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Final Report

Informal Consultation on Technical Specifications for a WHO International H5N1 Vaccine Stockpile

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Summary

This report reflects the presentations, discussions, and conclusions from a meeting convened by the World Health Organization (WHO) on 17-18 October 2007 in Geneva, Switzerland to consult on the 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; and logistical specifications for the proposed stockpile. The need for additional studies and guiding principles for access to the stockpile were also discussed. This was not a decision making meeting, rather a meeting to develop options for consideration by WHO.

Representatives from Ministries of Health, National Regulatory Authorities, National Control Laboratories, Influenza Reference and Collaborating Centres, industry, academia, non-governmental organizations, WHO, and members of the Global Action Plan (GAP) to increase pandemic influenza vaccine supply attended the meeting. 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 Directorate, Health Canada.

Meeting participants provided recommendations for the establishment, maintenance, operation, and governance of a WHO international H5N1 human influenza vaccine stockpile. Considerations for further studies, country preparedness to receive stockpiled vaccines, and ethical considerations were also identified. A comprehensive summary of the conclusions and recommendations is provided in Section 8 of this report and will be presented to the WHO Department of Immunization, Vaccines and Biologicals (IVB) Strategic Advisory Group of Experts (SAGE) on the 6-8 November 2007 for decision-making.

Introduction

Dr. Marie-Paule Kieny, Director of the Initiative for Vaccine Research, welcomed participants on behalf of WHO. The meeting was being held as one part of the response to the World Health Assembly (WHA) resolution 60.28, which requests the Director General of WHO to establish an international H5 stockpile and to develop transparent rules and procedures for its operation, prioritization, release of stocks, management, and oversight.

The objectives of the meeting were to generate recommendations for the establishment, operation, and sustainability of a WHO international H5N1 vaccine stockpile. Consensus was being sought on quality, safety, and efficacy specifications, regulatory pathways, logistics specifications, further studies, if applicable, and guiding principles for access to the stockpile. This was not a decision making meeting, rather a meeting to develop options for consideration by WHO. Recommendations from the meeting, along with recommendations from a consultation held on the use of H5 vaccines (1-3 October 2007) were reported to SAGE on 6-8 November 2007. SAGE advises the WHO Director General on all matters related to immunization.

A round table of introductions was initiated, after which Dr. Gary Grohmann was appointed Chairperson and Ms. Stephanie Hardy, Rapporteur.

Session 1: Setting the scene

Overview of an international H5N1 stockpile

(Dr. Peter Carrasco, Expanded Programme on Immunization, WHO)

The rationale for creating a WHO international H5N1 vaccine stockpile was presented. Resource poor countries consider H5N1 virus to be a national security and public health threat, and they perceive that they do not have timely and affordable access to sufficient quantities of the vaccine. In April 2007, SAGE recommended to the WHO Director General that there was sufficient evidence to create a WHO H5N1 stockpile for countries without influenza vaccine production capacity or ability to purchase stockpiles of H5N1 vaccines. Subsequently, in May 2007, the WHA approved Resolution 60.28 to establish a WHO international H5N1 vaccine stockpile.

GlaxoSmithKline announced in June 2007 that they would deliver, over three years, 50 million doses of H5N1 adjuvanted influenza vaccine to WHO in support of its stockpile. This would provide vaccination for 25 million people (two doses per person). Other manufacturers have also indicated willingness to make vaccine available.

Technical issues to discuss were mentioned and included: vaccine type, dosing schedules, stockpile location, release criteria, shelf-life, ancillary supplies, and testing stockpiled vaccine against drifting strains.

Summary outcomes of the "Use of H5 vaccines" WHO meeting from October 1-3, 2007 (Dr. Keiji Fukuda, Global Influenza Programme, WHO)

A WHO meeting was held on 1-3 October 2007 to develop consensus on policy options for the use of H5 vaccines, including vaccines in an international stockpile. Meeting participants were presented with available scientific data on H5N1 vaccines. The potential vaccine uses in the current inter-pandemic period and potential uses of a stockpile in a pandemic event were discussed. Based on available evidence, there were no known significant safety concerns with the H5 vaccines reviewed that were above those associated with seasonal vaccines.

