Report of the second WHO Consultation on the Global Action Plan for Influenza Vaccines (GAP)

Geneva, Switzerland, 12–14 July 2011

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Executive summary

In the five years since the first World Health Organization (WHO) consultation on the Global Action Plan for Influenza Vaccines (GAP) there has been growing acceptance that influenza and other infectious diseases are truly global concerns that cut across national boundaries. Nowhere was this more clearly demonstrated than during the 2009 H1N1 influenza pandemic. At the same time, increasing recognition of the significant disease burden and other impacts of seasonal influenza epidemics is leading to raised awareness of the continual threat posed by influenza viruses.

Since its launch in 2006, GAP has been the catalyst for a significant expansion in influenza vaccine manufacturing, with global production capacity increasing from 350 million doses to over 900 million doses by 2009. In addition, GAP has provided a feasible and implementable framework for increasing the number of countries with vaccine production capabilities in place. As of 2011, 11 developing-country manufacturers had received WHO seed funding grants and technology-transfer support, with five having brought licensed influenza vaccines to the market.

However, making more vaccines is not enough and in addition to continued expansion in production capacity, greater efforts are now needed to make influenza vaccines accessible to everyone. Ensuring equitable and universal access to influenza vaccines is not only an ethical requirement but is also a key public health strategy in both seasonal and pandemic influenza preparedness and response efforts. If this is to be achieved, there needs to be an expansion in the range of activities upon which GAP was originally based. Success in this endeavour will require concerted action from the broad spectrum of GAP partners.

As the first five-year phase of GAP comes to a close, there is an opportunity to review the progress made so far and to learn from the experiences of recent years – including the lessons of the 2009 H1N1 pandemic – and to inform the development of a strategic plan for the next five years. WHO therefore held the second WHO GAP consultation to bring together more than 100 representatives (see Annex 1) from national governments, United Nations agencies, funders, regulatory authorities, WHO technology-transfer projects, manufacturers, nongovernmental organizations and the research community. The participation of industry representatives was coordinated by the International Federation of Pharmaceutical

Manufacturers & Associations (IFPMA) and the Developing Countries Vaccine Manufacturers' Network (DCVMN).

The overall objective of the consultation was to review the progress and lessons learnt during the first five years of GAP in order to identify the approaches and factors which lead to the successful implementation of activities. A combination of working group and plenary discussions were held and were organized in accordance with the three principal "pillars" of GAP activities, namely increasing the use of seasonal influenza vaccine, increasing influenza vaccine production capacity, and promoting the research and development of new influenza vaccines and related technologies.

Working group discussions on increasing the use of seasonal influenza vaccine ranged from national vaccine policies and utilization, to consideration of global disease burden, particularly in at-risk populations, to the efficacy, safety and cost–effectiveness of both seasonal and pandemic vaccines, including in the context of competing health priorities. Following a series of presentations, a panel discussion was also held on the role of communication and media strategies in increasing awareness of influenza and improving the uptake of seasonal vaccination by target groups, including health care workers. This was followed by presentations from industry and from public health agencies in two WHO regions on the challenges and successes in promoting seasonal influenza vaccination.

Discussions on increasing influenza vaccine production capacity covered global and regional trends in both manufacturing capacity and shortfall, with consideration given to both current and future industry contributions to increasing production capacity, and to the activities of the WHO influenza vaccine technology transfer initiative. Further discussion topics included the regulatory and pharmacovigilance aspects of influenza vaccines, the use of adjuvants and live-attenuated influenza vaccines to increase production capacities, and new and upcoming production strategies and methods to ensure sustainability and permit scaling-up in the event of a pandemic.

Discussion of the current status of influenza vaccine research and development centred on a review of new vaccine platforms and pipelines, current thinking on the correlates of protection for evaluating vaccines, the development of new vaccine-delivery methods, perspectives from the pharmaceutical industry, an overview of the economics and financing of vaccine research, and a summary of WHO influenza research activities.

Following working group presentations in each of these areas, consultation participants then provided feedback on the issues, challenges and proposed actions put forward for consideration. It is intended that the overview of GAP activities in the first five years and the proposed action points presented in this report will be used to inform the upcoming development of a GAP strategy for the next five years.

1. The Global Action Plan for Influenza Vaccines

In 2005, following growing recognition of the threat posed by pandemic influenza and the need to significantly strengthen global preparedness and response activities, the Fifty-eighth World Health Assembly (*1*) requested that WHO work with its international and national partners to reduce the global shortage of influenza vaccines, establish vaccination strategies that economize on the use of antigens, and develop and license antigen-sparing vaccine formulations. Following this request, WHO convened a consultation in May 2006 to identify the most promising approaches to increasing the availability of vaccines during an influenza pandemic and to develop a corresponding plan for achieving this (*2*).

At that time it was recognized that if an influenza pandemic were to occur, the potential vaccine supply would fall several billion doses short of the amount needed to provide protection to the world's population. In addition, marked differences exist between countries in terms of their respective capacities, priorities and resources for establishing a seasonal influenza vaccination policy and national programme. At present, all the major influenza vaccine producers operate and supply almost exclusively in Australia, North America and Europe, and to a limited extent in Asia. It was clear that most resource-constrained countries did not have the means to access seasonal influenza vaccines and could face even more severe challenges during an influenza pandemic. The objective of the 2006 consultation was therefore to identify and prioritize practical solutions for reducing the anticipated gaps in vaccine supply. Participants identified three mutually reinforcing strategies:

- increasing the use of seasonal influenza vaccine
- increasing influenza vaccine production capacity
- promoting influenza vaccine research and development.

