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The Global Action Plan (GAP) to Increase Supply of Pandemic Influenza Vaccines

First Meeting of the Advisory Group (AG)

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INITIATIVE FOR VACCINE RESEARCH (IVR) & GLOBAL INFLUENZA PROGRAM (GIP)

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Objectives of the meeting

In May 2006, a Global Action Plan (GAP) was developed by WHO for increasing supply of influenza pandemic vaccines in order to reduce the anticipated gap between potential vaccine demand and supply during an influenza pandemic. This document summarizes the discussions at the first meeting of the GAP Advisory Group (AG) held at WHO Headquarters on 19 October 2007. This meeting was held with the purpose of updating the AG on the progress made in the following areas since May 2006, which have contributed to the implementation of the Plan: revision of key priorities among GAP strategies; revision and updating of GAP as science, technology and preparedness progresses; facilitation of identification of funding sources to conduct selected priority GAP activities and obtaining further recommendations for the path forward.

Introduction: the GAP

All populations in all countries are expected to be susceptible to infection with a pandemic influenza virus. In case of a pandemic, the world's population will find itself in a situation where potential vaccine supply will be short by several billion doses of the global need. In response to this challenge, WHO organized a consultation in Geneva on 2-3 May 2006 of all stakeholders, to identify and prioritize practical solutions to fill the gap between supply and demand of influenza vaccine. The consultation resulted in the establishment of a global influenza vaccine action plan outlining eight specific short-, mid-, and long-term strategies to increase influenza vaccine production and surge-capacity before and during an influenza pandemic. These priorities were ranked according to their expected impact on increasing the number of available vaccines doses over time. For each priority a strategy, barriers, drives and funding needs (when possible) were identified. Since the conception of the GAP in May 2006, significant progress has been made within the three major approaches to increase influenza vaccine supply.

Progress since May 2006 in implementing GAP strategies

Presentations and discussions held during the meeting served to review activities contributing to the implementation of the GAP.

Major progress has been made by the vaccine industry in developing H5N1 vaccine formulations, which will allow substantial antigen sparing in case of a pandemic. Indeed, three multinationals have shown appropriate immunogenicity of vaccine candidates containing as little as 3.8 to 7.5 ug HA, formulated with proprietary adjuvants. As a result of these efforts, the current potential maximum capacity has risen in 2007 to more than 2.5 billion monovalent adjuvanted immunization courses per year (two 5 µg doses), with the potential to rise to over 5 billion in 2010. This shows a significant increase in vaccine production capacity as compared to 2006.

As proposed under the first GAP approach, and in order to increase production capacity through market forces, WHO completed a global influenza vaccine survey among Members States in June 2007. In addition, an international consortium is being established to research technical solutions to improve HA yields with H5N1 seed viruses.

Technologies amenable to transfer to developing country manufacturers have been reviewed, and establishment of new production capacity in six developing countries was initiated with assistance from grants provided by WHO (GAP second approach). Funding of these grants came from the US Department of Health and Human Services and the Government of Japan through UNICEF. Although in terms of absolute number of immunizations made available to the global community the new producers are not expected to play a major role, as compared to multinational producers. This additional in-country production capacity may be critical to ensuring that developing countries have access to at least some vaccine in the early months after the onset of a pandemic.

Advances within the third approach of the GAP that target research and new technologies have also been recorded. New technologies and potential vaccine candidates are promising but not yet ready for mass production.

Business plan and influenza vaccine technology landscape

A business plan based on the GAP was developed with the assistance of an external consultancy company (McKinsey & Company, Inc.). The business plan evaluates the short to medium-term (2007-2017) options available to pursue the GAP overarching objective, which is to produce enough vaccine to immunize the world's population (6.7 billion people). While the GAP does not specify a time horizon within which vaccine should be made available, the business plan assumes six months after the transfer of the vaccine prototype strain to industry. Multiple sources indicate that intervention within this frame is likely to be critical to mitigate the effects of the first wave of a pandemic.

