

Global pandemic influenza action plan to increase vaccine supply: progress report 2008

Immunization, Vaccines and Biologicals



**World Health
Organization**

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Abbreviations and Acronyms

Ab	antibody
AEFI	adverse event following immunization
ATCC	American Type Culture Collection of LGC (Laboratory of the Government Chemist) Standards
BPL	β -propiolactone
ca	cold-adapted
CEF	chicken embryo fibroblasts
CHMP	Committee for Medicinal Products for Human Use
DNA	deoxyribonucleic acid
EMA	European Medicines Agency
EPI	Expanded Programme on Immunization
GAP	Global pandemic influenza action plan to increase vaccine supply
GMP	good manufacturing practice
H5N1	highly pathogenic avian influenza virus, type H5N1
HA	haemagglutinin
HAI	haemagglutinin-inhibiting antibodies
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IHR	International Health Regulations
ID	intradermal
IIV	inactivated influenza vaccine
IP	intellectual property
LAIV	live attenuated influenza vaccine
MDCK	Madin-Darby canine kidney cells

NA	neuraminidase
NACI	national advisory committees on immunization
NCIP	national committees for immunization practices
NIBSC	National Institute for Biological Standards and Control
NRA	national regulatory authority
NVI	Netherlands Vaccine Institute
PAHO	Pan American Health Organization
PATH	Program for Appropriate Technology in Health
PCT	Patent Cooperation Treaty
QC	quality control
QUIVER	WHO Advisory Committee on Quantitative Immunization and Vaccine Research
R&D	research and development
SAGE	Strategic Advisory Group of Experts
SEIR	susceptible exposed infectious recovered
SigA	secretory immunoglobulin A
SOP	standard operating procedures
TAG	Technical Advisory Group
TLR	toll-like receptors
UNICEF	United Nations Children's Fund
WHO	World Health Organization

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1. Policy and coordination for improved pandemic influenza vaccine preparedness

The first approach of the Global Action Plan (GAP) is to encourage countries to increase their seasonal vaccine use. This will primarily reduce the disease burden of seasonal influenza infection, but will importantly provide an incentive for industry to increase its manufacturing capacity for influenza vaccines.

The GAP therefore highlights the need for national immunization policies to make increased demand for seasonal influenza vaccine a priority, together with resource mobilization plans – at the regional and national levels – to secure sustained introduction. It also provides an overview of the policy and programmatic issues that need to be considered in this endeavour.

To assist countries to implement effective seasonal influenza vaccination programmes, to help those that cannot afford the US\$ 3–7 per dose, as well as to plan for equitable access to and deployment of pandemic vaccine, WHO initiated the following projects related to national policy and coordination:

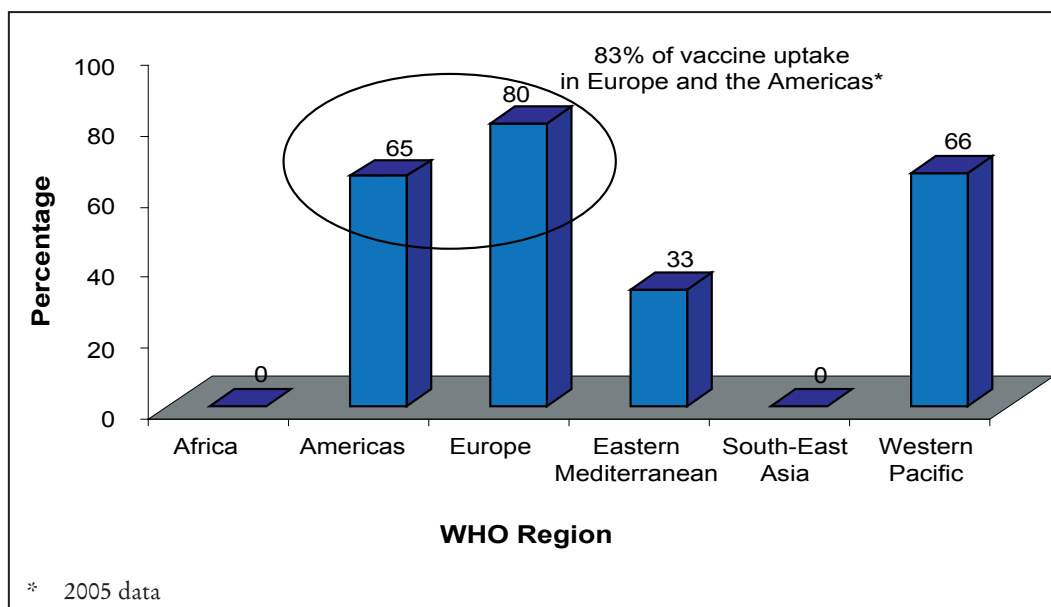
- assess current and planned seasonal vaccine use, and potential pandemic vaccine demand;
- strengthen national immunization advisory committees;
- assess and strengthen national capacity to deploy pandemic vaccine;
- consider the establishment of an H5N1 influenza vaccine stockpile;
- develop tools to estimate the impact and cost-effectiveness of different scenarios with limited pandemic influenza vaccine availability;
- promote activities to ensure equitable access for all Member States to a pandemic influenza vaccine;
- facilitate resource mobilization to implement seasonal vaccination programmes.

The progress of these projects is summarized below.

1.1 WHO survey on current and future use of influenza vaccine

Underpinning increased vaccine production capacity of seasonal influenza vaccine is increased demand. To assess the current and planned use of seasonal influenza vaccine, and to estimate demand for pandemic influenza vaccine in the event of a pandemic, WHO carried out a global survey in May 2006.¹ An analysis of the responses received from 136 Member States plus 12 territories is provided below.

Figure 1: Percentage of response by region that answered "yes" to using seasonal influenza vaccine



Countries currently using seasonal influenza vaccine

Half of the countries that responded had routine vaccination programmes for seasonal influenza, with the WHO European Region having the highest number of countries, and the African and South-East Asia Regions none (Figure 1). There had been a noticeable increase in the global uptake of seasonal influenza vaccine – from 192 million doses in 2004 to 261 million in 2005, of which the Americas and Europe accounted for 83% of total vaccine use. The northern hemisphere formulation for seasonal vaccine was used in 81% of routine vaccination programmes, while the southern hemisphere formulation was used mainly in Latin America and the Pacific Basin.

While the elderly have traditionally been considered at the highest risk of influenza-related illnesses, countries targeting the 6–23 month age group had increased from 13% in 2003 to almost 20% in 2005. The profile of the high-risk groups targeted by the Americas and Europe for seasonal influenza vaccination continued to be persons with renal dysfunction, or cardiovascular, lung and immunosuppressant diseases.

¹ *Mapping the landscape: current and future use of influenza vaccine.* Geneva, World Health Organization (in preparation).

With regard to seasonal influenza vaccine coverage, only 80 countries provided data for 2005, and of these 50 described the populations targeted. Data showed that routine vaccination coverage was higher in countries with smaller populations, particularly in older age groups. Countries with large populations are therefore encouraged to review their programmes to improve access for targeted cohorts, and thereby increase demand for seasonal influenza vaccine.

Countries planning to introduce seasonal influenza vaccine programmes

An additional 27 Member States or affiliated countries/territories indicated that they would introduce seasonal influenza vaccination before 2010, targeting the very young and the elderly. Over 63 million supplementary doses of seasonal influenza vaccine will therefore be needed within this time frame. These data are encouraging, even if they fall far short of the vaccine production capacity needed.

