



WORLD HEALTH ORGANIZATION

Meeting on Options for Increasing the Access of Developing Countries to H5N1 and other Potential Pandemic Vaccines
Geneva, 25 April 2007
Executive Board Room

Practical considerations based on relevant experience with existing vaccine stockpiles for other diseases¹

PART 1 -- An H5N1 Vaccine Stockpile and a Mechanism to Procure Pandemic vaccines

I. Introduction on the Challenges of H5N1 and Pandemic Influenza Vaccines

1. The threat of an influenza pandemic continues. While no sustained human-to-human transmission of the H5N1 virus has occurred, the persistence of H5N1 outbreaks in poultry in many countries increases opportunities for the virus to acquire the properties needed to start the next pandemic, thus reinforcing the need to enhance preparedness plans. Since late 2003, 291 human cases of H5N1 avian influenza, with 172 deaths, have been reported in 12 countries. Many of these cases have occurred in younger age groups; 59% of cases were fatal. Low-income countries have been the most severely affected. Should this virus start the next pandemic, the high mortality associated with infection could bring significant global consequences.

2. WHO has responded with concrete actions to control outbreaks of human cases of avian influenza. WHO has developed and disseminated a strategic action plan that guides the implementation of an early warning system and rapid response actions, and is heavily engaged in assisting countries in their development of pandemic preparedness plans. WHO works in close collaboration with FAO and OIE.

3. **Vaccines** are regarded as the most effective and powerful medical intervention to prevent influenza and reduce its health consequences during a pandemic. Vaccines are used routinely to protect populations from seasonal influenza in some countries, but not in others. All countries are encouraged to assess the costs and benefits of including seasonal influenza vaccine in their immunization programs. Increased routine utilization of seasonal influenza vaccines would lead to increased manufacturing capacity for both seasonal and pandemic vaccines.

4. Current limitations related to vaccine production and vaccine type constrain worldwide production capacity of a monovalent vaccine for H5N1 or a pandemic influenza virus to approximately 1.5 billion doses per year. New production technologies that would produce much higher yields are under development and are expected to become operational soon. In addition, local production capacity in some developing countries is continuing to evolve.

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5. The overall shortage of vaccine production capacity, particularly in developing countries, and the present cost of vaccines present obstacles for many countries wishing to procure vaccine to protect populations during an influenza pandemic. With present capacity, it will take approximately six months after the emergence of a pandemic virus to produce the first doses of a pandemic vaccine. Furthermore, potential access to an H5N1 vaccine or a pandemic vaccine is highly uneven in developing countries having no production capacity for influenza vaccines. This situation and a recent recommendation by the SAGE expert advisory committee to WHO has led WHO to consider two measures: the establishment of a vaccine stockpile for H5N1 influenza vaccine, and the creation of a mechanism for improving access to a pandemic vaccine in resource-constrained countries, once a pandemic has been declared

6. WHO has considerable experience in managing stockpiles, in collaboration with partners, for smallpox, meningitis, yellow fever, and (but not yet fully operational) polio vaccines. Lessons from these stockpiles provide insight into the issues surrounding development of a stockpile of vaccines for H5N1 or another pandemic strain. It should be noted, however, that these diseases pose different sets of problems. Longer-term solutions for improving influenza vaccine supply and access have been addressed in the recent WHO Global Pandemic Influenza Action Plan to Increase Vaccine Supply.

7. These different stockpiles share two needs: to manage a scarce commodity, and to respond quickly. WHO and its advisory groups play a leading role in decisions about when to use such stockpiles, the establishment of public-private partnerships to develop new vaccines, and the bundling of vaccines with required syringes and other equipment.

II. H5N1 Vaccine Stockpile and Pandemic Vaccine Procurement Considerations

8. On 18 April 2007, the WHO expert advisory committee on immunizations, vaccines, and biologicals (SAGE) met to review current scientific evidence. The following conclusions were reached. **"SAGE agreed to recommend to the Director-General that there was sufficient evidence for WHO to create a stockpile of H5N1 influenza vaccine for countries without influenza vaccine production capacity or ability to purchase stockpiles of H5N1 vaccines.... SAGE also agreed to recommend to the Director-General that WHO should establish mechanisms for ensuring access to pandemic vaccine, should a pandemic be declared by the Director-General, for distribution to developing countries, without influenza vaccine production capacity or resources to purchase such vaccines."** A series of additional recommendations established the groundwork for future WHO and partner action to make this a reality. These are set out in another document.