A combination of three complementary solutions would assist the GAP in reaching its objectives:

- Increase demand for seasonal vaccine (GAP objective 1)
- Increase and maintain production capacity beyond seasonal need after 2010 (GAP objective 2)
- Prepare for converting Inactivated Influenza Vaccine (IIV) capacity to Live Attenuated Influenza Vaccine (LAIV) at the onset of a pandemic (GAP objective 2)

New technologies offer the potential to dramatically shorten the time required to generate vaccine, but appear to be at least ten years away from mass production. More research is needed to develop new production techniques and delivery mechanisms (GAP objective 3).

In addition to ensuring sufficient pandemic capacity, there is a need to address enablers along the entire preparedness continuum. These include:

- Creating a robust supply and delivery chain (GAP objective 1)
- Developing stockpiles of H5N1 vaccines, ancillary supplies and antivirals (addition to the GAP)
- Resolving policy, regulatory and coordination issues (enablers to GAP objectives 2 and 3)

The total cost of this plan would rise to between US$3 and 5 billion annually by 2012 and continue at that level through to the end of the plan in 2017. The cost of increasing demand for seasonal vaccines would account for between US$2 and 3.5 billion of this total annually. The remaining initiatives to increase supply would cost between US$125 and 250 million annually. The cost of the enablers would be between US$0.75 and 1.1 billion annually.

Additionally, a project to determine influenza vaccine strategies for broad global access was presented by Oliver Wyman, external consultants working under contract with the Programme for Appropriate Technology in Health (PATH). The analysis conducted as part of this project suggests that the global community needs to distinguish between two different time frames with respect to access to strategies to increase vaccine production capacity: short-term (5 years) and longer term (greater than five years). The next five years are characterized by infrastructure and technology constraints, while the time period thereafter will have more relaxed constraints as innovative and advantageous technologies may become more available (cell culture technology and new vaccines: recombinant vaccines, VLP-vaccines, M-protein based universal vaccines, and others). In the short-term, pre-pandemic measures may be required given the shortfall in vaccine supply relative to global needs. Nonetheless, the current capacity to produce seasonal influenza vaccine through egg-based or cell culture methodology already exceeds that justified by seasonal demand. Moreover, this excess capacity is projected to increase considerably in the next two to five years. Pre-pandemic use of this capacity could be allocated to producing H5N1 influenza vaccine for stockpiling. However, there is no scientific evidence that the next pandemic will be due to currently circulating H5N1 viruses, and therefore stockpiling of current prototypic H5N1 vaccines may be of limited public health value if the pandemic virus is significantly different from the current strains. On the other hand, if the excess

capacity is not used; it will ultimately be rationalized by manufacturers. This analysis is convergent with that of the GAP business plan, which proposes subsidizing the industry to keep unused capacity in a state where if could be activated immediately in case of a pandemic.

GAP Advisory Group recommendations and priorities

The Group agreed upon the following key issues:

1) The overarching goal of the GAP to increase influenza vaccine production needs can be characterized by several concurring issues: a) development of creative financial strategies; b) building a strong marketing campaign; c) relying on lessons learned from previous vaccine-preventable disease control, elimination, or eradication campaigns, i.e. polio; and d) incorporating lateral thinking to leverage sister UN organizations and partners such as the United Nations Children's Fund (UNICEF), the Global Alliance for Vaccines and Immunization (GAVI) and others. In particular, GAVI should be approached as a source of financial assistance. In addition, the establishment of a financing mechanism such as the Pan American Health Organization (PAHO) Revolving Fund should be explored as a solution to reduce seasonal influenza vaccine prices.

2) The GAP business plan provides a global framework for increasing vaccine production capacity for influenza vaccines. Implementation of the GAP should also result in strengthening of surveillance, as well as providing an opportunity for improving the performance of national immunization programmes. Indeed, it may improve the world's ability to conduct mass vaccination campaigns and represents an opportunity to strengthen vaccine regulatory systems.

