Meeting summary

TECHNICAL CONSIDERATIONS ON HUMAN H5N1 INFLUENZA VACCINES:
Possible options for using a WHO H5N1 vaccine stockpile

During 1-3 October 2007, WHO held a consultation in Geneva to review available data on the safety and immunogenicity of H5N1 vaccines, and possible options for the use of H5N1 vaccines as well as a WHO stockpile of such vaccine. Invited participants included researchers, representatives from WHO Influenza Collaborating Centres, selected countries, SAGE, and industry. Observers were allowed. Several presentations were provided including a summary of the results of a recent consultation on H5N1 vaccines held by the European Centre for Disease Prevention and Control (ECDC).¹

1. Characteristics of currently-available human H5N1 influenza vaccines

Safety: Based on currently available data from animal and limited human clinical trials, there is no evidence so far of any identifiable major safety concern related to H5N1 vaccines, although additional local reactions with some adjuvanted vaccines have been noted. Additional controlled trials with long-term follow up, especially in children, are needed.

If a live attenuated vaccine based on the H5N1 virus is used in a non-pandemic period, there is a risk the vaccine virus could reassort with a circulating seasonal human influenza virus and create a hybrid virus, but this risk was considered small. If any type of H5N1 vaccine is used extensively, additional adverse safety signals can be anticipated. Part of the preparations for widespread use should include ongoing monitoring to ensure that adverse events are identified and appropriate responses are taken.

Immunogenicity: Currently there are no standard criteria to assess the immunogenicity of human H5N1 vaccines. Some candidate H5N1 vaccines elicit a greater antibody response than others after two doses with a 21 day interval between first and second dose. At comparable antigen dose levels, some human H5N1 vaccines elicit lower immune responses than seasonal human influenza vaccines. There is no indication of differences in immunogenicity based on whether H5N1 vaccine viruses were grown in eggs or cells. Live attenuated and inactivated whole virus vaccines may be more immunogenic than split or subunit vaccines. For some human H5N1 split and subunit vaccines, certain adjuvants allow the amount of antigen required to be reduced to elicit the same level of response. In some cases, adjuvants elicit a higher and broader antibody response, including improved cross-reactivity among strains. However, further studies, including direct comparisons of non-adjuvanted and different adjuvanted vaccines from different companies, are needed.

Cross reactivity: Animal data suggest human H5N1 vaccines produced from viruses from one clade may be cross reactive against viruses from other clades, as well as protective against re-challenge with virus from other clades. Some vaccine strains elicit higher antibody responses than others, and those that do often elicit response against variants. Oil and water emulsion adjuvanted vaccines eliciting high levels of antibody against homologous challenge also elicit higher levels of antibody to variants. Cross reactivity among current H5N1 strains might indicate potential cross-protection against future emerging strains, but such coverage could diminish as H5N1 viruses continue to evolve.

¹ www.ecdc.eu.int/Health_topics/Pandemic_Influenza/Guidance.html
**Degree and duration of protection:** In animal models, some human H5N1 vaccines, especially live attenuated vaccines, can confer levels of homologous and heterologous protection. In an immunologically naive population (i.e., such as in a pandemic situation) one inoculation may not be sufficient to stimulate protective response. No available evidence indicates any differences in protection based on either egg or cell production techniques or on antigen presentation. Only a few studies have considered duration of protection and cross-reactivity longer than twelve months. Initial results indicate that antibody duration varies depending on the vaccine strain.

2. **Options for using human H5N1 influenza vaccines**

   The scientific and public health rationales were discussed for some potential scenarios in which H5N1 vaccines could be used:

   1. In the current non-pandemic period, to protect people or selected groups from the risk of infection by currently occurring zoonotic avian H5N1 infections
   2. In the current non-pandemic period, to either “prime” or fully "immunize" selected groups in anticipation of the possibility that a pandemic specifically related to H5N1 could occur
   3. In the event that sustainable person-to-person transmission of H5N1 is identified early, the use of H5N1 vaccines to complement other disease control measures to try and contain the first start of an H5N1 pandemic
   4. In the event that there is sustained human-to-human transmission of H5N1 such as in a pandemic, to help protect people against severe disease

3. **Options for using the WHO H5N1 vaccine stockpile**

   In the summer of 2007, the Director General of WHO announced that a stockpile of human H5N1 influenza vaccine would be established by WHO. This was supported by some vaccine manufacturers. One company indicated that within 3 years, it would donate 50 million H5N1 vaccine doses – enough to immunize 25 million people. Two primary uses of this stockpile were discussed:

   1. To support an H5N1 pandemic containment operations
   2. To provide countries, especially the poorest ones, with some vaccine if an H5N1 pandemic occurs