These three approaches thus became the "pillars" of a global pandemic influenza action plan to increase vaccine supply which has subsequently become the Global Action Plan for Influenza Vaccines (GAP). It was clear that implementation of GAP would require substantial funding and that all stakeholders – including governments, industry, international agencies, nongovernmental organizations and the research community – would have important and complementary roles to play.

It was also recognized from the outset that activities in each of these areas could not fill the gaps in vaccine demand and supply in the immediate to short term, but that if immediate action was taken then progress could be made within five years with other longer-term objectives achievable within a decade. Following the reaching of the five-year point in May 2011 and in light of the experiences of the 2009 H1N1 pandemic, the time has come to review the progress made and to inform the process of developing a refined and expanded strategic plan of action for the next five years.

2. Review of GAP-related activities and achievements

2.1 Seasonal influenza vaccine use

ORIGINAL GAP OBJECTIVE

Increase use of seasonal influenza vaccine. This will reduce disease burden of seasonal influenza infections, contribute towards the preparedness of countries to respond to an eventual pandemic and motivate industry to develop greater capacity for manufacturing vaccines.

2.1.1 Developing national and regional seasonal influenza vaccination plans

Developing clear policies and plans for increasing the use of seasonal influenza vaccine will lead to solid demand forecasts and stimulate increased production capacity. Such policy development must be evidence-based and reflect national priorities. In support of this, a review of WHO recommendations on the use of seasonal influenza vaccine is being conducted by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) Working Group on Influenza Vaccine and Immunization. With a particular focus on priority target groups and on low- and middle-income countries, this review will be used to update the 2005 WHO influenza vaccine position paper (*3*) in the context of other disease priorities in a broad range of countries.

According to a 2010 WHO survey, the percentage of countries recommending seasonal influenza vaccination for specific target groups varies widely among regions, with few countries currently on target to meet the related resolution of the Fifty-sixth World Health Assembly (WHA56.19), which calls for 75% coverage among those aged over 65 years (*4*). Although pregnant women are also at higher risk for severe disease associated with influenza, many countries still do not specifically recommend vaccination of this group.

The percentage of WHO Member States incorporating seasonal influenza vaccination into national immunization programmes remains low (46% in 2010, projected to increase to 50% in 2012) with the overall figure masking large regional variations. High vaccine and service costs, competing health priorities, difficulties in measuring vaccine efficacy and cost–effectiveness,

and adverse public opinion regarding vaccination may all play a role in maintaining this situation.

National data on seasonal influenza vaccine coverage remain very limited, with the majority of WHO Member States unable to accurately calculate coverage by target group due to registration-system issues and problems in determining accurate denominators for different groups. The percentage of countries able to calculate vaccination coverage ranges from 12% in the WHO Eastern Mediterranean Region to 82% in the WHO European Region, with no data available for the WHO African Region and WHO South-East Asia Region.

2.1.2 Estimating disease burden

The lack of disease-burden and associated cost–effectiveness data in many countries highlighted during the 2006 GAP consultation remains a barrier to evidence-based decision-making on the introduction of seasonal influenza vaccines.

By extrapolating data from temperate high-income countries, WHO estimates that annual influenza epidemics result in about three to five million cases of severe illness and about 300 000 to 500 000 deaths worldwide each year (http://www.who.int/immunization/topics/influenza/en/). However, in the absence of vital statistics or clear influenza seasons in many parts of the world, the actual burden of influenza disease is unknown. As a result, there are major difficulties in measuring and modelling its incidence in both the general population and among at-risk groups. Other complicating factors include difficulties in measuring influenza-related clinical outcomes and mortality, especially in poor rural settings.

Evidence reviewed by the WHO SAGE Working Group on Influenza Vaccines and Immunization indicates that seasonal influenza-related mortality rates in Australia, China (Hong Kong Special Administrative Region (SAR)) and Singapore are similar to those observed in the United States of America (USA), with children and the elderly most affected. In South Africa the corresponding figure appears to be significantly higher. One review of studies conducted in sub-Saharan Africa indicates that between 1980 and 2009, 1–25% of outpatient visits for acute respiratory illness were due to influenza, and 0.6–15.6% of children hospitalized for such illness were found to have influenza (*5*).

There is now a need for better burden of disease data, particularly among children and other at-risk groups. As part of this, epidemiological data collection and modelling of influenza mortality and morbidity in low- and middle-income countries during the 2009 H1N1 pandemic by the Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA could provide insights into the disease burden of seasonal influenza.

Challenges to the development of informed policies and national plans include the complexities of determining the risks and patterns of severe disease or death in different groups. Although severe cases of H1N1 influenza continue to be observed more frequently

among young and middle-aged adults than older age groups, the probability of severe complications or death is lower. Over the age of 65 years, the risk of death resulting from H1N1 influenza is three times higher than in younger people. The situation with H3N2 influenza appears clearer, with severe disease predominantly observed in older age groups. Influenza type B viruses appear to disproportionately affect young children. In some countries, a higher number of severe cases of pandemic H1N1 infection were reported during the 2010/2011 influenza season compared to the previous year, with the virus exhibiting very little antigenic drift and remaining closely related to the strain used in the recommended trivalent seasonal vaccine.

In summary, epidemiological data from tropical regions remain sparse, and disease-surveillance efforts now need to be stepped up in many parts of the world. In Brazil, China (Hong Kong SAR and southern parts), India, Singapore and Sri Lanka some data are available, but disease surveillance is generally not extensive in many low- and middle-income countries, with very limited data available for sub-Saharan Africa.