Proposed options for use of a WHO H5N1 vaccine stockpile, included: (1) For rapid containment in response to a pandemic signal; (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; and (3) A third possible use, but only if stockpiled vaccine approached its expiry date, would be for select vaccination of people at high-risk of exposure in countries with extensive circulation in bird populations. Vaccine would be used along with other control measures such as antivirals and quarantine. The recommendations from the 1-3 October 2007 meeting, along with the results from this meeting were reported to SAGE in November 2007.

Lessons learned from other WHO vaccine stockpiles
(Dr. Sylvie Briand, Global Influenza Programme, WHO)

Key lessons learned from the management of the WHO yellow fever and meningitis vaccine stockpiles were presented. The characteristics of a stockpile depend on the disease, the use of the vaccine, and the underlying principles, such as solidarity and equitable access. Vaccines in the yellow fever stockpile that are not used for emergency response are made available for preventive campaigns.

It was highlighted that the stockpile was just one element of a complex process. Ancillary equipment, shipping, vaccination campaigns, waste management, and surveillance were also important elements that should be considered when establishing a stockpile. Funding and replenishment of the stockpile were important considerations. The yellow fever stockpile is funded through the GAVI Alliance; however, the meningitis stockpile is dependent on the country and replenishment has proven to be difficult due to lack of funds at the country level. For emergency vaccination campaigns, there has been a change in paradigm from vaccine stockpile to "vaccination package stockpile", which contains bundled vaccines with syringes and safety boxes.

An International Coordinating Group (ICG), comprised of four international partners, is responsible for making decisions on the release of vaccine from the yellow fever and meningitis vaccine stockpiles based on pre-defined criteria. For the yellow fever vaccine stockpile, these criteria are published in guidelines, and a country's level of preparedness to conduct a vaccination campaign is one of the criteria. A mechanism for needs forecasting is necessary. For the yellow fever stockpile, there was a need for a gradual increase to meet changing needs. Of importance is maintaining vaccine production capacity to ensure vaccine supply continuity. One

presentation is more desirable than different presentations as it allows for standardized training and protocols for vaccine reconstitution and administration. If the stockpile is to be used for emergency response, transportation and forecasting of supply and deployment to multiple sites would be of consideration. Ancillary equipment is usually sent separately by boat as most countries already have syringes and other supplies, thereby reducing costs.

Both the yellow fever and meningitis stockpiles are stored with the manufacturers, and only WHO pre-qualified vaccines are accepted into the stockpiles.

On average, deployment of vaccine from the stockpile takes 30.5 days between first case and start of the campaign. Potential ways to shorten this time would be to decrease the time it takes to confirm the event (epidemiological confirmation), or to improve country preparedness for the vaccination campaign.

Differences between existing stockpiles and the proposed H5N1 stockpile were discussed. Unlike the H5N1 vaccine, yellow fever immunization only requires one injection that offers 10 year protection and the same vaccine has been used for years. The proposed use of a WHO international H5N1 stockpile is for outbreak control rather than mass immunization; therefore, only a small proportion of the vaccine is expected to be released to a given population.

Session 2: Quality, safety, and efficacy considerations for a WHO international stockpile

Current WHO specifications to assure the quality, safety and efficacy of stockpiled H5 vaccines *(Dr. Gary Grohmann, Therapeutic Goods Administration, Australia)*

A WHO international H5N1 stockpile does not currently exist, but there are pledges from companies to donate vaccine in support of a WHO stockpile. An overview of the technologies currently being used to develop vaccines against novel human influenza viruses, including cell culture, recombinant haemagglutinin (HA), and egg-based technologies was presented. Both licensed and novel adjuvants are being investigated and a range of vaccine candidates are slowly becoming available. Live attenuated influenza vaccines (LAIV) for H5N1 are being developed with one dose, needle-free administration. This is ideal for administration to children; however, there may be storage issues.