9. Several manufacturers have developed H5N1 vaccines which meet criteria for licensing by the US Food and Drug Administration, (FDA), European Medicines Evaluation Agency (EMA) or other National Regulatory Agencies (NRAs). Moreover, initial evidence indicates that at least some of these vaccines can induce broad-spectrum neutralizing antibodies that provide some cross-protection, in animal models, against divergent H5N1 viral strains. The demonstration of cross-reactivity, although limited, provides some evidence that an international stockpile of H5N1 vaccine based on current strains may be substantially effective against future H5N1 strains.

10. An H5N1 stockpile would consist of H5N1 vaccines based on H5N1 viruses currently infecting humans. The vaccine to be stockpiled would meet criteria for licensing by NRAs and for prequalification by WHO. A mechanism, yet to be defined, would focus on future pandemic vaccine produced under cGMP using the actual pandemic influenza virus strain, which is unknown at this time. Legal issues related to the use of these vaccines would be addressed.

11. The full uses of such stockpiles have yet to be defined. However, in the current period, such a stockpile could potentially be used to protect some persons against infections from H5N1 avian

influenza. Should early outbreaks involving human-to-human transmission of the H5N1 virus occur, vaccine might be used to help limit early spread. If a pandemic were caused by H5N1, another potential use would be immediate immunization of persons performing essential functions, for example, those working to maintain the function of health systems and other critical national infrastructures. Vaccine might also be used to immunize persons to provide broad H5 immunity in anticipation of a future pandemic caused by the H5N1 virus. Evidence is continuously evaluated by WHO to ensure that policies are developed or updated in line with the evolving situation. All of these options deserve further investigation.

12. The potential public health benefits of using these vaccines for such purposes have not been assessed, and in some cases such an assessment would be very difficult.² Furthermore, there are potential risks linked to pre-pandemic use of H5N1 vaccines, including unexpected adverse effects. Such risks would have to be weighed against the fact that there might be no immediate benefit or even no benefit at all in using the vaccine if the vaccine virus strain does not match or provide cross-protection against the actual pandemic strain.³ Legal issues will need to be addressed.

13. Pandemic vaccines would likewise need to meet criteria for licensing by US-FDA, EMEA or other NRAs. Mechanisms are needed to ensure that, as these vaccines are developed, licensed and produced, they are added to the stockpile.

14. All influenza vaccines for stockpiling would need a particularly well-defined programme for stability testing to ensure continued vaccine potency and safety throughout the stockpiling period.⁴

15. The development of technical, practical and operational mechanisms must be further addressed by the WHO Secretariat based on guidance from its advisory bodies, giving due consideration to epidemiological, programmatic, policy, economic, governance, legal and other realities.

16. The WHO Global Pandemic Influenza Action Plan to Increase Vaccine Supply, released in September 2006, lays out an overall strategy for increasing seasonal vaccine use, increasing production capacity, and fostering research and development. Discussions about vaccine stockpiles are a logical next step in the process of bolstering global capacity to reduce the impact of a pandemic.

PART II - Recommendations for an H5N1 Stockpile

17. Given the specifics surrounding H5N1 and the lessons derived from other WHO-managed stockpiles, the following mechanism might be considered:

A WHO H5N1 Vaccine Reserve Stockpile

- WHO will develop an H5N1 vaccine reserve, with funding derived from an international appeal, to establish an initial stockpile with _____ doses.
- Decisions for release and use of vaccine stocks will depend upon pre-determined criteria. Criteria will consider epidemiological, logistic, laboratory, security, and infrastructural factors.
- The *Ad Hoc Advisory Committee* on avian influenza will be requested to assist in developing guidance on criteria for release and use of the vaccine
- Decisions to release vaccine stocks will rest with the Director-General under advice from the IHR(2005) Emergency Committee.

²WHO Guidelines on Regulatory Preparedness for Human Pandemic Influenza Vaccines (currently under development, April 2007) World Health Organization, Geneva, Switzerland

³ Id.

⁴ Id.

- WHO will serve as the procurement agent and will identify key partners to ensure that the vaccines meet quality standards, and are stored under proper conditions with necessary vaccine-delivery materials.
- Procedures for vaccine replenishment will be developed.
- Legal disclaimers and pre-registration for use in countries will be undertaken by WHO. (See Annex 1 for example used by the Global Smallpox Vaccine Reserve)

A WHO National Pledged H5N1 Stockpile

- WHO, working with its Member States and vaccine manufacturers, will immediately assess the extent to which manufacturers and/or countries with vaccine manufacturing capacity, or purchasing available H5N1 stocks, are willing to pledge some of their existing stock for use by WHO in the event of an emergency outbreak.
- Technical issues such as vaccine type and location of said stocks will be assessed.
- Decision criteria will be pre-determined.