2.1.3 Strengthening disease and virological surveillance and response activities

Timely disease surveillance data obtained by the WHO Global Influenza Programme and the virological surveillance activities of the WHO Global Influenza Surveillance and Response System (GISRS)[1] are the foundations of global influenza preparedness and response activities. Through its coordinated activities, the GISRS continuously assesses the ever-evolving epidemic and pandemic risks posed by influenza viruses and is responsible for the selection and provision of influenza viruses for use in both seasonal and pandemic vaccine development.

The GISRS continues to expand and currently consists of 136 National Influenza Centres (NICs) in 106 countries, six WHO Collaborating Centres, 12 H5 Reference Laboratories and four Essential Regulatory Laboratories. In addition, the GISRS has continued to undertake a broad range of capacity-building, information-sharing and networking activities. Preliminary results from the WHO Global NIC Survey 2010 (*7*) completed by 104 laboratories indicate that laboratory capacity for the virological surveillance of influenza continues to be enhanced worldwide. During 2010 over one million clinical specimens were tested in GISRS laboratories – with double this number being processed in 2009 following the emergence of the 2009 A(H1N1) pandemic virus.

Ongoing challenges include increasing the coverage of influenza disease and virological surveillance activities, particularly in the WHO African Region. For pandemic influenza surveillance and response, the challenges include promptly detecting novel viruses with pandemic potential following their emergence; making vaccines available as soon as possible; rapidly assessing clinical severity; and identifying groups at increased risk of severe infection.

[1] Formerly known as the Global Influenza Surveillance Network (GISN), the new name came into effect following the adoption of the Pandemic Influenza Preparedness (PIP) Framework in May 2011 (*6*).

Approaches under consideration include the development of validated diagnostic platforms for the rapid detection of novel influenza viruses, and strengthening partnership and collaboration with animal-sector agencies to promptly identify newly emerging influenza viruses in animals with the potential to affect human populations.

2.1.4 Improving communication and raising awareness

The development of national evidence-based communication strategies on influenza and the benefits of influenza vaccination remains a key strategic element in increasing the acceptance and uptake of seasonal influenza vaccination. Communication studies conducted by CDC over the past decade have led to a number of insights into the various factors which determine success in this area. It is clear that audiences are not simply passive recipients of messages but are instead influenced by the interplay between factors that act as barriers to behavioural change and those that motivate such change. It is important when designing communication approaches to understand both these types of factors. Some barriers can be classed as "personal" to individuals, while others are considered as external factors. It also appears that segmenting audiences by simple demographics is often not as effective as segmenting by other variables, while lessons can also be learnt from the advertising industry in recognizing that people base their decisions not only on the available "facts" but also on a wide range of aspirational and other values.

Success will depend upon addressing the broad range of attitudinal, policy, systemic and social-structural determinants which influence the decision-making of individuals and communities, and understanding the role played by social media. Tapping into local expertise and resources, and gaining the respect and trust of stakeholders at grassroots level is likely to be highly effective. Similarly, the increasingly recognized importance of health care workers in influencing vaccination choices is leading to the development of approaches based upon increasing vaccination levels among this group and strengthening their role as advocates of the importance of seasonal influenza vaccination.

2.1.5 Operational research

Operational research in support of seasonal vaccination programmes is under way in a number of areas but more is required, for example on vaccine efficacy, effectiveness and cost–effectiveness, especially in developing countries. At present, indications of an association between high influenza vaccination rates and subsequent lowered incidence of illness in some countries must be carefully evaluated. Other areas of operational research include the further development of effective communication approaches and optimum vaccine-deployment strategies.

2.2 Influenza vaccine production capacity

ORIGINAL GAP OBJECTIVES

Short term – produce enough vaccine to immunize two billion people; this vaccine should be available on the market six months after transfer of the vaccine prototype strain to industry.

Medium and long term – produce enough vaccine to immunize the world's population (6.7 billion).

2.2.1 Trends in global and regional influenza vaccine production capacity

GAP has been the catalyst for a significant expansion in global influenza vaccine manufacturing capacity, with seasonal vaccine production increasing from 350 million doses in 2006 to around 900 million doses by 2009 (*8*). In the past, increasing the global vaccine supply has been achieved primarily through increased investment by existing large-scale manufacturers in high-income countries. However, despite the gains made, it was clear that during the early stages of the 2009 H1N1 pandemic there were still significant gaps in the availability and supply of vaccines, with many developing countries receiving vaccine much later than developed countries, if at all. In order to ensure the more-equitable global availability of pandemic vaccines, the transfer of pandemic vaccine production technologies to developing regions remains a key GAP objective.

Strategies for approximately doubling the global production capacity for seasonal influenza vaccines to 1.7 billion doses by 2015 include shifting to higher-yielding technologies and the building and maintaining of new production facilities. Because seasonal influenza vaccines are trivalent and pandemic influenza vaccines are monovalent there would then be a potential threefold increase to 5.1 billion doses should a pandemic occur. However, even with this projected expansion and the surge potential offered by existing approved technologies (such as live-attenuated influenza vaccines and adjuvants), global capacity will still be insufficient to allow all developing countries access to pandemic vaccine in a timely manner. Another important factor to consider is the need to ensure the sustainability of such enhanced production capacity during inter-pandemic periods.

Although the regional availability of influenza vaccine is increasingly recognized as a crucial component of successful pandemic response activities, there is currently no influenza vaccine production capacity in the WHO African Region or the WHO Eastern Mediterranean Region.

