of activities, laboratory workers who may be at significant risk of HPAI H5N1 virus infection should be provided specific protective measures likely to be effective against H5N1 virus infection. Furthermore, inadvertent breaches of safety and security, although rare, can and do occur, leading to increased risk of infection.

**Recommendations for laboratory personnel**

Vaccination with licensed H5N1 vaccine is strongly recommended for laboratory workers involved in the following activities: large-scale production or manipulation of HPAI H5N1 virus; working with the virus over a long period; working with HPAI H5N1 virus strains that are resistant to licensed antiviral compounds; or working with strains with the potential for increased transmissibility in mammalian species. In countries with no licensed H5N1 vaccine, a candidate H5N1 vaccine may be used under informed consent. For laboratory personnel working with H5N1 virus, but not involved in these activities, the risks and benefits associated with H5N1 vaccination should be evaluated before it can be made available, and affected staff should be involved in decision-making for vaccination.

**Personnel involved in surveillance, investigation and response to avian outbreaks, sporadic human cases and especially clusters of suspect or confirmed human cases:** This group includes individuals conducting activities in which there is contact with potentially infected people, animal wildlife or laboratory specimens; or personnel first to respond to HPAI H5N1 outbreaks and/or clusters of suspected or confirmed human cases. It also includes poultry cullers and animal and public health workers responding to an outbreak. For personnel involved in surveillance and response to avian outbreaks, sporadic human cases and especially clusters of suspect or confirmed human cases, there is insufficient evidence to quantify the risk of H5N1 virus infection. The evidence shows that one poultry culler has been identified to date with HPAI H5N1 virus infection, and that government workers involved in culling operations were considered as having a low level of risk of infection based on seroepidemiologic studies in 1997.
Overall, this group may be considered to be at low risk of HPAI H5N1 virus infection, depending on the level of personal protection in place and the type of activity, extent of environmental contamination or possible human infection, and the likelihood for repeated first responder activities. Moreover, it is emphasized that protecting people who investigate possible chains of human-to-human transmission is also in the public health interest, as they may be the first contacts of an emerging pandemic virus that may affect wider populations.

**Recommendations for first response personnel**

Depending on the assumed risk of exposure and type of activities, vaccination is recommended for workers involved in a first response to possible H5N1 outbreaks in animals or humans.

*Persons in potential contact with animals infected with HPAI H5N1 virus in enzootic areas, including farmers:* The risk of infection with HPAI H5N1 in this large group as a whole cannot be quantified based on available information, although evaluated as lower than that for laboratory workers and first responders. However, it is important to acknowledge that individuals within this group account for many of the confirmed human H5N1 cases worldwide, including subsequent transmission to household contacts. The strategy of protecting these persons has depended on physical protective measures, sometimes in combination with the prophylactic use of antivirals, although the latter is not currently a long-term option for reasons of potential side-effects and antiviral drug resistance, and may not be cost-effective for such a large category of persons.

**Recommendations for persons in potential contact with infected animals**

H5N1 vaccination cannot be recommended at present for persons who may only potentially come into contact with infected animals (e.g. farmers). However, vaccine may be made available as a preventive measure to persons known to be in contact with poultry in confirmed active outbreak areas depending on the level of enzooticity, risk of exposure and effectiveness of other prevention measures in place. This does not currently concern large population groups, and WHO will develop guidance to assist countries to carry out a risk assessment in this population group before vaccine may be made available.

3.1.2 **Essential workers in areas where avian H5N1 virus is enzootic in wild birds or poultry**

*General:* The term “essential workers” includes a variety of groups for whom the risk of infection with avian H5N1 virus differs. It includes groups that maintain national and community security, public safety and critical infrastructure and services and may be defined differently by individual Member States. Health-care workers providing medical care to patients potentially infected or confirmed to be infected with HPAI H5N1 virus represent a distinct group of workers with evidence of low risk of H5N1 virus infection and are therefore considered as a subset of essential workers.

**Recommendations for essential personnel**

To date, there are no data indicating that the risk of infection from avian H5N1 influenza virus for essential workers, i.e. key workers in critical infrastructure sectors, is higher than that for the general population. Therefore, the evidence is insufficient to propose that H5N1 influenza vaccine should be made available to essential workers in general on the basis of risk in areas where HPAI virus is enzootic during the interpandemic period.