An Approach for Pandemic Influenza Vaccine

- A pandemic does not exist at this time and it is impossible to predict which influenza strain could trigger such an event. However, the time available to react to a pandemic will be very short.
- WHO, working with its partners and financing institutions such as GAVI, will explore how best to establish financing mechanisms supporting pre-contracting arrangements with manufacturers to produce and deliver a quantity of pandemic vaccine for use in developing countries.
- WHO and its advisory bodies will develop decision criteria concerning how companies could best release these reserved stocks, which may be limited.

PART III -- Lessons From Existing Vaccine Stockpiles of Other Diseases and Their Application to H5N1 and Other Pandemic Strains

18. Regardless of the type of vaccine, all of the stockpiles share common elements, although their application can vary by disease. (see box).

19. Vaccine stockpiles for influenza differ in one significant way from vaccine stockpiles for other diseases. **The highly mutagenic nature of the influenza virus introduces a level of uncertainty about how well the stockpiled vaccines will match wild-type viruses. This is not the case for diseases such as meningitis, yellow fever or polio.**

- Underlying strategy governing use of stockpiles
 - Normative standards governing choice of vaccine and multiple types
- Management mechanism(s) for distribution and logistics
- Location and storage
 - Risk management
 - Co-bundling with all materials needed (e.g, syringes)
- Governance
- Criteria and rules for release of vaccine
- Financing
 - Pre-contracting
- Regulatory/Legal
- Safety and quality assurance
- Timing
- Vaccine specific issues:
 - Shelf life
 - Availability of vaccine
- Monitoring and evaluation of effectiveness and adverse events

20. WHO manages stockpiles for four diseases: smallpox, meningitis, yellow fever, and one planned for polio. The methods by which these stockpiles are organized, managed and deployed have potential relevance for an H5N1 stockpile.

21. **Management.** In all cases WHO and its advisory bodies play a key role in decisions about when stockpiles are used. For smallpox, WHO manages a small, locally-held reserve stockpile, but countries also pledge to make part of their national stockpiles available to WHO if needed.

22. **Decisions on use.** For smallpox and polio, the DG would make the decision on use after consulting the IHR Emergency Committee. For meningitis and yellow fever, countries may apply for use of the vaccine stockpile; applications are reviewed, using pre-determined release criteria, by a multi-partner International Coordinating Group.

23. **Relevance of window period to H5N1.** For many of the stockpiled vaccines as well as for H5N1 or pandemic vaccines, the window of time is hours to days to assess and initiate a response following verification of an outbreak. Timely decision-making is critical

24. **Public-private partnerships for development of vaccine.** The meningitis control programme and its vaccine stockpile demonstrate that new vaccines can be developed through a mechanism whereby WHO signs a memorandum of understanding with industry, supported by an international appeal.

25. **Bundling of vaccine with required materials such as syringes.** Such bundling is required by all WHO-managed vaccine stockpiles. This requirement has implications for storage and shipping costs. In several cases, the manufacturer manages the stock with instructions coming from WHO.

26. **Costs to maintain stockpiles.** Beyond the actual cost of the vaccines and related materials, each of the stockpiles is managed by a few WHO staff. In the case of meningitis and yellow fever, there is the added cost of managing the ICG mechanism.

Conclusion

27. During the past decade, WHO and several partners have acquired considerable experience in designing and maintaining active vaccine stockpiles for rapid deployment to countries, often in response to the emergency conditions of an outbreak. In addition to vaccine stockpiles, WHO and its partners are engaged in managing several global drug facilities, including one involving a stockpile of an influenza antiviral drug, and one for first-line TB drugs.

28. Much experience has been acquired during these activities that can guide the development of a stockpile of a vaccine for H5N1 or another pandemic influenza virus.

29. Many industrialized countries have decided to support the development and purchase of pre-pandemic vaccine, for example, for H5N1. In addition, countries have contracted with vaccine manufacturers for the development and purchase of vaccine in the event of a pandemic. H5N1 vaccines are being developed and infrastructure created which will require, in the near future, that countries make policy decisions for using such vaccines. These decisions must take into account the need for developing countries to have equitable access to vaccines as part of a global response to reduce the health and socio-economic consequences of a pandemic. WHO has demonstrated that it has great experience in the development and management of stockpiles, and can draw upon this experience in responding to new challenges.