2.2.2 The WHO influenza vaccine technology transfer initiative

The WHO influenza vaccine technology transfer initiative is part of collaborative efforts between WHO and other GAP stakeholders to help create regionally based, independent and sustainable pandemic influenza vaccine production capacity in developing countries. The initiative is based upon a mix of financial support and technology transfer to manufacturers in low- and middle-income countries. Financial support for this initiative has been provided by the Public Health Agency of Canada, the Ministry of Foreign Affairs of Japan, the United Kingdom Department for International Development, the United States Department of Health & Human Services, and the Asian Development Bank. In total approximately US$ 28 million of seed funding has been provided, with corresponding local government and other investment reaching approximately US$ 367 million.

To support the technology-transfer process, WHO facilitated the creation of an influenza vaccine technology "hub". This relatively novel approach to the pooling of resources for vaccine manufacturing capacity-building bypasses the often cumbersome bilateral agreement for technology transfer by establishing a complete manufacturing process free of intellectual-property restrictions and other barriers, and making this process simultaneously available to multiple recipients.

Of the 11 manufacturers in low- and middle-income countries who received WHO seed funding grants supported by technology-transfer activities,[1] five (in India, Indonesia, the Republic of Korea, Romania and Thailand) have produced licensed pandemic influenza vaccines during 2009–2011, with several others having vaccines in late-stage development. To address the lack of vaccine production capacity in the WHO African and Eastern Mediterranean regions, WHO has provided seed grants and technical support through its influenza vaccine technology transfer initiative to manufacturers in Egypt and the Islamic Republic of Iran, with both countries expected to have production capacity in place within 5–10 years. There is, however, a clear need to build capacity in other under-served regions, notably sub-Saharan Africa and Central Asia. Eight new proposals have been made to the initiative and a decision on new grantees will be made in 2011.

Support and commitment from governments and the private sector for local vaccine production are essential, and business plans must take local and regional demand into consideration, along with the selection of vaccine production technologies appropriate to the local setting. Local production may not be sustainable in settings where there is a lack of seasonal vaccine demand, infrastructure, political will, and media and public support.

Although newer developments such as live-attenuated influenza vaccines offer the advantages of increased yields, shortened production time and simplified intranasal administration, the corresponding regulatory pathway for new vaccine technologies in many countries is

[1] Financial and technical assistance was provided to manufacturers in Brazil, Egypt, India, Indonesia, the Islamic Republic of Iran, Mexico, the Republic of Korea, Romania, Serbia, Thailand and Viet Nam.

complex and may involve costly and time-consuming vaccine-efficacy studies. Similarly, the use of potentially dose-sparing adjuvants has been associated with issues such as higher reactogenicity and other adverse events resulting in mistrust and doubts about vaccine safety among the public. This can lead to difficulties both in terms of product evaluation by national regulatory authorities and the development of balanced communication strategies on vaccine usage.

The provision of funding and technical support for pilot-scale influenza vaccine production to prepare developing-country manufacturers for eventual commercial-scale activities has been accompanied by the convening of a series of international stakeholders' workshops to inform the formulation and implementation of expanded GAP activities in this area. The lessons learnt clearly indicate that there are complex challenges, and that technology transfer and manufacturing capacity-building must be part of a broader system that incorporates regulatory, clinical and policy aspects supported by a robust business model for sustainable production capacity. Partnerships and strong local-government support will be needed throughout with full recognition by technical and funding agencies of the need to flexibly support and respect complex national situations and regulatory requirements. Efforts will also be needed to expand the range of technologies currently available under GAP agreements.

2.2.3 Ensuring equitable access to pandemic vaccines

Expanding or supporting the establishment of pandemic influenza production capacity in selected developing countries is not in itself sufficient to ensure universal access to influenza vaccine during a pandemic. Nor is it possible or desirable to establish influenza vaccine production in all countries. WHO funding grants to manufacturers are therefore contingent upon an agreement to sell 10% of their vaccine production at an affordable price to United Nations agencies such as WHO and the United Nations Children's Fund (UNICEF) for distribution to those countries without any domestic production capacity.

In 2008, efforts were initiated to ensure timely access to H5N1 pandemic vaccine in low- and middle-income countries through the establishment of a WHO-administered stockpile. At present, 125 million doses of vaccine against H5N1 or other potentially pandemic influenza subtypes have been pledged by manufacturers. The optimum strategy and logistical approaches for this activity are currently under review by the WHO SAGE Working Group on Influenza Vaccines and Immunization.

Potential technological advances in providing pandemic vaccine strains in a timely manner include the development of a risk-assessment algorithm for novel or variant influenza viruses in which each of the factors associated with pandemic potential are identified and defined.[1]

[1] Currently recognized risk-assessment elements include infection of secondary hosts by the novel virus (especially humans); transmissibility (using ferret models); susceptibility of the population (in terms of existing seroprevalence); geographical spread (including among secondary hosts); severity of infection in humans and other mammals; and virus characteristics such as degree of pathogenicity.

Assigning a "weight" to each factor as part of a multi-factorial analysis will then allow the assigning of a composite score. For high-scoring viruses, preparedness packages could be developed consisting of diagnostic resources and candidate vaccine libraries of high-growth reassortants, with clinical trial lots developed for vaccine trials in the case of high-risk viruses. For very high-scoring viruses, a candidate vaccine library could be developed and pre-pandemic vaccines produced and stockpiled.

The successful conclusion of the Open-Ended Working Group of Member States on Pandemic Influenza Preparedness (OEWG/PIP): Sharing of Influenza Viruses and Access to Vaccines and Other Benefits (http://apps.who.int/gb/pip/e/E_Pip_oewg.html) and the historic adoption of the resulting PIP Framework by the Sixty-fourth World Health Assembly (*6*) was the culmination of five years of protracted negotiations. The PIP Framework provides comprehensive political and technical guidance on ensuring a fair, transparent, equitable, efficient and effective mechanism for sharing influenza A(H5N1) and other influenza viruses with pandemic potential and sharing the benefits arising from their use. There is now a clear need for commitment and collaboration at bilateral, national and international levels, including public and private sector partnerships, to build adequate capacity for effective global influenza pandemic preparedness and response activities. This will be needed to ensure equitable access to pandemic vaccine and other benefits and is thus closely linked to GAP activities.