Stockpiling of H5N1 vaccines is an important part of a global pandemic plan. The acceptable non-clinical and clinical data requirements pre-licensure for an H5N1 vaccine in a WHO international stockpile, the provisions for strain change due to drift variance, and the provisions to ensure that donations in the stockpile remain adequately potent and acceptable to National Regulatory Authorities (NRAs) were identified in this session.

Potential target non-clinical and clinical minimum data requirements for regulatory oversight of human H5N1 influenza vaccines in an international stockpile

(Dr. Roland Dobbelaer, Belgium)

The potential target non-clinical and clinical data requirements for vaccines in an H5N1 vaccine stockpile were presented. The proposed requirements were derived from the draft WHO Guidelines on Regulatory Preparedness for Human Pandemic Influenza Vaccines (1) and set out in a background paper prepared for this meeting (2). Target data requirements for inactivated influenza vaccines that are (i) developed in the inter-pandemic period (vaccines against novel human influenza viruses), and (ii) human pandemic influenza vaccines that are developed once a pandemic is declared with the identified pandemic strain were laid out in the background paper. It was noted that the considerations are likely to change as knowledge accrues.

The data requirements in the WHO recommendations for the production and control of seasonal influenza vaccine (inactivated) (3) are generally applicable to inactivated vaccines intended for stockpiling. Specifically, a mechanism for providing data on the vaccine strain, biosafety level, adjuvants, and potency testing would be important. It was noted that reagents for potency testing may not be readily available. The stability of intermediates (bulk antigen) is important for storage in a stockpile, and a combination of real time and increased temperature stability data would be needed.

The WHO guidelines on non-clinical evaluation of vaccines (4) are generally applicable to stockpiled vaccines. For H5N1 vaccines, data should be derived from a vaccine prepared with a virus variant antigenically and genetically closely related to the virus against which protection is claimed; data on other strains could be considered supportive. Immunogenicity and challenge data in animal models (e.g. ferrets) should be required.

The WHO guidelines on clinical evaluation of vaccines (5) would be applicable to H5N1 stockpiled vaccines. The indications should reflect the target population and extrapolation should be conducted with extreme care. Immunogenicity in naïve population demonstrating as high an antibody response as possible and a comprehensive characterization of immune response, including duration would be desirable. Plans to assess efficacy and long-term safety during a pandemic should be established. Clinical pediatric data should be collected using a step-wise approach, from adults to children, taking into account existing relevant pediatric clinical data for that manufacturer's seasonal influenza vaccine.

The importance of collecting as much data as possible on vaccines developed during the inter-pandemic period, and to establish plans to further assess the vaccines in the case of a pandemic was stressed.

Strategies to ensure that internationally stockpiled H5N1 vaccines remain safe and effective with special consideration to virus drift variance

(Dr. Michael Pfeleiderer, Paul-Ehrlich-Institut, Germany)

In the European Union (EU), the shelf-life of seasonal vaccines is restricted to 12 months and limited holding periods are approved for the intermediates. These may be extended if strains do

not change. Due to the nature of the product, stability data is generated retrospectively rather than prospectively; therefore, there is no real experience with long term stability. For H5N1 vaccines, there is a strong interest in generating long-term stability data. There is currently very limited long-term experience with full scale lots.

A broad range of possibilities for long term storage of vaccines with respect to shelf lives and holding periods of starting materials, vaccine intermediates, and drug substance exists. Liquid frozen formulations can have a shelf-life of two years while the shelf-life of freeze-dried frozen formulations (e.g. smallpox vaccines) can be decades. Liquid intermediates can be held no longer than three years and final bulks can be held for weeks to months. The impact of cumulative holding periods of vaccine intermediates on the finished product is very difficult to investigate. Vaccine intermediates may reach a significant age before its shelf-life in the vaccine starts.

Available data on pilot lots suggests that storage period of 12-15 months for H5N1 is feasible. A participant noted that data from the United States suggest an 18 month storage period for bulks. Eighteen month stability data on commercial lots are expected in December 2007.

It is likely that the WHO stockpile could consist of vaccines from multiple manufacturers, contain multiple adjuvants, formulations and presentations. Concerns regarding diversity of stockpiled vaccines included differing quality, immunogenicity, safety profiles, lack of data on interchangeability of vaccine, and no standardized regulatory dossier content and labeling information.