Estimated demand for pandemic influenza vaccine

Countries provided information on their intention to purchase pandemic influenza vaccine, the population groups they would target, and their need for financial support. In the event of an influenza pandemic, 111 countries indicated that they would purchase pandemic vaccine. Although 20 of these did not estimate the number of doses they would require, 91 countries would request pandemic vaccine to protect, in total, 828 million persons. Based on these figures, and on the assumption that a single dose would provide protection, only 13% of the global population would be targeted for vaccination in an influenza pandemic, as shown in Table 1.

Table 1. Estimated demand for pandemic influenza vaccine by WHO Region*

No. of persons vaccinated (M)	WHO Region
42.0	Africa
385.0	Americas
15.4	Eastern Mediterranean
268.0	Europe
112.0	South-East Asia
5.5	Western Pacific
827.9	Global total

* N.B. The figures only reflect data from countries that responded to the survey and may be much higher.

Data from the survey indicated that funds would be required by low- and middle-income countries to procure 276 million doses at a cost of US\$ 734 million at the current Pan American Health Organization (PAHO) Revolving Fund vaccine price. An additional US\$ 16.6 million may be required to cover syringes.

Summary discussion and conclusions

The annual global production of trivalent seasonal influenza vaccine could exceed one billion doses within the next few years, with new adjuvants markedly increasing capacity for pandemic vaccine production by 5–10 fold. However, influenza vaccine manufacturers are understandably reluctant to invest in additional production capacity unless the demand for seasonal influenza vaccine increases. On the other hand, the short-term prospect of doubling the global demand for seasonal influenza vaccine through an increased number of countries introducing it, does not look promising.

The limited importance that countries placed on introducing a seasonal influenza vaccine programme may relate to cost and a lack of reliable disease-burden data, as shown by experience with the uptake of *Haemophilus influenzae* type b vaccine. Advocacy, surveillance to generate these data, and cost–benefit analyses, should be undertaken to enable decision-makers to assess the benefits of introducing seasonal influenza vaccine.

The survey, which was only issued in English, may have been too ambitious in its attempt to collect the required data. Moreover, the data that were provided suffered from inconsistencies and omissions. For example, 25 countries with populations ranging from 20 million to over 500 million either did not respond to the survey, or did not indicate the number of pandemic influenza vaccine doses required. Countries where the private sector provides seasonal influenza vaccine could not provide data, and even some countries with mature influenza programmes could not supply basic information on seasonal vaccine coverage. Despite these limitations, the survey provided for the first time a global landscape on the current and planned use of seasonal influenza vaccine, and an initial evaluation of plans for the use of a pandemic vaccine in the event of an influenza pandemic.

There is broad recognition that every country must plan now for a possible influenza pandemic in order to pave the way for influenza vaccine manufacturers, donors and funding agencies to meet the demand for a pandemic influenza vaccine. In addition, WHO encourages the development of regional plans, based on the results of the survey, to increase the use of seasonal influenza vaccine and define the role that a pandemic influenza vaccine would have in mitigating a pandemic. Funding will need to be sought to help secure the purchase of pandemic influenza vaccine and related supplies for resource-poor countries.

1.2 Assessment of national committees for immunization practices

National immunization programmes in most developing countries have, until recently, only needed to deliver six, well-established antigens. The arrival of new vaccines on the market, along with new funding opportunities, is good news, although many countries are suddenly having to make difficult decisions on the appropriateness and affordability of these new antigens. Given multiple demands for scarce health resources, the inclusion of seasonal influenza vaccine (although not a new vaccine) into national immunization programmes, is one of these difficult decisions.

In July 2007, the WHO Regional Committee for South-East Asia recommended that all countries establish a national committee for immunization practices (NCIP) to provide technical advice to governments so that informed decisions could be made on the uptake of new antigens. As at December 2007, 7 of the 11 countries of the Region had established such a body.

To strengthen and harmonize NCIPs, WHO and its partners organized the first ever region-wide workshop in Indonesia in March 2008². In addition to reviewing national Expanded Programme on Immunization (EPI) policies and strategies, the workshop examined processes for decision-making, methods of work and evidence-based analyses, to develop policies on the introduction and use of vaccines within national immunization programmes. This policy framework would also facilitate decision-making and strategic planning for the use of pandemic influenza vaccine. Regional and global networking opportunities were promoted through presentations and the sharing of experiences among NCIPs and with invited international specialists from the US Advisory Committee on Immunization Practices, the Influenza Task Force of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) and the Developing Countries Vaccine Manufacturers Network. The following paragraphs summarize the major discussion points of the meeting.

Current status of national committees on immunization practices in the WHO South-East Asia Region

A review of existing NCIPs showed wide variation in their composition, procedures, and roles and responsibilities. Sri Lanka and Thailand both had well-established NCIPs; similar committees had recently been established in India and Indonesia; while the remaining seven countries were on track to establish advisory groups within the year. In considering the strengths and weaknesses of existing NCIPs, as well as the WHO generic guidelines for the establishment of such bodies (see Annex 1 of the workshop report), detailed recommendations were made on the formal Terms of Reference of an NCIP, the core elements that should be included, and on good procedural and management rules.

Policies on seasonal influenza vaccine use and implications for pandemic preparedness

Since no country in the Region had a policy on the regular use of seasonal influenza vaccine, the workshop evaluated the types of evidence required to inform policy, the procedures for policy deliberation, and the format of policy recommendations for the potential use of seasonal influenza vaccine. Some countries reported that their private sector health services offered seasonal influenza vaccination, although few data were available.

² *Strengthening the capacity of National Committees for Immunization Practices for pandemic influenza preparedness. Report of the Workshop, Jakarta, 25–28 March 2008.* New Delhi, World Health Organization, 2008 (SEA-IMMUN-15).

The importance of using seasonal influenza vaccine to boost vaccine production capacity worldwide to prepare for a possible pandemic was discussed in detail. Countries – particularly those with limited resources – that do not currently use or produce seasonal influenza vaccine, may have little or no access to pandemic influenza vaccine. It was therefore considered critical that policies on the use of seasonal influenza vaccine be put in place, resources committed to ensure a sustainable seasonal influenza vaccination programme, and prioritization principles developed for the use of a limited supply of pandemic influenza vaccine.

Follow-up to the WHO survey on the use of influenza vaccine

In response to the WHO global survey on the current and planned use of seasonal influenza vaccine, and national intentions to purchase pandemic vaccine, participants discussed and adopted a series of recommendations for countries in the WHO South-East Asia Region. In particular, all countries agreed to review their influenza pandemic preparedness plan to ensure that the role of vaccination is clear and that the required regulatory pathways are in place. In addition, it was suggested that the Regional Office consider preparing a Regional Influenza Pandemic Preparedness Plan with its Member States.

The importance of influenza surveillance

The epidemiology of seasonal influenza infection is relatively unknown in the Region and consequently surveillance data are unavailable to make an informed decision on the need for vaccination. Several regional sentinel sites are part of the global influenza surveillance network that routinely provides WHO with information on circulating influenza viruses. Contrary to the general belief that seasonal influenza is not a public health issue in Asia, influenza surveillance, particularly in Thailand, has clearly shown that it causes significant morbidity and mortality. For example, 10% of hospitalized pneumonia cases in the country are associated with infection by influenza virus. In early 2008, the Government of Thailand decided to extend and finance seasonal influenza vaccination as part of its pandemic preparedness. Other best practice surveillance systems were presented, for example by the Republic of Korea and the United States of America (USA).