30. The new challenges to be faced in relation to H5N1 and pandemic influenza vaccines are:
a) the present lack of licensed products and the need to assess safety and efficacy as efficiently as possible are important immediate problems,
b) the exact identity of the virus strain that will cause the next pandemic cannot be known in advance, and
c) countries with production capacity will be facing a need to respond domestically to the same threat as developing countries that are in need of WHO and international support.

ANNEX 1 -- Legal Disclaimer Used by Global Smallpox Vaccine Reserve

DISCLAIMER ACCOMPANYING SMALLPOX VACCINE

FOR INCLUSION IN:

1. THE REQUEST FORM

2. THE LETTER TO THE GOVERNMENT ADDRESSED AS PER OFFICIAL LIST OF ADDRESSES; AND

3. IN THE NOTICE ACCOMPANYING THE VACCINE

PLEASE DELETE THE HEADINGS AND COMPLETE THE TEXT, BEFORE EACH USE

The supply of smallpox vaccine is to be used with the diluent provided, or with equivalent diluent as recommended by the manufacturer (if any) or with diluent consistent with the standards and use during the smallpox eradication programme or standards subsequently recommended by WHO. The vaccine and the diluent are hereinafter severally and jointly referred to as “the smallpox vaccine” or “the vaccine”.

By accepting delivery of the smallpox vaccine from WHO’s stockpile, the Government of[insert the name of the country], hereinafter referred to as “the Country”, accepts and agrees that this vaccine has been supplied by WHO on the following terms and conditions:

The vaccine is being supplied to the Government exclusively for emergency use under the control of the Government, in the event of a virologically and epidemiologically confirmed outbreak of smallpox in the Country. In this connection, although it is generally believed that the vaccine may still be useful in case of emergency, the Government confirms that it has full knowledge of:

- the known side effects of the vaccine, as described in the relevant and most recent literature (it being understood that the Government shall be responsible for identifying such literature); and
- the fact that the vaccine quantity supplied by WHO to the Government:
 - (a) may have been manufactured many years ago and may be past its original expiry date;
 - (b) may have been manufactured from old bulk product which was produced many years ago and may not therefore meet current standards;

(c) may have been manufactured through the use of techniques which do not reflect current standards and/or current state of the art, or techniques which have not or not yet been accepted by any regulatory authority;

(d) may not have been shown to be clinically effective in the prevention of smallpox (even if the vaccine may have satisfied the safety requirements of regulatory bodies).

(e) may possibly give rise to additional and/or more frequently occurring safety concerns (i.e. over and above those described in the literature referred to above), including serious, life threatening or fatal adverse reactions.

The Government further acknowledges that it has been duly informed that the vaccine is not, may no longer be, or may never have been licensed for use in any country of the world. Even if the vaccine may have been approved for emergency use by national authorities in the country of manufacture, the vaccine may not fulfil the requirements for licensing in other countries.

It is noted that the vaccine has been routinely tested for its potency and has at the time of last testing in(insert month and year of last testing) been found to be adequately potent with a titer of at least 5×10^7 pock forming units per ml when reconstituted, or a different level acceptable to WHO. Since no other analyses may have been performed on the vaccine quantity supplied to the Government, this vaccine quantity is being supplied "as is", without any warranties or representations whatsoever, whether express or implied, including, but expressly not limited to, any implied warranties as to the vaccine's fitness for a particular purpose or use, or as to its safety, efficacy, or quality in any respect. Similarly, neither WHO nor any (direct or indirect) supplier of the vaccine to WHO or the Country (including but not limited to any donor, manufacturer or distributor of the vaccine) warrants or represents that the vaccine quantity has been manufactured to meet its specifications and/or Good Manufacturing Practices (GMP), nor that it has been stored, handled and/or transported under appropriate conditions. The Government confirms that it will weigh the risks associated with a virologically and epidemiologically confirmed outbreak of smallpox in the Country against the risks associated with the use of the aforesaid vaccine quantity, including the possible occurrence of serious, life threatening or fatal adverse reactions in a potentially high number of cases. In deciding to use this vaccine quantity, the Government shall come to its own conclusion that such use is justified under the circumstances. The Government of the Country shall thus be solely responsible for, and accepts, any and all liability for the use of the vaccine. Specifically, the Government of the Country agrees to indemnify, defend and hold harmless WHO and any (direct or indirect) supplier of the vaccine to WHO or the Country (including but not limited to any donor, manufacturer and/or distributor of the vaccine) as well as their officers, employees and agents, for any and all costs, expenses and claims of any kind arising from, as a result of, or in connection with the supply, distribution and/or use of the vaccine in the Country, by or on behalf of the Government or otherwise.

If the Government does not agree with the above terms, the entire vaccine quantity should be returned to WHO, without being used in any way.