To monitor and control an international H5N1 stockpile, routine and extended stability testing programs would be needed to ensure that quality, and non-clinical (e.g. cross protection against vaccine and drift variants) and clinical performance remained unchanged. To identify the lower threshold for potency, end of shelf-life studies would be needed to determine whether the same non-clinical and clinical performance are achieved with decreased antigen.

Potential future options, such as “stockpiling in humans”, the development of tetravalent influenza vaccines (seasonal plus H5N1 vaccine), regional influenza vaccine production, and the development of stable (e.g. frozen, lyophilized) drug substance or drug product that could be maintained for long periods, were presented.

Assuring quality, safety and efficacy of stockpiled H5 influenza vaccines – industrial considerations *(Dr. Giuseppe Del Giudice, IFPMA)*

From an industry perspective, the quality and safety of stockpiled vaccines should be comparable to those of any other influenza (seasonal, vaccines against novel human influenza viruses). The stability of stockpiled vaccines should ideally be longer than seasonal vaccines in order to reduce stock replacements. Vaccine efficacy should be based on efficacy in animal models whenever appropriate, and cross-reactivity of antibodies with H5N1 strains in clades different from the one used for the preparation of the vaccine. The key characteristic of a stockpiled H5N1 vaccine should be its ability to provide acceptable immune response able to be functionally active against a pandemic mismatched strain.

The availability of virus strains and single radial immunodiffusion (SRID) reagents is essential to vaccine production. Reagents should be prepared as soon as the strain is available, and industry encourages the development of secondary standards to be calibrated based on primary standards provided by WHO.

Manufacturers should commit to share ongoing stability data with NRAs. Pro-active alignment with industry and National Control Laboratories (NCL), and the establishment of a mutual recognition system and national laboratory network are encouraged to avoid additional testing.

Session 3: Regulatory pathways

Regulatory oversight of donated H5N1 vaccine by a potential producing country

(Dr. Elwyn Griffiths, Health Canada)

The responsibilities for management and regulatory oversight of a stockpile need to be well-defined in advance. The location and nature of the stockpile will impact who is responsible for managing it. If bulk antigen or final formulated vaccine bulk is stockpiled, it would need to be stored with the manufacturer. However, if finished product is stockpiled, the product could be stored anywhere. The nature of the stockpile will also impact timelines and capacity for delivery and use of the vaccines. Finished product that is already released by the relevant NRA would enable a short-term response; however, it assumes that H5N1 vaccine can be stockpiled in its final form. Stockpile of bulk antigen and/or final formulated bulk would need formulation, filling, labeling, quality control and lot release. It would also require surge capacity and availability of filling lines to avoid delays in delivery.

The regulatory oversight of an H5N1 stockpile differs from existing stockpiles, which contain well known fully licensed products with established safety and efficacy profiles. Real protective efficacy and large scale safety of H5N1 vaccines is still unknown; therefore, post use surveillance will be important. The stockpile will need a well defined stability testing program to justify its design. Immunogenicity and safety must be maintained throughout the storage period, and replacement criteria should be established.

If the stockpile is located in the country of manufacture, the NRA could license and assume regulatory responsibilities. If the stockpile is located outside of the country of manufacture, special arrangements may be required. Pre-qualification of H5N1 vaccines may facilitate licensure and vaccine availability. However, WHO criteria may differ from the country's licensing criteria. Early discussion with NRAs of potential donor countries concerning prequalification criteria and licensing details is recommended.

Regulatory requirements in a potential recipient country of H5N1 vaccine from an international stockpile *(Dr. Lucky Slamet, National Agency of Drug and Food Control, Republic of Indonesia)*

As of 12 October 2007, there were 110 confirmed human cases of H5N1 in Indonesia. Indonesia is implementing a pandemic preparedness strategy that consists of containment of avian influenza and early response to pandemic influenza. Within Indonesia there is a policy that only Indonesian strains can be used in the development of pandemic vaccines. Discussions are underway regarding the use of other strains. Indonesia currently has one vaccine manufacturer; however, they do not have any seasonal influenza experience. Various approaches are being implemented to increase pandemic influenza vaccine manufacturing capacity.