Since 2002, the number of countries with a published pandemic preparedness plan has steadily increased. However, most of these plans were developed prior to the 2009 H1N1 pandemic and reflected to a large extent preparedness activities relating to a possible increasing incidence of avian H5N1 infection in humans. In light of a better understanding of the role and potential availability of pandemic vaccines, there is now a need for revised and updated pandemic preparedness plans in many countries.

2.3 Research and development

ORIGINAL GAP OBJECTIVE

Develop more-effective influenza vaccines using new technologies.

2.3.1 Current influenza vaccine landscape

The current influenza vaccine landscape is complex, with over 100 vaccine products licensed or undergoing evaluation. Although the near-term pipeline is still primarily focused on egg-based inactivated and live-attenuated vaccines, vaccines produced in cell culture are now on the market and there are a number of candidate vaccines in preclinical and clinical trials based on emerging technology platforms. These include the use of recombinant live-attenuated viruses, virus-like particles, viral-vectored vaccines, plasmid DNA, recombinant antigens produced in

various expression systems (such as plants) and the continued development of "universal" vaccines (Table 1).

2.3.2 Research into vaccines with broadly protective and long-lasting immunity

Broadening the degree of cross-protection offered by influenza vaccines and reducing the annual frequency at which seasonal vaccines must be administered remain significant challenges. Investigations are ongoing into novel immune targets and new formulations (including the use of adjuvants) to enhance cross-protection and provide longer-lasting immune responses. The development of universal vaccines is also a high priority.

Current obstacles to the introduction of novel vaccines, new formulations and delivery methods include ensuring the safety and immunogenicity of such vaccines, making corresponding advances in regulatory science, and developing simple low-cost approaches that provide sufficient and flexible production capacity.

Nevertheless, the ongoing pandemic threat posed by avian A(H5N1) and other influenza viruses continues to be a major catalyst for enhanced research and development efforts by both industry and academia. This has led to improvements in scientific knowledge and the development of new technologies to improve vaccine immunogenicity and allow dose sparing. From an industry perspective, active research and development efforts are continuing in all

Table 1

Current influenza vaccine landscape

	Number of vaccine products by stage						Number of vaccine products by target of use		
Technology	**PreCl**	**PhI**	**PhII**	**PhIII**	**MA**	**Total**	**Seasonal**	**Pandemic**	**Seasonal and pandemic**
Egg-based inactivated	10	7	5	2	12	**36**	6	14	16
Cell-culture inactivated	1	3	3	3	2	**12**	3	4	5
Live	3	2	3	0	3	**11**	2	7	2
Recombinant, protein & VLP	10	2	4	1	0	**17**	3	1	13
Universal protein	3	6	0	0	0	**9**	1	0	8
Viral vectored	6	4	0	0	0	**10**	0	2	8
DNA	2	4	0	0	0	**6**	3	2	1
Total	**35**	**28**	**15**	**6**	**17**	**101**			

MA: market-approved; PreCl: preclinical development; PhI–III: Phase I–III clinical trials; VLP: virus-like particle.
Source: R Bright (unpublished data, 2011).

areas, with a number of new vaccines and approaches (including adjuvanted and high-dose formulations, and the use of intradermal delivery) having been successfully introduced – though such novel approaches face challenges in terms of current levels of vaccine demand and coverage, financing, associated development costs, intellectual-property issues and regulatory requirements. Overcoming these and related issues will require open and constant dialogue with regulatory agencies and other public and private sector organizations.

Although the "holy grail" of a universal vaccine ideally suited for manufacture in developing countries is receiving increasing attention, this forward-looking approach remains unproven. Universal vaccine candidates are in Phase I trials and safety studies have been conducted or are in progress. There are, however, major technical and financial obstacles to the development of universal vaccines, including a lack of assays based on suitable correlates of protection, and regulatory issues.

One major problem identified during the 2009 H1N1 pandemic was the issue of "too little vaccine too late". Although the use of recombinant vaccine technologies could address this, there remains a need to assess the efficacy of such vaccines in humans and to establish regulatory pathways for their approval. At present, only one recombinant vaccine candidate is in Phase III.

2.3.3 Identifying correlates of protection

Currently used correlates of protection are problematic as the haemagglutination inhibition (HAI) assay does not measure antibody responses to other viral components which also contribute to protection, while the linkage between HAI data and clinical efficacy was established only in healthy adults. In addition, HAI testing has not been able to reflect the protection provided by live-attenuated influenza vaccines, even though their clinical effectiveness has clearly been demonstrated. These results indicate that other immune responses, such as cellular immunity, play important roles in protection.

An improved understanding of the correlates of protection therefore continues to be needed, particularly given the ethical and other issues in designing studies of vaccine efficacy using placebo-controlled trials. This is especially important as observational studies (particularly in at-risk groups) can be subject to wide variations in interpretation and confounding variables.

The main challenges in this area include the possibility of different vaccine types having different correlates, with this problem increasing as the diversity of vaccines increases. The effects of antigenic drift or recipient age may also affect how well correlates predict efficacy, thus requiring studies in different age groups and at-risk populations. In addition, as HAI remains the single acceptable correlate of protective immunity in the regulatory evaluation of influenza vaccines, other assays may be difficult to establish.

