The Global Action Plan for Influenza Vaccines

Report of the seventh meeting of the Advisory Group of the WHO Global Action Plan for Influenza Vaccines

Belgrade, Serbia, 29 March 2012
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## Abbreviations and Acronyms

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<tr>
<td>AG</td>
<td>Advisory Group</td>
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<tr>
<td>BARDA</td>
<td>Biomedical Advanced Research and Development Authority</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention, Atlanta, USA</td>
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<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
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<td>EPI</td>
<td>Expanded Programme on Immunization Plus</td>
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<td>EURO</td>
<td>WHO Regional Office for Europe</td>
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<td>GAP I</td>
<td>Global Action Plan to increase supply of pandemic influenza vaccines</td>
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<td>GAP II / GAP</td>
<td>Global Action Plan for Influenza Vaccines</td>
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<td>GACVS</td>
<td>Global Advisory Committee on Vaccine Safety</td>
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<td>GAVI</td>
<td>Global Alliance for Vaccines and Immunization</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>IHR</td>
<td>International Health Regulation</td>
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<td>IIV</td>
<td>Inactivated Influenza Vaccine</td>
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<td>IPR</td>
<td>Intellectual Property Rights</td>
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<td>LAIV</td>
<td>Live Attenuated Influenza Vaccines</td>
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<td>NRA</td>
<td>National Regulatory Authority</td>
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<td>PATH</td>
<td>Program for Appropriate Technology in Health</td>
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<td>PIP</td>
<td>Pandemic Influenza Preparedness Framework</td>
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<td>R&amp;D</td>
<td>Research and Development</td>
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<td>SAGE</td>
<td>Strategic Advisory Group of Experts on Immunization</td>
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<td>TAG</td>
<td>Technical Advisory Group</td>
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<td>TIV</td>
<td>Trivalent Inactivated Influenza Vaccine</td>
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<td>US-HHS</td>
<td>United States Department of Health and Human Services</td>
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<td>VLP</td>
<td>Virus-like Particle</td>
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<td>WHO</td>
<td>World Health Organization</td>
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1. Introduction

The Advisory Group (AG) of the Global Action Plan on Influenza Vaccines (GAP)\(^1\) oversees the implementation of the GAP objectives, established in the first global consultation in May 2006. The AG members, representing both industrialized and developing countries and with broad expertise, meet in closed session at least once a year. In July 2011, a second consultation (GAP-II) was organized to review the progress and lessons learnt during the first five years of GAP in order to identify the approaches and factors that lead to the successful implementation of activities.

In his role as Chair, Professor Pathom Sawanpanyalert welcomed participants to the seventh meeting of the AG. The agenda of the meeting included an update of progress on implementation of the AG recommendations; mapping of WHO and global activities in support of the GAP; harnessing global partnerships; agreement of planned activities for next year; recommendations; and next steps.

\(^1\) Originally called the Global Action Plan for Pandemic Influenza Vaccine Supply, and modified in 2011 to reflect the broadened scope of GAP to include seasonal influenza vaccines.
2. Progress on implementation of GAP AG recommendations

The WHO Secretariat presented the progress made in implementing the recommendations of the fifth and sixth meetings of the AG, held in May and July 2011, respectively.

**GAP-II:** The recommendation from the 2nd consultation on GAP were to reflect the broader scope of the GAP, while retaining its overall structure and continuing oversight by the AG, had been implemented, as had the launch of the new GAP web site. In addition, with a view to reflect the global ownership of the GAP and to recognize the significant contribution of key stakeholders, the nomination of GAP Partnership Offices was proposed and outlined in a draft concept note distributed to participants.

