Informal Consultation on Technical Specifications for a WHO International H5N1 Influenza Vaccine Stockpile
17-18 October 2007
Geneva, Switzerland

(Summary report - a more detailed report is in preparation)

Introduction

The meeting was convened by WHO to discuss technical specifications for a WHO international H5N1 vaccine stockpile. The objectives of the meeting were to develop consensus on: quality, safety and efficacy specifications; regulatory pathways; logistics specifications; further studies, if any; and to discuss guiding principles for access to the stockpile. It was noted at the outset that this was not a decision making meeting, rather a meeting to develop options for consideration by WHO. The meeting Chairperson was Dr. Gary Grohmann from the Therapeutic Goods Administration, Australia and the Rapporteur was Ms. Stephanie Hardy, seconded staff from the Biologics and Genetic Therapies Directory at Health Canada.

To provide context for the discussions, participants were informed that proposed options for use of a WHO H5N1 vaccine stockpile, based on the outcomes from a WHO meeting on use of H5N1 vaccines (1-3 October 2007), include:

1. For rapid containment in response to a pandemic signal. WHO will advise countries when such a signal has been identified and validated;
2. To provide assistance to countries that otherwise would be without access to vaccine to enable vaccination of selected parts of the population considered to be critical to maintain functionality of the country;
3. A third possible use, but only if stockpiled vaccine approaches its expiry date, is for select vaccination of people at high-risk of exposure in countries with extensive circulation in bird populations.

It was stressed that vaccines from the stockpile are not intended for use in mass immunization programs; only a small proportion of a population would likely be immunized using vaccine from the WHO stockpile. Furthermore, it was highlighted that decisions on the use of vaccine from the WHO stockpile rested with the WHO Department of Immunization, Vaccines and Biologicals (IVB) Strategic Advisory Group of Experts (SAGE), who had yet to consider this matter, and may differ from the options outlined above.
Conclusions and recommendations

Based on the presentations and meeting discussion, the consultation group provided the following recommendations for the establishment, operation, and sustainability of a WHO international H5N1 human influenza vaccine stockpile:

1. Establishment of a WHO H5N1 vaccine stockpile

- Vaccine(s) to be stockpiled should be likely to protect against novel human influenza viruses that are considered to have the potential for causing high rates of morbidity and mortality in humans.
- The stockpile should also consist of ancillary products, such as syringes, required for delivery of immunization.
- Vaccine strain selection for influenza H5N1 vaccines to be stockpiled should be based on recommendations from WHO. Such strains should be expected to produce vaccines that are cross-reactive with currently circulating wild-type H5 strains.
- Vaccines included in the WHO stockpile should be licensed by a functional National Regulatory Authorities (NRA) and also be submitted for WHO prequalification; WHO should have discussions as soon as possible with the NRA's of the country of manufacture concerning the licensure and prequalification.
- To simplify stockpile management, clear selection criteria for acceptance of vaccines into the stockpile should be developed. Based on current evidence, only inactivated influenza vaccines should be considered.
- The data requirements for regulatory approval of a WHO H5N1 stockpile vaccine are additional to the requirements for seasonal vaccines.
- The data requirements are set-out in a draft paper on target specifications that was developed in preparation for this meeting. Key elements include, but are not restricted to:
  - an appropriate stability package
  - immunization/challenge data in animal models, against both homologous and heterologous strains
  - neutralizing antibody data from clinical trials
  - evidence for cross-reactive human antibodies
  - evidence that all 3 EMEA/CHMP serological criteria are met
- The majority of data should be available pre-licensure, but some may be submitted post-licensure. WHO should define what is required pre- and post-licensure in a revision to the draft target specifications paper.
- Since we are still learning about H5N1 vaccines, WHO should retain flexibility about these data requirements and their interpretation.
- Lessons learned from the establishment of other WHO international stockpiles should be used, where applicable.