As the kind of strategy contained in the GAP business plan has never been pursued, the Group noted that there were obvious risks. A major risk factor is the underlying assumption that there will infact be a pandemic. If there is not a pandemic within the next five years, there may be loss of interest and political awareness, and other public health needs may shift investment away from pandemic influenza. Therefore, it is critical to identify the best possible strategy to maintain political commitment and WHO is working with partners (UNICEF) and donors to mitigate this risk. The Advisory Group appreciated that the business plan was developed by independent consultants following discussions with country representatives and other stakeholders to achieve buy-in by the international community, and to prevent the GAP from being considered a bureaucrat-driven solution.

3) In the context of GAP approaches 2 and 3, there is a need to develop reproducible assays to evaluate immunogenicity of influenza vaccines and to establish adequate correlates of protection. The efficacy of potential cross-reactive vaccine candidates to induce broad-spectrum protection should continue to be addressed in a critical manner. Stockpiling of potential H5N1 viruses should be assessed with caution; use of this may be justified in the absence of optimally matched and approved vaccine during the early phases of an influenza pandemic. WHO, Member States, and other stakeholders are currently establishing criteria, guidelines for use, maintenance issues, operational, and ethical issues of a WHO international influenza pandemic vaccine stockpile.

Another major potential risk is the absence of a suitable public health structure in communities to piggyback on the growing influenza vaccine production capacity. It is important to note that the business plan, as presented, did not assume the cost of new facilities for conversion of IIV into LAIV, but the use of existing facilities converted at a certain cost. Another risk identified is that LAIV based on H5N1 viruses have not yet been shown to induce the level of antibodies thought to be required for protecting against these viruses. The feasibility of converting a production facility from inactivated trivalent influenza vaccine to monovalent live-attenuated vaccine in a defined time frame needs also to be carefully assessed. Nevertheless, as the GAP AG suggested, continuing to focus on the overarching goal of being able to vaccinate the world's population within a six month period focusing on LAIV, may be the only available approach in the short- to medium-term. In addition, data gathered from PATH-Oliver Wyman also suggests that efforts to accelerate further development of LAIV and recombinant technologies should be a global priority. Of note is the fact that deployment of LAIV in mass immunization campaigns may not require trained health workers, whereas IIV would.

From a marketing and financial perspective, the right engine to achieve this plan has to be selected based on a financial perspective. It will be critical to choose the right channel, which may include

hosting the GAP under the umbrella of the implementation of international health regulations, as a global health security issue, or under health system strengthening. The business plan should work towards alignment with other organizations, harmonization of strategies with donors and maintenance of commitment of stakeholders/donors to avoid donor fatigue.

While some assumptions should be revisited before the cost of the business plan is finalized, the Advisory Group welcomed the overall analysis presented in the business plan and noted that the three options presented in the plan were complementary. Regarding the feasibility of the business plan, the AG underlined the fact that potential intellectual property rights issues should be looked into, and that political considerations need to be taken into account.

The Advisory Group suggested focusing on the following priorities over the coming months:

1) The main priorities for WHO for the year 2008 should be to choose the appropriate spin to be placed on the business plan in association with the right marketing strategy. WHO also needs to establish a detailed operational plan and to define financial resources i.e. donors, countries, and other stakeholders. Leveraging the GAP with twin programmes from sister agencies or other stakeholders, as well as making sure that the need for increasing influenza vaccine production capacity is addressed in the political arena are key priorities.

2) Additional priorities include:

- Maintaining global commitment through information, communication, and educational activities.

- Addressing any potential liability issues associated with the business plan.

- Developing a diagnostic test to identify individuals who may become immune as a result of infection with the pandemic influenza strain, in order to vaccinate those who are still unprotected.

- Investigating the seasonal influenza disease burden in developing countries. It was suggested that seasonal influenza surveillance needs to be added to ongoing national surveillance activities, or attached to other health-related programmes to avoid duplication of surveillance programs and to optimize available resources. Identifying existing laboratory and disease-reporting mechanisms in individual countries is crucial so they can be augmented to achieve sustainable capacity for surveillance for influenza and other emerging diseases.The need for simplified rather than sophisticated surveillance methodology was highlighted.

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