An overview of the regulatory framework for vaccines in Indonesia was presented. Vaccines against novel human influenza viruses can be made available either through a priority for normal track licensing/registration process or through a Special Access Scheme (SAS). Under the priority registration process, market authorization for stockpile purposes could be granted within 75 days. The SAS would make vaccine available, prior to marketing authorization, to particular patients in limited amounts based on doctor justification. Once a pandemic is declared, a fast track marketing authorization process would be triggered and post-market/post-licensure issues would be managed (e.g. risk management and risk communication on adverse events following immunization). Key challenges include preparedness for quality control testing and lot release procedures. For stockpiled vaccines, testing will depend on the national quality control laboratory.

Lot release testing of internationally-stockpiled H5N1 vaccine *(Dr. Florence Fuchs, Afssaps, France)*

Possible scenarios for stockpiling H5N1 vaccines were reviewed. Final lots, final bulk, or monovalents could be stockpiled. If final lots are stockpiled, the lots could be released by the NRA of the country of manufacture. If final bulk is stockpiled, this could help to limit the stockpile size. The bulk could be released by the country of manufacture; however, filling and packaging would need to be performed either by the bulk producer or by a second manufacturer in another country. Stockpiling monovalent may be of interest for antigen sparing; however, similar to stockpiling bulk, clarification would be required on who would be responsible for remaining filling and release activities. WHO and national lot release procedures may need to be adapted if final bulk or monovalents are stockpiled. In all scenarios the lot release testing and roles and responsibilities for release need to be defined in advance. Interaction between NRAs, NCLs, inspectorates, and manufacturers should be promoted.

Stability, potency, and availability of test reagents are key issues for lot release of stockpiled vaccines. A stability testing program is needed to ensure continued immunogenicity and safety throughout the stockpiling period. Delay in availability of strain specific reagents for SRID testing is of concern. If necessary, surrogate or additional tests may need to be used, instead of the SRID test. Alternative HA content measurement tests for formulation should be agreed upon if no reagents are available.

Collaboration between the National Institute for Biological Standards and Control (NIBSC) and NCLs for fast track antigen calibration procedures should be promoted. NCLs need to evaluate testing capacities and opportunities for mutual recognition of batch release should be explored in advance. The presentation was closed by sharing Afssaps experience with the French national influenza stockpile, which involves a six-year stability monitoring program.

Post-use regulatory expectations for an international H5N1 stockpile

(Dr. Karen Midthun, Food and Drug Administration, USA)

There will be limited safety and effectiveness data available for H5N1 vaccines at the time of licensure; therefore, robust safety and effectiveness monitoring with post-licensure use is essential. Post-marketing surveillance (PMS) will enable national authorities to make informed and timely decisions regarding changes to the vaccination program and to communicate and share relevant information with different stakeholders.

As part of regulatory preparedness for PMS, NRAs and Public Health Authorities (PHA), working together with other stakeholders should strengthen and test PMS systems before a pandemic occurs. NRAs and PHAs should work with WHO to pilot information exchange on seasonal influenza vaccine safety or other vaccine programs, in preparation for sharing such data in a pandemic situation. Risk communication strategies at the national and international levels should be developed. Consideration among NRAs, WHO, and other stakeholders could be given to the development of similar approaches to adverse event reporting.

Regulatory pathways for stockpiled H5N1 influenza vaccines – industry viewpoint *(Dr. Francois Verdier, IFPMA)*

According to International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), many NRAs have indicated that it would be desirable to have registered vaccines within a stockpile. Regulatory procedures for licensing vaccines intended for stockpiling need to be defined quickly. Given the urgency, industry proposes that an initial limited database for safety and immunogenicity data be accepted, and additional data be collected during the stockpiling period to expand the database.

WHO pre-qualification processes need to be defined for stockpiled vaccines; the current document only addresses seasonal vaccines. WHO pre-qualification could facilitate access to H5N1 vaccines by developing countries. The process needs flexibility to respond to emergency situations.