2.3.4 New vaccine-administration methods

Research into improved modes of delivery is another important activity area. The main goals of such research are to determine the potential for dose sparing and for needle-free administration. Simplifying the vaccination process through needle-free delivery methods would not only bring great benefits in developing countries by avoiding the dangers inherent in conventional syringes, but could also potentially simplify vaccine administration and improve coverage in all settings.

A wide variety of novel delivery technologies were reported to be under development. The five main areas of research are jet injection, intranasal spray, pulmonary inhalation of aerosols, oral ingestion and cutaneous administration. Technologies for cutaneous administration include classic and improved intradermal methods, mechanical disruption of the stratum corneum, coated microtines, hollow microneedles, dissolving microneedles, and kinetic electromagnetic, chemical and sonic techniques. As with other areas of research and development, there remain a number of significant technical, regulatory and financial challenges to overcome.

2.3.5 Financing influenza vaccine research and development

The development and production of influenza vaccines is a high-risk and expensive endeavour for manufacturers, and a continual race against time to detect the emergence and spread of new influenza variants and provide vaccine in time to control widespread disease outbreaks. In the USA, funding strategies and investment in vaccine research and development have fluctuated markedly over the last decade. Prior to 2004, government funding through annual appropriations was primarily only for early-stage research and development, and was of the order of several tens of millions of US dollars. During 2005–2009 such funding increased to tens of billions of US dollars and covered basic research and early development (through annual appropriations) as well as advanced development, manufacturing and stockpiling (through supplemental appropriations). However, in the current financial situation, government financing is now down to US$1 billion. In addition, there are increasing economic pressures on industry from shareholders for reliable opportunities and faster returns on investments, while venture capital investments are also drying up.

Ideally, realizing new and better vaccines sooner would involve a new set of goals and strategies which would include aiming to produce pre-pandemic vaccines, recombinant vaccines and both egg- and cell-based vaccines with adjuvant within 16–20 weeks. In reality, however, a number of practical solutions in the short, medium and long term will need to be considered. In the short term, it will be important to nurture public–private partnerships with more cooperative agreements in light of static funding. A focus will also be needed on shortening the current influenza vaccine manufacturing timeline, and on utilizing multipurpose product technologies while supporting multi-product and flexible manufacturing facilities. In the long term, the goal should be to support "universal" influenza vaccine development.

2.3.6 WHO influenza research activities

A number of documents produced by WHO and other agencies and organizations in recent years were highlighted to demonstrate the importance of influenza research and to illustrate the wide spectrum of subject areas. Emphasis was then given to the five "streams" of the WHO Public Health Research Agenda for Influenza (*9*) with its overall goal to:

> *support the development of evidence needed to strengthen public health guidance and actions essential for limiting the impact of influenza on individuals and populations.*

In particular, Stream 3 – *Minimizing the impact of pandemic, zoonotic and seasonal epidemic influenza* – has particular relevance to GAP-related activities with its three principal areas of recommended research activities ranging from the assessment of disease burden and social impact to the use of pharmacological interventions and the informing of public health policies to reduce the impact of disease. In the case of specific vaccine research and development activities, the use of pharmacological interventions incorporates the development of new-generation vaccines, evaluation of vaccines and increasing pandemic influenza vaccine production capacity.

In order to accelerate the development and optimal use of new and improved influenza vaccines and technologies – with a special focus on the needs of developing countries – WHO will also continue its activities in the following areas:

- monitoring vaccine research and development
- vaccine policy development research
- vaccine implementation research
- vaccine operational research
- regulatory research.

Taken together, research in these areas represents a comprehensive programme of guidance and support for influenza vaccine research and policy-development activities. One important outcome of WHO efforts will be to systematically map the global landscape of influenza vaccine research and development.

3. Proposed actions in key areas

3.1 Increasing the use of seasonal influenza vaccine

Policy and planning

- To meet the needs of all those at risk from seasonal influenza epidemics, an evidence-based approach is required for the further development of national and regional seasonal influenza vaccination policies and implementation in the context of other competing health needs.
- Influenza immunization activities should be integrated into countermeasures that may already be used to prevent or mitigate other acute respiratory infections, including respiratory-hygiene initiatives, use of antivirals and administration of vaccines against other respiratory conditions in children and the elderly.
- Where new influenza vaccine production facilities are put in place, commitments should be sought from government ministries in moderate-resource countries to purchase the vaccines produced.

Burden of disease

- The burden of influenza disease in different countries and regions, and among different population groups, needs to be determined.
- Large-scale probe and other studies that seek to demonstrate the effect of seasonal influenza vaccination in reducing the burden of disease in the principal target groups should be conducted to demonstrate its precise impact and cost–effectiveness, and to guide decision-making.

Communication and awareness

- Effective and targeted communication strategies should continue to be developed and shared for specific audiences to promote the uptake of seasonal influenza vaccines among the public and among health professionals.
- Vaccination outcomes other than influenza prevention should be assessed and communicated to resonate with the concerns of decision-makers and the public. Such outcomes should

include the impact of influenza vaccination on maternal and child health, on rates of pneumonia and associated deaths in all age groups, and on health-care infrastructures and service quality.

Operational research

- Specific strategies for the innovative and sustainable deployment of seasonal and pandemic vaccines should be evaluated to meet identified key needs, particularly in resource-limited countries.
- A toolkit listing all the requirements needed to successfully implement GAP-related activities in countries should be developed. This should cover issues such as vaccine effectiveness and safety monitoring, health-economics and cost–effectiveness studies, and the development of communication and advocacy packages.