**Increase association between seasonal and pandemic immunization.** This recommendation had been extensively discussed by the SAGE Working Group on Influenza Vaccines and Immunization (SAGE WGIVI) and, subject to endorsement by SAGE in April 2012, may lead to an updated WHO recommendation on seasonal influenza vaccination. A review of available evidence had also resulted in the development of a research agenda to address gaps in knowledge identified in specific risk groups, e.g. the use of adjuvanted influenza vaccine in children. Also presented were the results of a survey comparing expected demand with supply of influenza vaccine based on global disease burden; and the planning of a WHO-HHS international workshop in June 2012 on the global disease burden and economic analysis of influenza vaccine as well as a number of regional and country workshops on policy development for seasonal vaccine use.

**Standardized practices to monitor burden of disease.** WHO is in the process of publishing guidelines on surveillance and other standardized methods for disease burden assessment; and a manual on influenza disease surveillance. It was noted that a joint WHO/CDC meeting on vaccine effectiveness is being organized to promote standardized methodologies for the study of influenza vaccine effectiveness, particularly in low- and middle-income countries.

**Equitable access to pandemic vaccine.** Two new manufacturers have joined the WHO Technology Transfer project, one in South Africa and the other in Kazakhstan. This broadens geographic distribution of grantees and should increase regional access to pandemic influenza vaccines. In addition, within the WHO Pandemic Influenza Preparedness (PIP) Framework, endorsed by the World Health Assembly in May 2011, WHO should receive US$ 28 million during 2012 to ensure benefit sharing on viruses and global equity in vaccine supply. These funds will be allocated partly for preparedness – including stockpiles, effectiveness and burden of disease studies – and partly for response activities such as the sharing of viruses, antivirals and diagnostics, and procuring vaccine for deployment in the event of a pandemic. Details of the distribution of funds are under discussion. Good collaboration, e.g. through representation on the PIP Advisory Group, is ensuring that GAP activities are aligned with and integrated in the PIP Framework.

**Mapping of local vaccine supply and use.** Results of a survey performed in collaboration with the regions in 2010 on the policies and implementation rates of H1N1 vaccine in countries is in press, and

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1 Initially proposed as "Implementation Officers".
may be useful in setting coverage goals and priority target groups. In addition, the third survey on global production capacity is being finalized and will also be published in the near future.

**Increase attention to communication strategies across the three GAP pillars.** The need for solid communication with policy-makers, the public and others has been recognized and spearheaded in grantee countries. Other communications activities planned include a workshop hosted by the WHO European Region to assess experiences during the H1N1 pandemic; and a series of WHO/HSS meetings on cost-effectiveness, successful business plans, and media communication. The GAP Secretariat has also been collaborating closely with the now centralized WHO Communications Team in the Director-General’s Office to develop effective, evidence-based messages to promote influenza vaccines and vaccination. It was noted that HQ Communication Officers work closely with their counterparts in the regions, and may consider convening a global meeting on risk communication. The report from the EURO communications meeting would be made available to the AG.

**Facilitate implementation of IHR and other recommendations on influenza.** The GAP Secretariat facilitates implementation of five IHR recommendations related to influenza vaccines, as follows:

*Revised pandemic preparedness guidance.* Country pandemic preparedness plans are being updated to reflect the H1N1 experience, as well as the WHO Guidance on pandemic vaccine deployment. The GAP goal to meet pandemic supply-demand by 2015 remains valid and takes account of donated vaccine for developing countries through the GAP and PIP Framework.

*Measures to assess severity of disease.* In this respect, GAP is working to quantify demand through disease-burden and economic analyses that estimate the cost-effectiveness and cost-benefit from severe cases down to mild infections that require minor medical attention.

*Advanced agreements for provision of vaccine.* This relates to the PIP Framework, whereby approximately 10% of production is to be donated or reserved for procurement by WHO. High-level discussions are under way on this pledge with major vaccine manufacturers.

*Sharing of viruses and access to vaccines.* This is the driving force of the PIP Framework and encompasses the major GAP focus on equitable access to vaccines.

*Pursue influenza research programme.* Policy and implementation research are also pursued in this research-related recommendation. While vaccine research is carried out by GAP partners, WHO is continuing to monitor and communicate these advances to the broader community.