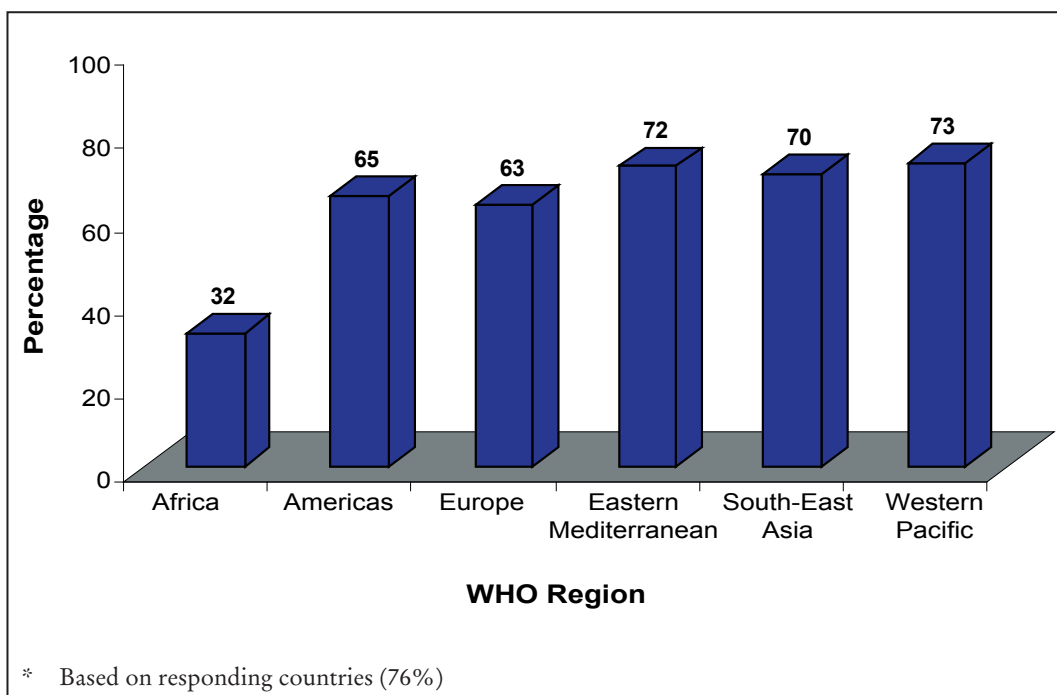
Conclusions

The value of a national advisory body to guide the government on immunization policies and practices was agreed. National ownership was deemed essential for its long-term sustainability as an integral component of systems development. NCIPs would update their terms of reference to reflect the outcome of the workshop, and propose a policy on the routine use of seasonal influenza vaccine. The WHO Regional Office for South-East Asia has since followed up on the meeting and shared progress during the global videoconference with other WHO regional offices in November 2008.

Expanding to other regions

Since the meeting of countries in the WHO South-East Asia Region, a global survey has been carried out to document the existence and characteristics of national advisory committees on immunization (NACI) across the globe (Figure 2). In addition, quarterly videoconferences are held with immunization staff at WHO regional offices to share progress in establishing and strengthening NACIs. Most regions are adapting the global guidelines to assist countries to establish or strengthen their NACI, to explain the purpose, roles and responsibilities of such committees, and to increase their heterogeneity. In many regions, the vastly differing geographical scope of some countries presents additional challenges.

Figure 2: Presence of a National Technical Advisory Committee on Immunization*



1.3 Guidelines for the deployment of a pandemic influenza vaccine

In the event of an influenza pandemic, Member States must be able to deliver a pandemic influenza vaccine to all distribution sites (districts or equivalent) within seven days of its availability in the central stores.³ This will be no mean feat, particularly in developing countries with fragile infrastructures and limited human and financial resources. WHO has therefore drafted comprehensive guidelines for the deployment of a pandemic influenza vaccine,⁴ comprising seven mutually reinforcing chapters that detail every aspect of deployment operations. Whether the pandemic vaccine is produced within or outside the country, or delivered from a stockpile, the guidelines offer extensive procedures, flow charts, checklists and links to further information, to assist Member States to ensure that their deployment plan is a successful component of national influenza pandemic preparedness.

The importance of advanced planning and simulation exercises are stressed at each step, especially for the surge capacity that will be required, i.e. the additional resources needed during an emergency and the ability of a Member State to access and use them.

The guidelines presuppose that certain core processes and structures are in place, notably a national policy for use of a pandemic influenza vaccine, along with funds for its deployment.

The legal aspects of deployment

Even during an emergency, national and international laws must be respected. Chapter 1 of the guidelines discusses how to assure that all legal/regulatory requirements to import, transport, stockpile, distribute and dispose of a pandemic influenza vaccine are in place well in advance to avoid dilemmas during a pandemic. Caution is drawn to the potential need of authorization for medical devices, which may fall under different qualification procedures than for vaccines.

Some countries may need to establish a legislative process to modify laws to allow the deployment of a pandemic vaccine. In such cases, contact with the appropriate legal authorities is a priority. The specific legal obligations of everyone involved – customs, regulatory authorities, airport authorities, transportation and logistic companies – to achieve timely deployment should be documented. The vaccine manufacturer, for example, must provide production protocols, lot-release documents, clinical trial dossiers and registration papers, but may also need to cover liability issues on the use of the vaccine, or compensation following an adverse event. Customs and tax regulations may also require that specific documents accompany the vaccine, e.g. to endorse its use.

³ The seven day criterion is based on the successful control of outbreaks during smallpox eradication operations, as well as subsequent efforts to control measles and polio outbreaks in the Americas when these two diseases were the subject of eradication/elimination. In addition, an individual requires approximately 14 days to develop measurable antibodies to a seasonal influenza vaccine, and thus it is critical to administer the pandemic vaccine as rapidly as possible so that individuals can develop an adequate immune response.

⁴ *Guidelines for the deployment of a pandemic influenza vaccine.* Geneva, World Health Organization (in preparation).

A flowchart of what needs to be done, by whom and when, should be set up in advance and will uncover any grey areas that lack legal and regulatory processes, and provide an opportunity to deal with them.

Management

If a pandemic influenza vaccine reaches the designated distribution points within seven days of its availability, it will be because effective management and coordination have been put in place at all levels. Chapter 2 of the guidelines provides tools for pre-event assessment and planning, a managerial and operational framework, and exercises to test and perfect the deployment plan.

Effective management begins with a clear line of command to provide oversight, accountability and a framework for rapid decision-making. The person with overall responsibility for the response effort should develop and execute a command-and-control protocol containing at least:

- the deployment plan;
- the contact details, responsibilities and duty roster of key persons at each level during deployment;
- a proposed implementation schedule, e.g. the mode of transport for each shipment;
- a security plan for areas where personnel or vaccine are considered to be at risk.

In many countries, the emergency services at regional and district levels are managed by a range of agencies with different local responsibilities. Deployment committees with broad representation are therefore recommended at each level to ensure multisectoral participation and joint effort.

Logistics

Chapter 3 provides extensive details on the art of assuring the supply chain. Logistics involve the management of critical information on timely delivery, transportation and storage, inventories and tracking, packaging and repackaging and distribution and redistribution.

A logistics action plan, which depends as for all aspects of pandemic influenza preparedness on pre-event planning, is a first priority. Countries should use their current vaccine delivery systems as a basis for the deployment of a pandemic influenza vaccine, although private-sector networks may well be needed for the surge capacity required during a pandemic. In the case of imported vaccine, each Member State should designate the warehouse(s) to which all vaccine supplies will be delivered prior to their redistribution to sublevels.

The chapter also includes a discussion on budgeting and financial administration.

Waste management preparedness

An influenza pandemic will generate a vast amount of medical waste at delivery points throughout the country in a very short space of time, and health authorities need to be prepared for this. The traditional waste-disposal infrastructure will not be able to cope with this surge.