It is proposed that the initial vaccine license be obtained with a limited shelf-life, and ongoing data collection allow for extension of the shelf-life during the storage period. There is a potential need to explore alternative stability conditions in case maintenance of cold chain is not possible. Cross protection against other strains is essential for stockpiled H5N1 vaccines. Available data should be submitted as part of the licensure process and could be updated throughout the stockpiling period to include data against drifting strains.

Global organizations can facilitate the development of a regulatory framework that allows for rapidly registerable vaccines at a national level by having harmonized or centralized batch release and pre-qualification by cross-reference to already approved files. Updated data should continue to be accepted throughout the stockpiling period. A mutual recognition system is promoted by industry; however, it was noted by at least one participant that the importing NRA should have the ability to scrutinize the license.

WHO pre-qualification of H5N1 vaccines (*Dr. Huib van de Donk, Consultant for WHO, The Netherlands*)

In response to a need expressed by the United Nations (UN) and to stimulate increased production capacity to facilitate availability of pandemic vaccines, WHO developed a process to pre-qualify seasonal influenza vaccines. A process to pre-qualify vaccines against novel human influenza viruses is also being developed in anticipation that knowledge of such vaccines will assist the evaluation of human pandemic influenza vaccines in a pandemic event.

The pre-qualification process for vaccines against novel human influenza viruses will include specific modifications, but it will be based on the WHO process for seasonal influenza vaccines as outlined in the "Special considerations for the expedited procedure for evaluating seasonal influenza vaccines".¹

It is proposed that application for pre-qualification of pandemic vaccines be restricted to manufacturers with pre-qualified seasonal influenza vaccines and/or pre-qualified vaccines against novel human influenza viruses. The intent is that existing vaccines be pre-qualified now in order to expedite the pre-qualification process for pandemic vaccines following the identification of the pandemic strain. Guidelines with conditions for pre-qualification will be posted on the WHO website. WHO is proposing that vaccines accepted into the stockpile be pre-qualified.

Session 4: Discussion on regulatory oversight of a WHO international H5N1 stockpile

This session was aimed at developing initial conclusions, including potential needs for further studies on target quality, safety and efficacy considerations, and the regulatory pathway for internationally stock-piled H5N1 vaccines. Critical questions were used to trigger discussion and to formulate conclusions.

A stockpile generated now would contain vaccines against novel human influenza viruses. In the event of a pandemic, the stockpile would be used while modified vaccine, developed using the pandemic strain, was being developed.

The non-clinical and clinical data requirements for vaccines against novel human influenza virus differ from those for seasonal influenza vaccines. The majority of data for stockpile vaccines should be available at the pre-licensure stage; however, it was acknowledged that some data

¹ http://www.who.int/immunization_standards/vaccine_quality/final_expedited_procedure_flu_240207.pdf

could be collected post-licensure during the stockpiling period. This would require post-approval commitments. The target specifications paper presented by Dr. Dobbelaer could be updated to clarify this. Because we are still accumulating knowledge on H5N1 vaccines, the data requirements should not be rigid.

In order to evaluate whether vaccines in a WHO stockpile are likely to remain effective against H5N1 drift variants, the antigenic properties of the stockpiled vaccine could be compared against those in circulation. Sera from clinical trials could be used for this purpose. If the stockpiled vaccine strains are no longer appropriate, the stockpile would need to be updated. Criteria to trigger replacement of stockpiled vaccines would need to be developed. A mechanism for ongoing testing of stockpiled vaccine is also required, along with clear roles and responsibilities for testing and information exchange.

Session 5: Logistical considerations

Experience with practical management of international stockpiles for vaccines: from the factory to the vaccinee *(Dr. Ann Ottosen, UNICEF, Denmark)*

Based on UNICEF's experience, there are three elements that are essential to the successful management of international vaccines stockpiles. First, there must be incentives to industry. Upfront funding and firm contracts can help to assure credibility of commitment and to maintain vaccine security. In the case of influenza vaccine, advance purchase agreements may be needed to ensure continued replenishment of vaccine when strains change or expiry dates are reached. Second, a clearly defined governance structure is needed. Roles and responsibilities need to be defined for security, ownership of the facility, and access and risk management, especially taking into consideration a pandemic situation. Third, clear specifications for account management are essential. Challenges with existing international stockpiles include unclear roles and responsibilities, and the expiry of product due to lack of contingency plans for usage of prepaid vaccines.