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2. Maintenance of the WHO H5N1 vaccine stockpile

- Written criteria are needed to define expectations of what needs to be done, by whom and when. These written criteria should include clear guidance about when the stockpiled vaccine needs to be changed due to the emergence of drift variants, loss of potency, or other reasons, and how to manage the intervening period until new stock is acquired.
- The written criteria should include guidance about what should be done with the vaccine that is changed out; there will be questions and uncertainty about whether discarded vaccine still can be used.
- The continued appropriateness of the H5N1 strain in the stockpiled vaccine to induce immunity against drift variants should be reviewed by WHO.
  - Sera from clinical trials with the stockpiled vaccines should be used for tests against drift variants to provide one type of data to facilitate this decision. Having processes in place to make sera available for this purpose should be a criterion of acceptance of vaccine into the stockpile. Other types of data may also be useful and should be defined in advance.
- To assess the continued suitability of the potency of stockpiled vaccine, WHO needs to develop, at a minimum the following, as an update to the draft target specifications document:
  - an agreed set of stability indicating parameters;
  - agreement on how these data will be collected (i.e. by the manufacturer, or the NRA, or by WHO-contracted labs) and how the information will be shared;
  - potency criteria, with the requirement that vaccines that do not meet the criteria would be rejected from the stockpile.
- WHO should arrange for exchange of data between laboratories studying the stability of stockpiled vaccines.

3. Potential need for further studies

The following suggestions were made for further studies; however, it was recognized that it is not an exhaustive list:

- More data on the shelf-life of vaccines, and also the effect of freeze-thawing on vaccines for inclusion in the stockpile;
- Data on the inter-changeability (both safety and immunogenicity) of influenza vaccines in the stockpile should be generated;
- Protocols for co-ordinated post-marketing surveillance (both safety and effectiveness) studies (e.g. pediatric studies).

4. Operational considerations

- The WHO H5N1 stockpile should be designed to be as simple to manage as possible.
- Further analysis is needed of the pros and cons of key issues including, but not restricted to:
  - the number of vaccines from different manufacturers in the stockpile
  - whether bulk or final product, or both, should be stockpiled
  - the possibilities of having harmonized vaccine presentations (i.e. multidose) in the stockpile, while retaining flexibility to include two-vial (i.e. antigen and adjuvant in separate vials) presentations
- the location and number of stockpiles
- whether only donations should be accepted into the stockpile, or should vaccine for the stockpile be purchased

Decisions on the above issues should be evidence informed where possible, and exercises, including at the national level, may be run to help generate appropriate data.

- The comparative advantages of sister UN agencies working with WHO to strengthen the management of the stockpile and to deploy vaccines from the stockpile should be further evaluated.
- Vaccine from the stockpile will be accompanied by a disclaimer of liability. The draft disclaimer should be reviewed as soon as possible through a consultative process.
- WHO should develop mechanisms to share information with countries on the technical basis on which vaccines have been accepted into the stockpile.

5. Country preparedness to receive vaccine from the stockpile

- The recent development of H5N1 vaccines which, based on current limited evidence are not unsafe and are suitably immunogenic, potentially provides a new tool for pandemic influenza preparedness.
  - Country pandemic preparedness planning should be modified to include plans for (a) acceptance of vaccines from the stockpile and also (b) in-country deployment of vaccine from the stockpile.
  - WHO should assist by including guidance on deployment of stockpiled vaccine in its draft deployment guidelines, and also by prioritizing the actions to be taken to enable effective deployment. Countries are encouraged to assess themselves against the guidelines.

6. Governance of a WHO H5N1 vaccine stockpile

- The WHO protocol for rapid containment does not yet include use of H5N1 vaccine; the protocol needs to be updated to accommodate this development.
- Guiding principles on who should receive vaccines from the stockpile will be helpful to countries. These guiding principles need to be effectively communicated to both the policy makers in countries and also to the populations within countries. WHO should seek to learn lessons from countries who have already established priorities for vaccine distribution from a national stockpile to limited segments of the population.

7. Ethical considerations

- Country decision making for use of vaccine from the WHO stockpile should take into account ethical considerations; ethical issues are best considered before the pandemic occurs.
- For rapid containment in response to a pandemic signal, guidance is needed on how to inform the population within the affected area.

The conclusions and recommendations from this meeting were presented to the Steering Committee for the Global Action Plan to increase accessibility to pandemic influenza vaccines on 19th October 2007, and will be presented to the Strategic Advisory Group of Experts (SAGE) on the 6-8th November, 2007.