A sound waste management plan is based on assessment, decision-making and implementation, each of which are described in detail in Chapter 4 of the guidelines, together with background information, checklists and recommendations.

To minimize risks and establish an effective waste management process, Member States are also invited to consult the WHO document *Management of waste from injection activities at district level*.⁵ Lessons can also be learnt from previous vaccination campaigns and waste management “best practices”.

Human resources

In an influenza pandemic there will be a critical shortage of health staff, and contingency plans need to be drawn up to minimize the impact of this on deployment operations. Well planned and supported human resources means the effective management of the categories and numbers of individuals required, along with their roles and responsibilities.

Chapter 5 describes the range of personnel who may be involved in deployment operations, measures to assure their well-being, and procedures to ensure that they receive appropriate training.

Information and communications

An effective information system is a powerful ally of the Chief of Logistics, who needs to know, in real time, the exact location and condition of the pandemic influenza vaccine. Chapter 6 discusses the principal tasks to make sure that systems are functioning during a pandemic, namely: (i) stock inventory management; (ii) information on the movement of vaccine; (iii) maintenance tasks; and (iv) evaluation of the communications grid.

This chapter notes, for example, that national inventory and routine communications channels may not be able to cope with the breadth, speed and timeliness of information needed to support deployment activities. Current practices and software should therefore be rapidly assessed and simulation exercises crafted to test them. Another recommendation is to establish official communication focal points at central, provincial and district levels, and to create guidelines, messages and supportive media materials in advance of deployment operations.⁶

⁵ *Management of waste from injection activities at district level – Guidelines for district health managers*. Geneva, World Health Organization, 2006 (www.who.int/entity/water_sanitation_health/medicalwaste/phe_wsh_mwi_injections_report_en.pdf).

⁶ See also *Outbreak communications guidelines*. Geneva, World Health Organization, 2005 (WHO/CDS/2005.28, www.who.int/entity/csr/resources/publications/WHO_CDS_2005_28en.pdf).

Termination of deployment operations

Whether linked to a one- or two-dose campaign, termination must be planned and coordinated. This includes sending personnel back to their original duty stations, returning resources to the ministries or agencies that provided them, and documenting the overall experience.

The final chapter of the guidelines addresses how and when official notification of the end of the pandemic should be made. The final report should document all the resources used during the campaign and detail the breakdown of costs. To record the lessons learnt during the response to the crisis, deployment officers are encouraged to conduct surveys and interviews of those involved as well as, importantly, formally recognizing their dedicated service.

Next steps

It is planned to field-test the WHO guidelines for the deployment of a pandemic influenza vaccine in at least one country in 2009, before their finalization and wide dissemination. It was also noted that the guidelines should discuss the use of WHO H5N1 stockpiled vaccine.

1.4 Assessment of national delivery capacity in the WHO Western Pacific Region

To prepare for pandemic influenza vaccination, countries need to assess and possibly enhance their capacity to deploy pandemic vaccine, and develop a national policy on first access to the vaccine. WHO and UNICEF therefore elaborated a tool to evaluate national capacity to deliver pandemic vaccine within seven days. The tool sought to address chronic issues identified in pilot assessments, such as poor management and supervision.

Using the tool, the WHO Western Pacific Region undertook pilot assessments on vaccine deployment in five countries in 2006, the outcomes of which are summarized below.

Cambodia: the assessment showed the need to strengthen the cold chain at the health-centre level. Moreover, cold-room facilities at the central level would need to be renewed if new vaccines are introduced. Secondary infection control measures and refrigerated transport of large quantities of vaccine during a pandemic were also identified as priority needs.

Lao People's Democratic Republic: the top priority identified was to improve storage capacity for vaccines at provincial/district levels. Other priority needs were to reinforce the distribution system and the disposal of medical waste. Since the latter may not be assured in areas far from the Provincial Health Office, it was recommended that the number of incinerator sites should be increased to two per province.

Papua New Guinea: the storage capacity for routine immunization at provincial and district levels needs to be further reviewed to ensure that sufficient, functioning refrigerators exist for all vaccines. Since some health centres had no refrigeration capacity at all, this was considered essential, both for routine immunization as well as for a pandemic influenza outbreak response.

Philippines: the study showed that the cold-chain equipment at the provincial/city level – which stores vaccines before distribution to the rural health unit – should be improved to avoid the risk of vaccine deterioration and consequent massive losses.

Viet Nam: vaccine storage facilities are being strengthened with support from Luxembourg, although this may not cover the logistics and management of pandemic influenza vaccine distribution. The assessment noted vaccine carriers at the periphery to be the most needed equipment. It was also deemed necessary to install incinerators to implement proper waste disposal, and familiarize staff on their importance.

Provided that follow-up assistance is available to meet these priorities, the targeted countries will be much better prepared to respond to an influenza pandemic.

1.5 WHO H5N1 influenza vaccine stockpile under the auspices of the Strategic Advisory Group of Experts (SAGE)

A major GAP priority is to promote equitable, timely and sufficient access to influenza vaccines in the event of a pandemic, with a special focus on countries that have no influenza vaccine production capacity. A summary of WHO activities towards assuring this objective through the establishment of an H5N1 influenza stockpile is provided below.

In March 2007, WHO convened the High-Level Technical Meeting on Responsible Practices for Sharing Avian Influenza Viruses and Resulting Benefits in Jakarta, Indonesia, the recommendations of which were endorsed at the ensuing ministerial meeting. One of these recommendations called on WHO to seek international support for a stockpile of safe and effective H5N1 influenza vaccine that would benefit developing countries.

WHO therefore presented a background paper on considerations for the constitution of influenza vaccine stockpiles⁷ to SAGE in April 2007, requesting a recommendation in principle on the establishment of a WHO H5N1 influenza vaccine stockpile, based on avian H5N1 viruses currently circulating and causing sporadic human infections. The background paper focused on egg-based inactivated influenza vaccine (IIV), although noted that other types could be considered as technology developed. The vaccine could be used in combination with antiviral drugs to control and mitigate H5N1 virus outbreaks or to immunize pre-selected populations, if WHO confirmed that a pandemic was due to the H5N1 virus. It was agreed that wider availability of an H5N1 influenza vaccine would be critical to maintain social, economic and health security in countries without influenza vaccine production, should this virus prove to be transmitted efficiently from human to human.

⁷ Meeting of the immunization Strategic Advisory Group of Experts, April 2007 – conclusions and recommendations. *Weekly Epidemiological Record*. Geneva, World Health Organization, 2007, 82(21):181–196.

SAGE noted that many practical and operational details needed to be addressed, including the size and location of the stockpile (and ancillary supplies), criteria for the inclusion, shelf-life, rotation and release of vaccine, funding, and regulatory and liability issues. Members also considered potential risks linked to the use of stockpiled H5N1 vaccines, including adverse effects, and indicated the need to study the use of such vaccine in children. If stockpiled vaccine were used in the interpandemic period, extensive data on safety and immunogenicity would be needed.

WHO agreed to consult with countries to define the potential size of the stockpile, policy options on its use, and costs and funding options. WHO would also ensure that other essential studies, e.g. on regulatory considerations, were addressed.

SAGE concluded that, in combination with other measures, an H5N1 vaccine stockpile could mitigate the early stages of human-to-human transmission of the virus, and thus recommended to the Director-General of WHO that such a stockpile be created to benefit countries with no access to pandemic influenza vaccine.

At their meeting in November 2007,⁸ SAGE members recommended an initial stockpile size of 150 million doses, along with related ancillary equipment, enough to vaccinate 75 million people. Based on modelling, it was indicated that up to 50 million doses should be maintained for rapid containment of a potential influenza pandemic, the remaining 100 million doses to be equitably distributed among low- and middle-income countries for use in their self-defined essential populations. As at November 2008, 110 million doses had been pledged by industry for the WHO H5N1 stockpile.