*Health-care workers:* In contrast to essential workers in general, HCWs represent a population that can be at direct risk of infection with avian H5N1 virus through human-to-human transmission due to occupational exposure to H5N1 virus-infected patients in a health-care setting, especially in areas where H5N1 virus is endemic in wild birds and/or poultry. Public health measures that reduce the risk of human-to-human transmission of avian H5N1 viruses are desirable as this may limit the potential of the virus to acquire mutations that may promote adaptation to the human host. Evidence in support of this risk include one human case of HPAI H5N1 virus infection identified in an unprotected HCW.
and limited seroepidemiologic studies conducted during 1997–2004 suggesting that the risk of H5N1 virus transmission from patient-to-HCW is low, but has occurred.

**Recommendations for health-care workers**

Vaccination is recommended for HCWs who evaluate or manage suspected or confirmed H5N1 patients in designated outpatient or inpatient referral facilities. These HCWs may be at a higher risk of infection than others, especially if a virus with increased potential for human-to-human transmission emerges. Based on a risk assessment, licensed H5N1 vaccines may be made available to other HCWs in countries where avian H5N1 virus is enzootic and where human cases may continue to emerge and pose the threat of exposure for HCWs. This includes HCWs at the many primary health-care facilities where suspected H5N1 patients may first present for care.

### 3.1.3 General public in areas where HPAI H5N1 virus is endemic in wild birds and/or poultry

The current level of risk in the general population is very low, even in populations with direct or indirect exposure to domestic poultry. Nonetheless, it is important to acknowledge that this group accounts for most of the confirmed human H5N1 cases. In these conditions, determinants of vaccine use will be related to either the existence of disease foci or a particular perception of risk in a geographic area in which human cases of avian H5N1 infection have been identified. This risk may be compared to that related to relatively rare vaccine-preventable diseases for which a vaccination strategy has been implemented or rejected at country/regional level (e.g. Japanese encephalitis in South-East Asia).

Current evidence is that the various licensed H5N1 vaccines are immunogenic in humans, inducing antibodies that appear to cross react with related clades. Based on modest numbers of vaccine recipients to date, the vaccines also appear to have a good safety profile (with most data coming from healthy adults, less in children and the elderly, and virtually no information concerning immunogenicity in infants or the immunosuppressed). Results of ongoing large-scale demonstration trials will provide additional information on immunogenicity in different populations.

**Recommendations for the general public**

Since one cannot exclude a risk, albeit low, of vaccine-related serious adverse events, and at the present low level of risk of infection, H5N1 vaccination is currently not recommended in the general population, and evidence does not suggest that vaccine should be made available to the general public unless there is judged to be a particular risk.

### 3.2 Is the evidence sufficient to recommend the interpandemic use of licensed human H5N1 influenza vaccine among essential personnel or the general public to prime or immunize them against infection with a potential pandemic H5N1 virus?

One of the biggest uncertainties with regards to priming any population group against potential infection with a pandemic influenza virus is whether one of the currently circulating HPAI H5N1 virus strains will cause the next human pandemic. Current strains circulating among birds continue to evolve, and other avian influenza A virus subtypes, e.g. avian H9, H7 viruses, have been suggested as having potential pandemic capability. In addition, the decision to prime or immunize large populations with one of the licensed human H5N1 influenza vaccines would depend on the generation of significantly more vaccine safety data from extensive use of these vaccines, including in infants and persons with underlying conditions. Although some studies have been carried out to date on priming and boosting,* more research is required before priming can be considered. Finally, priming large numbers of persons entails numerous practical considerations that may not be feasible in many countries. These include: keeping accurate records of who receives the vaccine and how many doses; carrying out surveillance; and assuring effective monitoring for adverse events.

* Among others, Bridges et al. Effects of priming with two doses of clade 0 rH5 influenza vaccine on immune response to vaccination nine years later with clade 1 H5N1 vaccine, on a cohort of CDC workers.
Recommendation on priming or immunizing essential personnel or the general public against infection with a potential pandemic H5N1 virus

Currently, there is insufficient scientific evidence to make available or recommend the use of licensed human H5N1 influenza vaccines in the interpandemic period among essential personnel or the general public either to prime or immunize them against infection with a potential pandemic H5N1 virus.