Good collaboration between the former IHR review team, the GAP and the PIP Framework is facilitated by mutual membership and shared goals, including the critical importance of communicating messages on the value of influenza vaccine.

**Collaboration with the Decade of Vaccines.** This collaborative initiative is now using progress towards a universal influenza vaccine as one of its target indicators. Although influenza vaccine R&D is not currently a priority of GAVI, this may change as more disease burden data become available and development of a single-dose, broadly protective vaccine with long-lasting immunity progresses. Discussions are ongoing to promote seasonal influenza vaccine research and use, particularly addressing topics under the maternal and child health umbrella.

**Ideal number of new manufacturers in technology transfer project.** With a view to improve the regional balance of influenza vaccine production, WHO has added one grantee, each in South Africa and Central Asia, and is continuing discussions with a further applicant from Africa. At the same time and given the current global surplus production, efforts are being stepped up to assure the sustainability of existing grantees and to assist potential new producers to develop their business plans. Moreover, since economic return on investment may not suffice for policy-making, WHO is
emphasizing a focus on selection of the best technology and volumes, from a regional perspective. This is the case in Kazakhstan, which is also aiming to supply neighbouring countries.

The Chair commended the planned series of meetings by WHO and the US-HHS that are open to all grantees and partners of GAP, and particularly the meeting on the development of robust business plans, which is a prerequisite to sustainability.

**Continuously monitor evidence on the safety of adjuvanted vaccines.** The GACVS is monitoring safety and efficacy in specific groups, in collaboration with SAGE.

**Ascertain funding for GAP activities highlighted in the PIP Framework.** Discussions with the PIP Advisory Group and with industry, the source of PIP funding, are ongoing. It is anticipated that some funding may be available for GAP objective 1 activities, e.g. studies on disease burden, cost-effectiveness, evidence-based use of influenza vaccine and adjuvants.

** Longer-term strategy to sustain GAP.** Besides a potential contribution from the PIP Framework, the Secretariat is actively seeking additional partners, although it is difficult to identify donors to match the current support. Recent funds from Japan will support a study in Thailand to compare the cost-effectiveness of vaccinating schoolchildren with LAIV or IIV.

**Promote studies on surveillance and burden of disease.** This falls under the remit of the SAGE Working Group on Influenza Vaccines and Immunization, which has identified areas for further research. WHO is preparing comprehensive guidelines for surveillance and analysis of disease burden in different risk groups. Each WHO regional office has a focal point for infectious diseases responsible for surveillance and disease burden data, although the extent of activity differs per region. The GAP Secretariat promotes seasonal influenza policy development in regions where data are insufficient, although activities in this area will depend on PIP funding and would, as always, require a call for proposals.

**SAGE review of priority target groups for immunization.** The results of the reviews on disease burden, vaccine performance, cost-effectiveness and implementation issues in target populations has been submitted in the form of a background document to SAGE, which may make a recommendation on influenza vaccine.

**Discussion**

Increasing data on pneumonia in young children may accelerate a recommendation on vaccinating the under 2 years of age group. However, an alternative to inclusion in the EPI schedule would be needed, such as the National Immunization Days adopted in the Americas, since the seasonal trivalent inactivated influenza vaccine (TIV) requires two doses for the development of effective immunological response and live attenuated influenza vaccine (LAIV) is currently not approved in this age group because of safety concerns. It was felt that a GAP AG recommendation may facilitate access to available safety data in infants, as well as in the elderly and pregnant women.

Sustained quality control and strengthened national regulatory agencies (NRAs) were considered critical to secure the achievements of GAP. WHO works hand-in-hand with manufacturing and regulators to assure the highest levels of quality and safety, which has led to the development of functional NRAs in most grantee countries. BARDA, CDC, PATH and other partners are also carrying out activities to strengthen NRAs.
3. Mapping of WHO and global activities to support GAP

A draft GAP Work Plan was presented that brings together all the activities being carried out by the Secretariat and GAP partners, with the aim to establish a global five-year strategic plan structured along the three major objectives of the GAP. The work plan will have clear areas of responsibility for implementation, and allow the identification of gaps that need to be filled.