1.5.1 Informal consultation on technical specifications for an H5N1 influenza vaccine stockpile

In response to the SAGE recommendation and resolution WHA60.28 in May 2007, WHO invited a wide range of experts to a consultation in October 2007 to develop consensus on the quality, safety, efficacy and logistic specifications of an H5N1 influenza vaccine stockpile.⁹ The perspectives of all stakeholders – industry, developing country recipients, regulatory agencies and donors – were discussed. The meeting generated detailed recommendations on the establishment, operation and sustainability of the stockpile, along with proposals for further studies and guiding principles on regulatory pathways, rules and procedures, prioritization, management, and oversight.

The meeting noted the outcome of a WHO consultation on the use of H5 vaccines held on 1–3 October 2007 that proposed two policy options for the use of the WHO H5N1 influenza vaccine stockpile: (i) rapid containment in response to a pandemic signal; and (ii) assistance to countries with no access to vaccine, to vaccinate essential groups. Scientific data had indicated no known safety concerns on the use of H5N1 vaccines aside from those associated with seasonal vaccines, although the number of recipients of the various H5N1 vaccines had been limited.

⁸ Meeting of the immunization Strategic Advisory Group of Experts, November 2007 – conclusions and recommendations. *Weekly Epidemiological Record*. Geneva, World Health Organization, 2008, 83(1):1–16.

⁹ *Informal consultation on technical specifications for a WHO international H5N1 vaccine stockpile, 17–18 October 2007*. Geneva, World Health Organization, 2007 (www.who.int/entity/vaccine_research/diseases/ari/Final_H5N1_Stockpile_Meeting.pdf).

Experience showed that the characteristics of a vaccine stockpile depended on the disease, the purpose of the vaccine, and principles such as equitable access. Details of the yellow fever and meningitis stockpiles were discussed, both of which are stored with the manufacturers; only WHO pre-qualified vaccines were accepted. UNICEF experience dictated three keys to successful management of international vaccine stockpiles: incentives to industry; well-defined roles for security, ownership, access and risk management; and clear account management.

Quality, safety, and efficacy considerations

Although the non-clinical and clinical data requirements for vaccines against novel human influenza viruses may differ from those for seasonal vaccines, the WHO guidelines on clinical and non-clinical evaluation of vaccines^{10,11} were considered applicable for an H5N1 vaccine stockpile. Specifically, data on the vaccine strain, biosafety level, adjuvants and potency testing are critical, although concern was noted that reagents for potency testing may not be readily available. The stability of bulk antigen is essential for storage in a stockpile, and real time and temperature stability data should be sought. To identify the lower threshold for acceptable potency, end of shelf-life studies should determine whether the same non-clinical and clinical performances are achieved with decreased antigen.

For H5N1 vaccines, data could be derived from studies of a vaccine prepared with a virus antigenically and genetically related to the virus against which protection is claimed. Immunogenicity and challenge data in animal models are required, as well as laboratory results showing cross-reactivity of antibodies with H5N1 strains in clades different from the one used for the preparation of the vaccine. Clinical indications should reflect the target population, and extrapolation should be conducted with extreme care. Immunogenicity in a naive population demonstrating robust antibody responses and a comprehensive characterization of immune responses, including cross variant reactivity and duration, are also desirable. Clinical paediatric data should be collected using a step-wise approach, from adults to children, taking into account data from the manufacturer's seasonal influenza vaccine.

It was suggested that a database could be established on already stockpiled H5N1 influenza vaccines, to which supplementary information on safety and effectiveness, shelf-life, and cross protection could be added. To this end, WHO has drafted detailed post-marketing surveillance requirements so that data can be collected in the event that stockpiled H5N1 vaccine is deployed, whether in the interpandemic period or during an influenza pandemic situation.¹²

¹⁰ *Guidelines on nonclinical evaluation of vaccines. Fiftieth report of the WHO Expert Committee on Biological Standardization.* Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 927, Annex 1).

¹¹ *Guidelines on the clinical evaluation of vaccines: regulatory expectations. Fifty-second report of the WHO Expert Committee on Biological Standardization.* Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 924, Annex 1).

¹² *Post-marketing surveillance requirements for influenza vaccines deployed from the WHO H5N1 vaccine stockpile* (to be published on www.who.int/immunization).

The WHO stockpile may emanate from multiple manufacturers, and thus contain different vaccine presentations. In this regard, concerns were raised on differing quality, immunogenicity and safety profiles, and the interchangeability of vaccine. Standardized regulatory issues, such as content and labelling information, should also be considered in advance. The stockpile should be maintained under good manufacturing practice (GMP) conditions, with storage warehouses protected with controlled access.

Regulatory pathways

The responsibilities for management and regulatory oversight of an H5N1 vaccine stockpile need to be well-defined in advance, and possible scenarios were reviewed. If the stockpile is located in the country of manufacture, the national regulatory authority (NRA) could license and assume regulatory responsibility. Otherwise, special arrangements may be needed; early discussion with NRAs of potential donor countries on prequalification criteria and licensing is thus critical.

The location and nature of the stockpile will impact who is responsible for managing it: bulk antigen or final formulated vaccine bulk needs to be stored with the manufacturer, whereas finished product could be stored anywhere. The nature of the stockpile will also determine timelines and capacity for delivery and use of vaccine. Finished product that is already released by an NRA would enable a short-term response, assuming that H5N1 vaccine can be stockpiled in its finished presentation. Stockpile of bulk antigen would need formulation, filling, labelling, quality control and lot release.

Global harmonization of regulatory pathways could accelerate registration of vaccines at national level. Collaboration between the National Institute for Biological Standards and Control (NIBSC) in the United Kingdom, and national control laboratories for fast-track antigen calibration procedures, for example, should be promoted.

Ethical and liability considerations

With regard to liability associated with a WHO H5N1 influenza vaccine stockpile, manufacturers and/or suppliers are responsible for developing vaccines in accordance with WHO standards. Countries requesting vaccine from the stockpile would assume responsibility for their use. It was recommended that the terms of a disclaimer to reflect responsibility for liability should be developed in advance to circumvent delays in a pandemic situation.

Participants were informed that, upon an influenza pandemic signal, the global threat would fall under the International Health Regulations (IHR). In these circumstances, an expert committee would advise the WHO Director-General on measures for rapid containment, including on the use of an influenza H5N1 vaccine stockpile. If the vaccine is to be used as part of a rapid containment strategy, the stockpile is likely to cover all persons in the containment zone. If stockpiled vaccine is used for protection at the start of a pandemic in countries with no other access to the vaccine, criteria for vaccination of priority groups will be needed. It was agreed that while norms and values differ, WHO guiding principles to assist national decision-making would be welcome.

Summary conclusions and recommendations

- In the event of human-to-human transmission of H5N1 virus, stockpiled vaccine would be used for rapid containment of a pandemic, and equitable distribution to low- and middle-income countries to immunize essential populations as defined by the Member State.
- Strain selection, and the continued appropriateness of the H5N1 strain to induce immunity against drift variants, should be based on WHO recommendations.
- Vaccines should be licensed by a functional NRA and submitted for WHO prequalification.
- Clear selection criteria for acceptance of vaccines should be developed. Based on current evidence, only IIV should be considered.
- Data requirements for regulatory approval of an H5N1 stockpile vaccine are additional to those for seasonal vaccines.
- Written criteria should define what needs to be done, by whom and when, e.g. when stockpiled vaccine should be removed from the stockpile and whether it can still be used.
- WHO should update the draft target specifications to assess continued potency of stockpiled vaccine.
- WHO should facilitate exchange of data among laboratories studying the stability of stockpiled vaccine.
- Country pandemic preparedness plans should include acceptance of vaccines from the stockpile.