3.2 Increasing influenza vaccine production capacity

Increasing local and regional vaccine production capacity

- New methods and approaches for optimizing production should continue to be evaluated. For example, modular facilities have potentially shorter construction times and can be operated using disposable equipment.
- The feasibility of building multipurpose facilities that can be used to manufacture compatible products other than human influenza vaccines should be investigated to promote sustainable manufacturing capacity – for example by producing live-attenuated yellow fever vaccine in eggs with the option of switching to influenza vaccine production in the event of an influenza pandemic, or by producing veterinary influenza vaccines.

The WHO influenza vaccine technology transfer initiative

- Technical and financial support to the 11 developing-country manufacturers who are currently participating in this WHO initiative must be sustained until product registration.
- Global seasonal and pandemic influenza vaccine supply and demand should continue to be mapped to identify regions where access to vaccines is limited, and to initiate or expand vaccine production in these areas.

Equitable access to pandemic vaccines

- During the early stages of the 2009 H1N1 pandemic there was too little vaccine too late and efforts should continue to be made to reduce the influenza vaccine production timeline – from the earliest identification of viruses to the development of seed strains and the production and regulatory approval of vaccines.

- During a pandemic there will also be a need to optimize surge capacity for vaccine production to produce more and better vaccines more promptly. Relevant approaches here include dose sparing (for example through the use of adjuvants) and increasing yield (for example by producing live-attenuated influenza vaccines). As part of this, WHO should continue its efforts to ensure access to oil-in-water adjuvants for influenza vaccine production.
- As the number of vaccine manufacturers increases so does the number of different types of vaccines. It would be helpful in the event of a pandemic to produce vaccines that require the same dose schedule. This would help to harmonize the regulatory review process and meet surges in demand during a pandemic. It might therefore be useful to define a product profile to assist manufacturers.
- Greater emphasis should be placed on improving downstream processes (such as fill-finish) in addition to upstream processes.

Regulatory issues

- The strengthening of national and other regulatory agencies to promote the timely and efficient assessment and approval of locally manufactured or imported influenza vaccines will require a long-term strategy and strong political commitment.
- Safety and risk communication between governments, the media and the public is a crucial aspect of strengthening regulatory capacity, and particular attention should be paid to post-marketing surveillance to promptly detect and manage any concerns associated with vaccine use.
- Regulators have a role to play in making vaccine quickly available and need to be flexible in pandemic situations. A database is needed for regulators on the safety and efficacy of new technologies, including adjuvant safety and efficacy.
- Despite increased demand for reagents to test the potency of influenza vaccines, only a small number of laboratories currently produce such reagents. Efforts in this area should include the creation of a stockpile of potency-testing reagents, and coordination of potency studies and associated assays.

3.3 Promoting influenza vaccine research and development

- A systematic mapping of the landscape of influenza vaccine research and development should be undertaken to support the overall research effort, increase awareness and improve harmonization of the activities of the different groups working in this area.
- Vaccine performance needs to be improved through better immunogenicity and through improved breadth and duration of protection.

- The long-term goal of developing "universal" vaccines should remain a priority.
- Improved understanding of the correlates of protection is now needed given the ethical and other obstacles to the study of vaccine efficacy using placebo-controlled trials in many population groups.
- Standardized assays for neuraminidase as well as haemagglutinin should be developed along with reference preparations for the evaluation of live-attenuated influenza vaccines.
- The technological challenges of developing and improving vaccine-delivery methods that can induce better immunity should be addressed, the stability of novel delivery approaches assessed and time-and-motion studies conducted to evaluate their operational utility.
- As part of the optimization and prompt development of influenza vaccine donor and candidate viruses, the genetics of high-yield donor viruses from different laboratories should be analysed and high-yield reassortant strains produced and evaluated. In support of this, stockpiles of potency-testing reagents should also be established.
- Further studies are needed to address issues of vaccine shelf-life and to assess the stability of stockpiled vaccines.
- Clear short-term, medium-term and long-term research and development goals should be identified and the underlying assumptions driving these goals should be made explicit and periodically revisited.
- The influenza vaccine research and development landscape is active and rapidly evolving, but faces significant funding challenges which will require continued stakeholder support and strategic prioritizing.

4. Next steps for GAP

The three primary objectives of GAP remain:

- increasing the use of seasonal influenza vaccine
- increasing influenza vaccine production capacity
- promoting influenza vaccine research and development.

As part of determining the next steps to be taken, careful consideration should now be given to expanding and refining these original three "pillars" of GAP to incorporate new areas of activity. Broader attention needs to be given to all aspects of influenza vaccine production and use, including efforts to develop an evidence-based approach to increasing public and professional understanding of the importance of influenza vaccination and ensuring its acceptability; increased surveillance of influenza disease and research into its burden and the impact of vaccination; strengthened virological surveillance and response activities; development of new vaccine technologies; further expansion of production capacity; the use of new modes of vaccine administration; and a broadening of the range of settings in which vaccinations can be given. Enhanced national and regional regulatory processes and deployment capabilities will also be required, along with more-responsive post-marketing monitoring of vaccine effectiveness and safety to allow for the prompt addressing of any public concerns.

Countries with existing policies and identified targets for seasonal influenza vaccination should be encouraged to focus on achieving their objectives. Where countries lack such policies, disease-burden and operational research will be required to inform vaccine policy development. The strengthening of national pandemic and pre-pandemic planning will also help to ensure that the vaccines produced are used – supported by evidence of their public health impact – and that production capacity can be established where needed. In selected low-income countries, proof-of-concept programmes encompassing the broad range of required activities could be undertaken which if successful could be rolled out in other low-resource settings. Specific strategies for resource-limited countries should be developed to meet identified key needs using lessons already learnt from the success of GAP-related activities in a number of WHO regions.