Deployment of H5N1 vaccines

(Ethel Palacios-Zavala, Ministry of Health, Mexico)

Deployment of vaccine encompasses all procedures involved in getting the vaccines from storage site to immunization site. It also includes procedures to collect and store remaining vaccine and ancillary supplies. An overview of the draft WHO vaccine deployment guidelines was provided. Some of the factors to consider in the deployment of vaccine include, but are not limited to, national and international coordination, laws that enable vaccine deployment and use, management and coordination within the country for deployment, logistics and security, information management and communication, adequate resources for deployment, capacity building, and training, and considerations related to the termination of deployment. The guidelines recommend that countries evaluate current deployment systems and exercise procedures in advance.

It was noted that the draft WHO guidelines focus on deployment for mass immunization campaigns. Deployment of vaccines from the WHO H5N1 stockpile will most likely be for immunization of small portions of a population. WHO could assist by including specific guidance for effective deployment of stockpiled vaccines within the draft guidelines. National preparedness plans need to take into account acceptance of vaccines from the stockpile and deployment of the vaccines within the country.

The question was raised whether multiple stockpile locations would be better for timely delivery of vaccines. It is difficult to apply everyday experience to a pandemic situation because there will most likely be transport and travel restrictions.

Liability issues (*Anne Mazur, Legal Office, WHO*)

Legal liability issues associated with the use of a WHO H5N1 stockpile were presented. Supplies from the proposed stockpile would most likely be subject to a disclaimer. When completing the request form for vaccine from the stockpile, countries would be assuming responsibility for the use of the vaccine in the population of their country. Governments would need to take informed decisions about the use of vaccines from the stockpile. The disclaimer would also be sent to the appropriate NRA at the time of shipment and would accompany the actual shipment. Manufacturers and other suppliers would be responsible for developing vaccines in accordance with the registered specifications. WHO would accept and deliver the vaccine "as is".

Participants commented that, if possible, the terms of the disclaimer should be agreed upon in advance given the need for timely delivery of vaccine in a pandemic situation. It was noted that distribution of vaccine could be impacted if the vaccine was not licensed in the receiving country. Countries would have to establish a fast-track authorization process or accept WHO pre-qualified vaccines. WHO could assist by providing countries with the technical basis for acceptance of vaccine into the stockpile.

Operational issues – an industrial perspective

(*Dr. Norbert Hehme, IFPMA*)

Regulatory approval for stockpiled vaccines should be centralized and pre-defined. Lot release procedures for stockpiled vaccines should also be pre-defined. As there will be different suppliers, different vaccine presentations may need to be accepted into the stockpile (e.g. 2 vial, 1 vial, mono-dose, multi-dose); however, there are advantages to using a multi-dose presentation. As the final destination of the vaccine is unknown, the labelling will not be adapted to a particular destination; this needs to be recognized upfront and appropriate labelling should be agreed upon.

The stockpile should be maintained under GMP conditions and be under the control of qualified personnel. Storage warehouses need to be protected (security) and have controlled access. Consideration should also be given to the organization of the warehouses to avoid mix-ups of different products or batches, to allow for stock replacement, and to enable rapid deployment.

Industry proposed decentralized warehouses be used to allow for rapid deployment of vaccine stocks, especially if transport restrictions are implemented during a pandemic situation. It was also proposed that the stockpile be under UN protection and that decision-making management be maintained with WHO. Consideration should be given to multiple smaller stockpiles to allow for rapid local deployment. WHO should consider working with other experienced organizations, such as UNICEF.

Session 6: Discussion on logistics considerations

The purpose of this session was to develop initial conclusions, including the potential need for further studies on target logistical considerations for a WHO H5N1 vaccine stockpile.