1.5.2 Operationalization of the WHO H5N1 influenza vaccine stockpile

To collect the data and information needed, and in line with recommendations from SAGE, research was commissioned in 2008 from a consultancy firm, to design appropriate and sustainable options for the WHO H5N1 influenza vaccine stockpile. Operational elements for decision included the geographical location, size, rules and procedures for deployment, management, costs and financing mechanisms.

A survey being carried out within the auspices of this research is expected to elicit country views on the size of their essential populations in order to evaluate the optimal size of the stockpile, the results of which are due in mid-2009.

Criteria for acceptance of vaccines into the stockpile will be based on supplementary data expected in the first half of 2009 on safety, efficacy, and licensure of candidate vaccines. It is hoped, therefore, that eligible donations of vaccine could be included in the stockpile during the second half of 2009. To this end, WHO is working with manufacturers to accelerate regulatory pathways for their licensure and prequalification.

Governance of the stockpile would rest with WHO, and vaccine would be released for one of two purposes:

- 1) *Rapid containment*: decisions would be made jointly by affected countries and WHO. Doses used, if the equitable distribution component is not disbursed, would be replenished.
- 1) *Equitable distribution to low- and middle-income countries*: decisions would be based on recommendations to the WHO Director-General by the IHR Emergency Committee related to the determination of a public health emergency of international concern.

After careful evaluation of the considerations noted above, three basic models were identified:

- Option 1.* WHO holds a long-term (10 year) physical stockpile of filled and finished vaccine at two or three locations selected for optimal logistics and lowest risk profiles. Vaccine doses would be stored in filled form, with the option of storing adjuvant and antigen separately, and the stockpile would be replenished as vaccine reaches its expiration date.
- Option 2.* WHO holds a short-term (3 year+) physical stockpile, with no upfront provision for replenishment as vaccine reaches its expiration date.
- Option 3.* Manufacturers hold a stockpile of filled and finished vaccine. Industry would ensure that all products released from the stockpile have at least six months' remaining shelf-life.

A final decision on which of these three options will be used will be made through a consultation with Member States, most likely during the first half of 2009. Injection equipment would always be held with the vaccine. Other ancillary supplies could either be held with the vaccine for containment operations, or with the Member State.

1.5.3 SAGE Working Group on H5N1 influenza vaccine

In order to determine whether evidence-based policy recommendations could be made on the use of H5N1 influenza vaccines in high-risk groups in the interpandemic period, and on the use of stockpiled vaccine reaching the end of its shelf-life, a SAGE Working Group was established with the following terms of reference:

- to review the safety and immunogenicity of currently licensed and late development H5N1 vaccines and their appropriateness for use;
- to analyse risk- and cost-benefit ratios and ethical issues associated with the use of these products in the interpandemic period;
- to review and assess potential H5N1 vaccine policies and their implications: propose indications for use of H5N1 vaccine in the interpandemic period (a) in populations with different risks of exposure to avian H5N1 virus, and (b) for priming or immunization against future human H5N1 virus;

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- to review new evidence that could influence the proposed size of the WHO H5N1 influenza vaccine stockpile and consider potential uses of vaccine approaching expiry date; and
 - to identify and prioritize knowledge gaps to facilitate SAGE decision-making on the roles/options for H5N1 vaccine use in the interpandemic period.

The SAGE H5N1 Vaccine Working Group comprises two members of SAGE plus seven experts from a wide range of disciplines.

At its first meeting in November 2008, the Working Group outlined a work programme and methodology to achieve its objectives in the most timely manner. Members examined the current state of development of H5N1 vaccines, discussed ongoing research studies in three countries, and agreed to plan country consultations to discuss H5N1 vaccination policy issues before the next meeting of SAGE in April 2009.

A set of questions was drawn up to identify current gaps in knowledge that need to be addressed before SAGE could formulate evidence-based recommendations on the use of the H5N1 vaccine stockpile in the interpandemic period, and on vaccine approaching the end of its shelf-life. These questions, along with a plan of action, were presented to SAGE at its meeting in November 2008.

SAGE welcomed the formation of the Working Group, and acknowledged the scope of work and tight deadlines to enable a recommendation to be made to the WHO Director-General. Population groups that might be considered “essential” in the event of a pandemic – laboratory staff, field and surveillance workers, staff needed to maintain national infrastructure, health workers and pandemic influenza deployment staff – were discussed. Information was also offered on the size and rationale of several national influenza vaccine stockpiles. It was agreed that, while SAGE would recommend the size of the WHO stockpile, it was the prerogative and responsibility of each Member State to allocate H5N1 vaccines according to its own priorities in the interpandemic period.

1.6 Mathematical modelling for national policy on influenza vaccine use

It is likely that the amount of vaccine available for use in developing countries in the event of an influenza pandemic will be insufficient to vaccinate all populations at risk. In this situation, countries need an evidence-based framework within which to structure decisions on the use of the vaccine, i.e. which groups, in which order, for which purpose. Decisions on the use of vaccine in a pandemic will depend not only on the quantity of vaccine available, but also its protective characteristics, national population dynamics, and the severity and transmission dynamics of the pandemic strain.

Mathematical models provide an alternative method, in the absence of valid evidence, to evaluate the potential impact of various immunization strategies. In August 2007, with a view to synthesizing the assumptions and results of potential models, WHO issued an open request for research proposals that could provide country-specific evaluations of immunization options against a set of specific parameters, in the event of a pandemic. The following five proposals were selected for support. The rationale was to focus on scenarios where a limited supply of pandemic influenza vaccine would be available, and where modelling might identify gaps in data, point to priority research for data collection in this inter-pandemic climate, and promote dialogue among scientists, policy-makers and other stakeholders to inform the decision-making process.

Quantifying the effect of vaccination and non-pharmaceutical interventions during an influenza pandemic using a simulation model. This project expanded its existing census-based model to produce a generic tool with a user-friendly interface into which vaccine, virus and demographic parameters can be entered. The model enables the user to determine optimal use of a limited supply of vaccine to decrease overall and daily attack rates. A series of simulations with vaccine and non-pharmaceutical interventions alone and in combination can be generated. The researchers concluded that pre-emptive vaccination was effective to prevent high mortality, although a combination of reactive vaccination and aggressive social distancing would be equally effective. Outstanding issues concerned the effect of scaling, different demographic and contact patterns, and costing data.

Simulator of pandemic influenza intervention strategies. This project modified a large-scale simulator model to run on a desktop computer with a graphical interface that contains age-specific contact probabilities and allows examination of a range of pharmaceutical and non-pharmaceutical interventions. The model chosen tracks the number of individuals in a given place at a given point in time, provides best- and worst-case outcomes for a variety of scenarios, and can be adapted to different intervention strategies. The researchers noted that the model served as a planning simulator rather than an end-user tool, although it could be refined for this purpose.

Evaluating optimal vaccination strategies against pandemic influenza in Mexico. This project adapted an existing model to evaluate vaccination strategies for pandemic influenza based on the Mexican demographic and epidemiological situation. This was a dynamic, compartmental, age-structured model based on census data for Mexico, but with contact patterns from the Netherlands. Two epidemic scenarios and three vaccination scenarios were compared. The researchers noted that, based on historical data, the ideal vaccination strategy in Mexico depended on the age structure (one strategy vaccinated proportional to age-specific cumulative hospitalization at the start of the pandemic, and the other proportional to the size of the age group). It was noted that this would be a good model to inform policy, provided that it could rely on good data collection in the early phases of an outbreak.