Table 3. Summary of SAGE recommendations on the use of currently licensed human H5N1 influenza vaccines in the interpandemic period

<table>
<thead>
<tr>
<th>Category</th>
<th>Strongly recommended</th>
<th>Recommended</th>
<th>May be made available</th>
<th>Not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory workers:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>higher risk groups</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other laboratory workers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First responders to avian outbreaks</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons in potential contact with HPAI H5N1 virus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential workers (excluding HCWs)</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>HCWs, enzootic areas:</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in designated referral facilities</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other HCWs</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>General population</td>
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<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Priming or immunizing essential personnel or the general public against a potential pandemic H5N1 virus</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

* Strongly recommended: persons should not carry out their functions unless they are vaccinated.
* Recommended: persons are encouraged to be vaccinated.
* May be made available: responsible authorities should assess whether licensed human H5N1 influenza vaccines might be made available, without encouraging persons to be vaccinated. This does not imply that vaccine should be provided free of charge.

3.3 What might be recommended for stockpiled H5N1 influenza vaccines approaching their expiry date during the interpandemic period?

H5N1 vaccine stockpiles have been constituted with the goal to allow vaccination of all or parts of populations immediately after the onset of a potential H5N1 pandemic. Therefore, their use before such an emergency event was not considered at the time of their establishment, excepting for specific research projects. However, calls have been made to reconsider whether vaccine held in stockpiles might be used in the interpandemic period. Holders of a licensed H5N1 vaccine stockpile should therefore be encouraged to gain experience with H5N1 vaccine use, which will provide additional data on safety, immunogenicity, cross-reactivity, priming potential and duration of immunity in order to inform public health policies. Such experience could be acquired through pilot projects, clinical studies and/or limited vaccination of incremental numbers of persons. Studies might start in populations that would be at increased risk of infection in the event of a pandemic (e.g. HCWs). Additional knowledge could be acquired through pilot projects and/or clinical studies in special population groups (e.g. children, older persons, immunosuppressed and individuals with specific health conditions).

In the event that such projects or studies are carried out, it will be important to establish post-licensure or postmarketing surveillance procedures that can collect long-term safety data for ongoing risk-benefit analyses. The results of these studies should be shared promptly with WHO and the
international community in order to allow reconsideration, if and when appropriate, of the recommendations.

Stockpile holders will need to decide whether vaccines coming close to their expiration date should be used rather than discarded when they reach this date. At present, there are insufficient data on the shelf-life of H5N1 vaccines. Furthermore, the expiration dates accepted by different licensing authorities, as well as the requirements for demonstration of stability, may vary. Processes for the extension of shelf-life for vaccines stocks should therefore be analysed, and the stability and extension of shelf-life for antigens and adjuvants should be studied separately, if possible. Stability studies on stockpiled vaccines that have passed their expiry date would also be useful. A consortium of stockpile holders might be formed to ensure the harmonized implementation of studies on stockpiled H5N1 vaccine.

Recommendation on the use of WHO stockpiled vaccines

Without waiting for stockpiled vaccines to approach their expiry date, holders of licensed H5N1 vaccine stockpile are encouraged to gain experience with H5N1 vaccine use, and to build knowledge further on safety, immunogenicity, cross-reactivity, priming potential and duration of immunity in order to inform public health policies. In addition, use of stockpiled vaccines may be considered for the studies outlined above, as well as the specific indications identified under 3.1 above for which vaccination in the interpandemic period is recommended.

3.4 Should SAGE recommend a change in the size of the WHO stockpile?

The above-mentioned pilot projects and clinical studies are not expected to deplete vaccine doses held in the substantial current and planned stockpiles for use in a pandemic or for other purposes. Thus, there is no evidence to recommend a change in the size previously recommended by SAGE for the WHO international stockpile, i.e. 50 million doses to complement rapid containment operations in the event of human-to-human transmission of H5N1, and 100 million doses for equitable distribution to low- and middle-income countries to help maintain the services considered most essential.

Recommendation on the size of the WHO stockpile

Currently, there is no evidence to recommend a change in the size recommended by SAGE for the WHO international stockpile:

- 50 million doses to complement rapid containment operations in the event of sustained human-to-human transmission of H5N1 virus, and
- 100 million doses for equitable distribution to low- and middle-income countries to help maintain the services considered most essential.

1 The following WHO guidance on protective measures are available:
Advice for people living in areas affected by bird flu or avian influenza. 8 November 2004. www.wpro.who.int/NR/rdonlyres/04FA6993-8CD1-4B72-ACB9-EB0EBD3CDB10/Advice10022004rev08112004.pdf.