4.1 WHO Work Plan

As a first step, a matrix was presented detailing all WHO current and planned activities, including the recommendations of the AG. Following approval by the AG, this matrix will be incorporated into the broader, global action plan of all GAP stakeholders.

Most of the WHO activities had been discussed in-depth during the two-day meeting of international partners of GAP. Additional discussion focused on communication and the success of the new GAP web site and the comprehensive database on pandemic, and now seasonal vaccine clinical research development. In addition, WHO will establish the Expert Support Group for countries planning to carry out vaccine effectiveness studies and work with grantee countries to measure the impact of their efforts. Critical regulatory work was also a priority to determine assays and correlates of protection for upcoming recombinant, virus-like particles (VLP) and DNA-based vaccine technologies, among others. The AG was invited to suggest indicators for success, particularly for Objective 1. Other issues raised were the level of detail required for economic analyses and platforms for fund-raising.

4.2 Global Work Plan

The draft matrix of activities carried out by the various GAP partners was presented for review, in parallel with the proposal to nominate host institutions that could assume responsibility to implement specific GAP goals. It is planned to publish the Global GAP Work Plan during the third quarter of 2012.

The AG suggested that, in addition to the elements presented, the following topics are highlighted:

- Alternative methods to ultracentrifugation in the purification process in vaccine manufacturing;
- Common vaccine production facilities to support sustainability;
- Streamlined business plans (technical, finance and deployment for the introduction of vaccines);
- Equitable access to influenza vaccine in developing countries;
- IP barriers to new technologies such as reverse genetics;
- Networking and empowering regulators, particularly for new technologies;
- Regional cooperation;
- Evaluation of delivery systems, particularly in countries in Africa; and
- Acceptance of results of clinical trials from neighbouring countries for regulatory evaluation.

To address these issues, WHO will further its collaboration with NRAs and encourage regional support to knowledge and acceptance of influenza vaccine.
4. Global partnership building: concept of GAP Partnership Offices

The GAP-II consultation had noted that success in the face of budgetary constraints required the harnessing of the comparative strengths of all GAP partners. WHO therefore proposes the recognition of host institutions that are already working on specific GAP objectives as GAP Partnership Offices. These lead institutions would serve as observers on the AG and have strategic goals and measurable implementation plans. Advantages of such a network of partners include reduced duplication of efforts and the potential to embark on projects that are beyond the capacity of a single institution. It was proposed that CDC serve as Partnership Office for activities under Objective 1, and BARDA for Objective 2; further Partnership Offices for economic analyses, viral strain sharing and communications are envisaged, but their total number will be limited. The GAP Secretariat will map the contribution of the Partnership Offices within the global GAP Work Plan.

The link between such groups with the AG and TAG was also clarified.

Discussion

CDC noted that its objectives were aligned with many of the GAP activities and thus this mapping exercise would ensure harmonization. BARDA reiterated that the benefits of information sharing at the global level would in turn feed into the domestic agenda. The HIV Enterprise used a similar model, where partners agree to assume specific priority activities. It was clarified that achievement of the GAP objectives through the Partnership Offices is not a legally binding programme, but rather an organized commitment to share information on what is happening and what is deliverable. Official endorsement of the synergy between GAP and others initiatives such as the PIP Framework would also be useful.

To be successful, the GAP programme needs to be widely visible, and the new GAP web site is a major modern to achieve this and to encourage global input. A suggestion was made to post on the GAP site outcomes from maternal and child health, and the vaccine research agenda. Another recommendation was to enhance synergies among national surveillance networks to facilitate data collection on disease burden.

Recommendation

The Secretariat should integrate the activities and responsibilities of WHO and all partners into the GAP Global Work Plan. Efforts should also be made to promote the Plan and attract the needed financing.
5. Future activities

Using the draft WHO work plan as a guide, the Secretariat proposed to carry out the following activities over the next year.