Modelling cost-effectiveness of pandemic influenza vaccination: an international model piloted in three countries. Two collaborating institutes updated and piloted an existing cost-effectiveness model in Germany, the Netherlands and the United Kingdom (UK). The antiviral dynamic model was adapted to Germany and the UK, and then tailored to pandemic influenza vaccine use. Epidemiological adaptations included vaccine availability and efficacy. A susceptible → exposed → infectious → recovered (SEIR) model was used for transmission data. Based on state-of-the-art cost-effectiveness methods, its user-friendly interface allows scenarios to be altered based on country, target group, and treatment and opportunity costs. Sensitivity analyses include increases in fatality rates and changes in vaccine price. Researchers concluded that interpandemic vaccination is effective to minimize influenza-type illness and that early vaccination of the elderly population is the most effective to reduce hospitalization. The highest costs were the indirect costs of production losses, and interpandemic vaccination due to its relatively high price.

Modelling to determine the optimal use of limited quantities of pandemic influenza vaccine: global and Russia-specific model. This project determined how vaccination and intervention policies to contain a human influenza pandemic vary in their benefits and costs, both globally and within a single country. The researchers modified an existing global epidemic simulation model to study different vaccination and other containment scenarios within the Russian Federation in the context of global disease dynamics. The analysis examined the importance of vaccine stockpiling (and the sharing thereof) and interpandemic priming. It was concluded that the sharing of stockpiles with countries already infected by pandemic influenza would be counterproductive, and that interpandemic vaccination can play a role in disease mitigation. It was also noted that improved age structure and contact matrices would be useful to scale transmission with population density.

Review by the WHO Advisory Committee on Quantitative Immunization and Vaccine Research (QUIVER)

The results of the above research were reviewed by QUIVER in October 2008. While reiterating the value of the mathematical modelling as a tool to enhance developing country decision-making on the optimal use of pandemic vaccine, they considered that two elements needed further attention so that the results of different influenza models are meaningful:

- 1) define the appropriate public health questions to be effectively addressed and, based on this definition;
- 2) define the most important parameters to be adopted/standardized by different groups.

A joint WHO meeting with the US National Institutes of Health to address these issues has therefore been scheduled for June 2009. The meeting will bring together public health influenza experts and modellers to clarify the public health questions that mathematical modelling may help to answer, supported by previous case-studies. The outcome of the meeting will be integrated into the global research agenda on influenza and shared with the various researchers working on models for pandemic influenza vaccine use.

More specific comments were made by QUIVER members, such as the need to standardize input values and output measures, to determine contact matrices, and to describe in more detail other costs, such as those for stockpiles and indirect costs of school closures. In addition, the issue of social distancing, albeit difficult to quantify, could receive more attention in compartmental models, along with behaviours that may change according to the rate of mortality, thus affecting contact patterns.¹³

1.7 Influenza vaccine procurement through WHO prequalification procedures

United Nations vaccine procurement agencies concur that seasonal influenza vaccines should be prequalified. In addition, in view of the risk of an influenza pandemic, WHO considers that such prequalification will assist countries given that pandemic influenza vaccine needs to be made available within a short time frame. In view of the particular challenges for regulatory oversight of influenza vaccines, an ad hoc expedited procedure to assess the quality of influenza vaccines was developed.¹⁴ The procedure is applicable to vaccines routinely used for immunization against seasonal influenza. Only vaccines licensed by a functional regulatory authority are considered. The product summary files of two major manufacturers of seasonal influenza vaccine were evaluated in February 2008.

In addition, it is agreed that vaccines in the WHO H5N1 influenza vaccine stockpile should also be prequalified, and WHO is therefore adapting the above prequalification procedures for vaccines against novel human influenza viruses.

To enhance the interpandemic procurement experience of the UNICEF Supply Division with seasonal vaccine, WHO plans to carry out site visits to countries where WHO and UNICEF country officers can explore the value of UNICEF procurement to increase national uptake of seasonal influenza vaccine.

1.8 Innovative financing mechanisms

One mechanism being explored by WHO to facilitate access by developing countries to pandemic influenza vaccine consists of vaccine-producing countries pledging to release manufacturers from supply contracts up to a pre-defined quantity for the WHO stockpile when they produce the actual pandemic vaccine. The vaccine, which would be purchased for or donated to developing countries with no influenza vaccine manufacturing capacity, could be funded through arrangements such as advance purchase or donation commitments by GAVI or donors. The mechanism, called the Guaranteed Advance Commitment, was discussed by SAGE members at their meeting in April 2007.

¹³ The report of the meeting is available on request from the QUIVER Secretariat, IVR, WHO.

¹⁴ *Special considerations for the expedited procedure for evaluating seasonal influenza vaccines.* Geneva, World Health Organization, undated (www.who.int/immunization_standards/vaccine_quality/final_expedited_procedure_flu_240207.pdf).

Under the auspices of external consultants, discussions have also been held with finance experts from the public and private sectors, potential partners (manufacturers, insurance providers, capital-markets experts), donors and recipient countries. Various financing options, including cost modelling and trade-off analysis, have been tested with stakeholders for feasibility and desirability. Casualty insurance, product warranty and an annuity mechanism were reviewed as options to match the risks inherent in a given type of financing need, with solutions that place the risk with parties who are best positioned to handle them. These options can be used to finance the WHO H5N1 influenza vaccine stockpile, pandemic vaccine purchase, and other GAP activities.

Additional interactions with potential partners will be carried out to understand the exact role that they can play in the various financing options, and to obtain wider feedback. More work is needed in the coming months to ensure that this mechanism becomes a reality for the protection of developing country populations.

2. Increasing vaccine production capacity and supply

An influenza pandemic that causes high mortality will no doubt call for vaccination of the entire global population in the shortest possible time. Today, if two immunizations were required to assure immunity in a naive population, this would mean the need for up to 13.4 billion doses of pandemic vaccine.

The vintage hen egg-derived vaccine production technology has been widely used in the industrialized world since the 1940s for seasonal influenza vaccination. However, in the face of a pandemic, the overall global production capacity and timely scale-up potential would be acutely inadequate. Moreover, most developing countries do not have domestic production of influenza vaccine and are totally dependent on the availability and accessibility of vaccine produced by multinational manufacturers.

Fortunately, with political commitment and advances in technologies, prospects are improving. Significantly more seasonal, H5N1 and potential pandemic vaccine doses are expected to be available over the next five years, either from expansion of existing facilities or from the creation of new ones. Antigen per dose requirements are now lower due to the development of new adjuvants, and production yields have improved. Most multinational manufacturers have already expanded their production of seasonal influenza doses and, with new cell-based facilities due to become operational in 2012, this capacity should increase even further.

Despite this progress, the number of doses available in the event of a pandemic to immunize the world within six to nine months will still fall short of need by several billion doses, with the need no doubt occurring first in countries with little or no access to influenza vaccine. Modelling of increases in production capacity¹⁵ until 2015 indicates that the situation is unlikely to change for at least the next 10 years.

This chapter describes the activities carried out by WHO to date to close that gap.

An Advisory Group was convened by the WHO Director-General to oversee implementation of the GAP activities and to update the scope and priorities of the Plan as necessary. The Group comprises ten independent representatives from developing and industrialized countries, with and without influenza vaccine manufacturing capacity. The Advisory Group met in Geneva, Switzerland in October 2007 and in Pune, India in November 2008. A summary of their deliberations and recommendations can be found in Section 2.10.

¹⁵ IFPMA data to be released in March 2009.