Key issues raised during the discussion included the level of preparedness of a country to receive vaccine from the proposed stockpile, and the potential advantages of establishing an international coordinating group to manage decisions related to the stockpile. Dr. Fukuda described the decision making process envisaged by WHO to respond to a pandemic signal. If sustained person to person transmission was identified, this would be considered a global threat and decision-making would fall under the International Health Regulations. An expert committee would advise the WHO Director General on measures for rapid containment to prevent the spread of a pandemic. The use of stockpiled vaccine would be considered one part of a group of containment measures.

The question was raised as to whether all vaccines in a stockpile would be considered equal. If so, interchangeability studies may be necessary. Also, the advantages and disadvantages of having more than one stockpile location need to be further analyzed.

Session 7: Ethical considerations and the use of a WHO international H5N1 stockpile

Guiding principles *(Dr. Paul Gully, WHO)*

Possible policies for use of a WHO H5N1 vaccine stockpile and the WHO policy statement on vaccine donations (WHO-VSQ-97.05) were reviewed. The WHO rapid containment protocol does not yet accommodate the use of H5N1 vaccine; therefore it will need to be modified. If stockpiled vaccines are used to prevent infection after the commencement of a pandemic, the vaccines would be intended for a defined group. Ethical considerations and the monitoring of vaccine use would need to be considered. Plans for use would be required ahead of time. One issue is that definitions differ among countries i.e. varying definitions for health care worker among countries. There is a balance between the demand of a country for vaccine and the ability of that country or humanitarian agencies to use the vaccine in the way it was intended. Should guiding principles be provided by WHO on the use of stockpiled H5N1 vaccines within countries?

Ethical issues (*Dr. Andreas Reis, WHO*)

An overview of the major ethical issues that may arise in the use of an international H5N1 stockpile was presented. Priority-setting for the use of vaccine should be within the human rights framework and should not discriminate against individuals based on inappropriate characteristics. Appropriate communication strategies should ensure the public has access to timely and accurate information regarding the applied priority criteria.

If vaccine is used as part of a rapid containment strategy, there would be no major questions raised about distributive justice as the stockpile would most likely cover all persons in the particular containment zone. However, communication of information to the affected population needs to be considered. If stockpiled vaccine is used to for control purposes at the start of a pandemic in countries with no other access to the vaccine, there may be ethical issues at the global level, including how to allocate the vaccines among countries. At the country level, ethical issues could include which population subgroups or age groups should have priority (e.g. health care workers). At both levels key questions include, who should decide and by what process?

Based on a WHO survey, some decisions have already been made at the country level related to the use of vaccine in the event of a pandemic. Discussion ensued that while norms and values differ among countries and countries need to take their own decisions on the use of vaccine, there would be benefits to WHO providing guiding principles to assist with country decision-making.

Session 8: Conclusions and recommendations²

The proposed options for use of a WHO H5N1 vaccine in a stockpile, based on the outcomes from a WHO meeting on use of H5N1 vaccines (1-3 October 2007), were reiterated:

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. Decisions on the use of vaccine from the WHO stockpile rest with the WHO Department of Immunization, Vaccines and Biologicals (IVB) SAGE.

² This session was restricted to participants without disclosed conflicts of interest.

Based on the presentations and discussions, the consultation group provided the following recommendations on the establishment, maintenance and operational considerations for 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 functional National Regulatory Authorities (NRA) and also be submitted for WHO prequalification; WHO should have discussions as soon as possible with the NRAs 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 (2). 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 three 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 paper².
- 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.

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 document²:
 - 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 PMS (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 do not seem 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 outbreak 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 19 October 2007 and to SAGE on 6-8 November 2007.

Acknowledgments

The first draft of this report was prepared by Ms. Stephanie Hardy, seconded staff from the Biologics and Genetic Therapies Directorate, Health Canada to WHO Headquarters in Geneva, Switzerland.

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4. Guidelines on non-clinical evaluation of vaccines. WHO Expert Committee on Biological Standardization. Fifty-fourth report. Geneva. World Health Organization, 2005, Annex 1 (WHO Technical Report Series, No. 927).
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Appendix 1: List of participants - WHO Informal Consultation on Technical Specifications for an International H5N1 Vaccine Stockpile