**Objective 1:** Increased attention will be given to this area. Subject to approval by SAGE, WHO will prepare a position paper with a new WHO recommendation on seasonal influenza vaccine usage. Attention would then focus on support to the development/enhancement of policies in countries, prioritization of risk groups and refining coverage goals. Capacity-building for surveillance in developing countries will be carried out in collaboration with regional offices and the WHO Influenza Programme. Communications for risk and vaccine use will also be a priority activity.

Regarding the WHO stockpile on pre-pandemic H5N1 vaccines, SAGE is considering three options for the virtual 120 million doses of unused pledge: (1) keep it as a virtual stockpile until the next pandemic, although this would incur delays in access; (2) turn part of the current stockpile into a physical stockpile, which would require numerous formulation and logistic decisions; or (3) integrate the entire virtual stockpile into the PIP Framework, subject to final negotiations. A stockpile of adjuvants is also under consideration which, unlike antigen, continues to be produced for antigen sparing with pandemic vaccine once the strain is known. While it may not be possible to all manufacturers to carry out clinical trials of their antigens with adjuvants to be stockpiled, some manufacturers have indicated interest to consider this possibility. Such clinical trials would benefit from standardization and coordination. Moreover, it may be useful to develop and stockpile vaccine seeds. Indeed, the high expense of storing vaccine in bulk has led the USA to explore a stockpile of seeds that are deemed to be of threat.

**Objective 2:** Particular focus under this capacity-building umbrella will be to strengthen business planning, promote sustainability, and training regulators on issues such as correlates of protection for newer technologies.

**Objective 3:** WHO will continue to monitor and share the latest research results to inform evidence on vaccine safety and performance. WHO should also continue to underline the need for research and development of more effective seasonal vaccines for the elderly population.

Overarching activities include the following:

- For the next meeting of the AG, WHO will liaise with GAP stakeholders and present preliminary indicators to assess progress.
- Potential investment from partners such as GAVI will be explored, both to sustain work at country level as well as to assure the Secretariat functions.
- Collaboration will be scaled up with PIP to ensure that work plans are aligned.
- The GAP web site will be used to communicate the Global Work Plan, encourage networking and attract new stakeholders.
- Barriers to success of the GAP objectives, such as IPR, will be identified and added to the work plan for action.
- Guidance will be developed on the use of adjuvanted vaccines and LAIV.
- Technical and regulatory preparation will be undertaken to ensure access to reverse genetic technology.
- Support to developing robust business plans will emphasize commitment to regional/global coverage goals and sustainability of production capacities.
- WHO will ensure that appropriate tools are available to guide countries on how to collect and evaluate disease burden data. In this context, the SAGE WGIVI is reviewing the possibility of extrapolating data on vaccine effectiveness and efficacy data for use in countries that have no data.
6. Recommendations

The following recommendations were added to those already proposed above.

- Ensure compatibility between global capacity and regional and national business plan estimates and coverage goals, particularly for pandemic preparedness. When assessing regional capacity and plans, it should be remembered that neighbouring countries are not necessarily in the same WHO Region.

- Ensure that GAP requirements are noted in the PIP Framework reports to the Executive Board.

- The concept of GAP Partnership Offices was approved.
7. Next steps

Following the meeting, the Secretariat will:

- Circulate the report of meeting.
- Circulate a link to the 2010 survey, lessons learnt from deployment of H1N1, and guidance on deployment of vaccines.
- Finalize the global work plan and ensure the AG recommendations are reflected.
- Integrate the WHO responsibilities into the Global Work Plan and discuss with partners which elements they wish to take responsibility for, and publish the Plan by the third quarter of 2012.
- Map what is being carried out by other initiatives and inform them of the GAP objectives.
8. List of Participants

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Dr Daniel Camus, Institut Pasteur de Lille, Lille, France

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