Accountability mechanisms should be strengthened and independent auditing and assessment conducted of GAP projects and their impact. Although the first five-year phase of GAP is widely considered to have been a success, there is now a need for more-rigorous assessments with indicators developed to track progress. There is also a need for increased flexibility of approach with both the definitions and indicators of success likely to vary in different settings. As part of this process, confidential or anonymous appraisals by institutional recipients of technical and financial support are likely to provide important insights.

The role of the GAP process in the broad context of responding to the recommendations of the International Health Regulations (IHR) Review Committee and in implementing the internationally agreed PIP Framework – which includes the strategic development of WHO-administered vaccine stockpiles – should be clearly defined and its central importance in these initiatives highlighted. The original vaccine production target for GAP was to have in place sufficient capacity in the long term to vaccinate 100% of the world's population with two doses within six months of the availability of a prototype pandemic vaccine strain. However, emerging mathematical modelling of the effect of herd immunity indicates that virus transmission could be brought under control by vaccinating 70% of the world's population. Further research should be carried out to verify this model and, if confirmed, this target should be integrated into preparedness planning across all countries, and should not range from 0% to 100% in different populations.

In spite of the many successes of the international response to the 2009 H1N1 pandemic, it was clear that once again too little vaccine was available too late with large variations in the availability of vaccine in different countries and regions of the world. It now seems likely that had pandemic vaccines been more universally available even 4–6 weeks earlier this would have brought significant benefits in terms of vaccine acceptance and disease reduction. At the same time, the pandemic clearly illustrated that increasing access to vaccine also means having in place sufficient regulatory capacity and storage and deployment infrastructure. The logistical and personnel requirements of these activities are considerable to the extent that during the pandemic the delivery of other health programmes was jeopardized – including those for seasonal influenza vaccination. Distribution constraints such as cold-chain capacity currently place a ceiling on the theoretical level of vaccine deployment during a pandemic. Integration with existing programmes to avoid the need for vertical deployment of influenza vaccines should therefore be considered.

Success in all these areas will require increased collaboration, partnership and networking, while greatly improving the delineation of roles and responsibilities of WHO and other international agencies, governments, funders and other stakeholders. In light of current budgetary constraints, a robust assessment is needed of the capabilities and comparative strengths of all the various stakeholders, especially where progress needs to be made in settings with minimal resources. Efforts should also be made to expand and diversify the

present funding base. Improving national, regional and interregional communication channels between the current myriad of different organizational structures is also likely to be a key requirement of success.

The research and development landscape is active and rapidly evolving but faces significant challenges ahead, with an over-arching need for continued stakeholder support. As research and development funding decreases, strategic prioritizing will become ever more important. Vaccine performance needs to be improved through better immunogenicity, longer duration of protection and broader cross-protection. In addition, overcoming the regulatory challenges posed by novel vaccines and new technologies will require close collaboration with regulatory authorities.

Across the range of GAP-related activities, effective communication and advocacy approaches will be required, for example to enhance understanding of the importance and benefits of seasonal influenza vaccination, address misinformation and promote acceptance by health professionals and the public. Policy-makers must be convinced of the vital importance of effective risk communication with the public and others, and innovative use of a wide range of media encouraged.

WHO should continue its advocacy and communication activities aimed at raising both the visibility of influenza as a public health priority and the credibility of the GAP initiative. Further development of the WHO GAP web site (http:/www.who.int/influenza_vaccines_plan/en/) will help to meet the objective of providing a sustainable information hub for all GAP-related activities. This will permit the exchange of timely information among an expanding community of stakeholders, and the coordination of appropriate coverage and reporting of activities in the scientific and general media. The web site and associated use of social media represent one of a number of innovative approaches, which also include the use of a new visual identity for GAP, strategies for information dissemination, and partnership mapping and development.

Further refinement and implementation of GAP will continue to be guided by the work of the WHO SAGE and by the recommendations of the GAP Advisory Group (*10*). As part of this process, the development of a strategic plan of action for the next five years is now under way with inputs from all GAP stakeholders.

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In May 2006, the World Health Organization (WHO) held the first WHO consultation on the Global Action Plan for Influenza Vaccines (GAP). At that time it was recognized that if an influenza pandemic were to occur, the potential vaccine supply would fall several billion doses short of the amount needed to provide protection to the world's population. At the same time, awareness was growing of the significant disease burden and other impacts caused every year by seasonal influenza epidemics. It soon became clear that ensuring equitable and universal access to influenza vaccines was not only an ethical requirement but was also a crucial element in both seasonal and pandemic influenza preparedness and response efforts.

In the years following its launch, GAP has proved to be an effective catalyst for a significant expansion in influenza vaccine manufacturing, with global production capacity increasing from 350 million doses in 2006 to over 900 million doses by 2009. In addition, GAP has provided a successful framework for increasing the number of countries with vaccine production capabilities in place. As the first five-year phase of GAP comes to a close, there is now a need to review the progress made so far and to learn from the experiences of recent years – including the lessons of the 2009 H1N1 pandemic.

In July 2011, WHO therefore held the second WHO GAP consultation to bring together more than 100 representatives from national governments, United Nations agencies, funders, regulatory authorities, WHO technology-transfer projects, vaccine manufacturers, nongovernmental organizations and the research community. The overall objective of the consultation was to review the progress made and lessons learnt during the first five years of GAP in order to identify which approaches and factors lead to the successful implementation of activities. Following wide-ranging discussions of all the major areas, consultation participants then proposed a set of key actions. It is intended that the overview of GAP activities in the first five years and the proposed action points presented in this report will be used to inform the development of a GAP strategy for the next five years.

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