2.1 Assessment of production capacity for influenza vaccine in Asia

With the aim of increasing and diversifying influenza vaccine production in Asian developing and middle-income countries, WHO carried out in 2006 an assessment of current and potential medium-term production capacity in this region. Data were gathered from Australia, the People's Republic of China, India, Indonesia, Japan, the Republic of Korea, Thailand and Viet Nam, using mission assessments, manufacturer data and published information.

Overall, it was noted that Asian countries had huge vaccine manufacturing capacity but little experience with influenza vaccine. Seasonal influenza vaccine production in 2006 was estimated at 60 million doses, up to half of which was produced in Australia and China. Australia planned to expand its production capacity, which should facilitate export beyond the national market. It was also understood that some Japanese producers exported or planned to export bulk vaccine. With some technical input, production capacity may also be exported from the Republic of Korea. The current production capacity in China for seasonal vaccine matched demand; however, for the manufacturers visited, capacity was far less than the projected national need would be if there were a seasonal influenza vaccination policy in place. A switch to live attenuated influenza vaccine (LAIV) could theoretically much enhance capacity. Encouraging results obtained by Microgen (the Russian Federation), presented at the 5th WHO meeting on evaluation of pandemic influenza vaccines in clinical trials (Geneva, February 2009), suggest that this option is realistic and worth pursuing.

Of facilities not yet producing influenza vaccines, the Republic of Korea, with a strong vaccine production history and NRA, planned to construct its own influenza manufacturing facility to produce up to 20 million doses annually by 2014.

The WHO assessment recommended that the following avenues be considered to expand production capacity in Asia:

- process improvements for a 300% increase in capacity in the six facilities visited in China;
- improved egg supply in all influenza vaccine producing countries;
- acceptability and feasibility of LAIV production on a large scale for pandemic response;
- technical assistance to ensure optimal yields.

2.2 Review of production technologies for influenza virus vaccines

Building in-country capacity for influenza vaccine production is a central element of the GAP. Several methods of production and types of influenza vaccine exist, each with advantages and disadvantages, and vastly different requirements in terms of capital investment, technology transfer and production time. In order to assist manufacturers in developing countries interested in establishing influenza vaccine production capacity, and to enable a sound allocation of grants for this purpose, WHO commissioned in 2006 a full review of considerations on the sustainable production technology appropriate in developing countries.¹⁶

A manufacturer's pandemic influenza vaccine production will depend to a large extent on its seasonal influenza vaccine production capacity. The pandemic strain will be a new strain for which there is little or no immunological memory in the population, and two doses of IIV will probably be required to induce protective immunity. When establishing pandemic vaccine production capacity, a significant reduction in functional yield compared to seasonal influenza may need to be taken into account. Other factors considered were the regulatory pathway to licensure; the use of adjuvants; alternative delivery mechanisms; whether the facilities could produce other vaccines; and the supply of critical components such as fertilized eggs, which may be jeopardized in emergency situations.

Several assumptions were made, notably that the process and facility would be established by an existing developing country manufacturer of human vaccine with access to trained staff familiar with GMP requirements and the necessary quality control (QC), quality assurance (QA) and other supporting functions.

The technologies reviewed relied on egg- and cell culture-based propagation of influenza virus for the preparation of either inactivated or live attenuated vaccines. New recombinant technologies may have significant potential for vaccine production in the future, but were outside the remit of the review.

The requirements of each technology were detailed for laboratory- and for industrial-scale manufacture, along with the cost and time it would take to be fully operational. Industrial- scale production should be sufficient to meet local demand for seasonal influenza vaccine, and readily scalable to meet at least domestic need for a pandemic vaccine. Advantages as well as pitfalls were tabled to guide developing countries seeking to invest in influenza vaccine production.

¹⁶ *A review of production technologies for influenza virus vaccines, and their suitability for deployment in developing countries for influenza pandemic preparedness.* Geneva, World Health Organization, 2006 (www.who.int/entity/vaccine_research/diseases/influenza/Flu_vacc_manuf_tech_report.pdf).

A. *Inactivated influenza vaccine in eggs*

Egg-based production of inactivated virus is long-established and still the most widely used technology. Laboratory-scale production of IIV in eggs should be readily achievable. The equipment needed is minimum, standard and inexpensive, and the skills required for the process straightforward. A plant and process could produce a clinical lot in less than 18 months for an investment in the order of US\$ 100 000.

Scaling up to industrial level requires significant investment, since the automated procedures are not used in the manufacture of other vaccines and will therefore require training of personnel in facilities already equipped and performing automated inoculation and harvesting. In addition, the expertise is not readily transferable, and is costly.

The capital investment to establish a plant for large-scale production of influenza vaccine in eggs on an existing vaccine manufacturing campus is around US\$1 per dose, i.e. US\$ 20 million for a plant capable of producing 20 million doses of trivalent vaccine per year, and requires at least three years to become operational. The cycle of seasonal influenza vaccine manufacture for a single market is four to five months, and therefore additional markets may need to be identified in a different hemisphere.

Advantages: the standard method for influenza vaccine production; reassortant virus vaccine strains optimized for growth in eggs; regulatory pathway to licensure and analytical assays well established.

Disadvantages: cost; specific expertise resides with multinational manufacturers; time to establish a large-scale plant; egg supply (IIV requires 20-fold more eggs than LAIV) may not be easily and rapidly accessible during a pandemic; potential allergic reaction to eggs; waste disposal (potentially 4000 kg/day); selection of antigenic variants during passages in eggs; difficulties in obtaining high-growth reassortants; and yield.

B. *Inactivated influenza vaccine: cell-culture*

The three cell lines currently in late-stage development as substrates for the growth of influenza virus – Vero cells, MDCK and PER.C6 – were described (see also 2.3 below). Of note is the fact that one vaccine produced on Madin-Darby canine kidney (MDCK) cells is already approved in the Netherlands, with European Medicines Agency (EMA) approval of at least two additional cell-derived products pending.

At the laboratory scale, the cell-culture process is as manageable as for eggs, although the first clinical lot may take slightly longer. More complex QC assays are required, although they are standard. The investment will be similar to egg-based technology, i.e. around US\$ 100 000. The costs associated with scale-up to industrial size are 10-fold higher than that for egg-based production, i.e. US\$ 100 million. Interested manufacturers might wish to investigate whether the technology could be used to produce other vaccines to mitigate their investment.

Advantages: a more rapidly-scalable process; long lead time for egg supply and related issues such as avian retroviruses and eliminating allergic reactions; reagents and cells can be stockpiled and expanded when needed; cleaner, better characterized vaccine; and reduced theoretical risk of selection of variants during the growth of vaccine strain.

Disadvantages: more expensive if less than 25 million doses/year, and 2–3 years longer to become operational; specific expertise resides with multinational manufacturers; proprietary cells would have to be licensed; selection of antigenic variants during passages in cell culture.

C. Live attenuated influenza vaccine: egg-based manufacture

All LAIV are delivered intranasally and thus expected to elicit a similar immune response to natural infection. Currently, only LAIV produced in embryonated eggs have been licensed. The vaccines use temperature-sensitive (with limited growth at 37–39° C), attenuated and cold-adapted donor strains that grow at reduced temperatures, such as those in the human upper respiratory tract.

Laboratory-scale production of LAIV should be as readily achievable as that for IIV and produce at least one order of magnitude more vaccine. Expanding to large-scale LAIV production does not involve automation or large-scale equipment. The manual process involves more monitoring but less risk of losing a large harvest to contamination. At full capacity, a non- or semi-automated plant could produce more than 10 million doses of monovalent vaccine per week and be established at a cost of US\$ 1–2 million.

Advantages: speed to establish and validate a plant and shorter vaccine production cycle; 30–50 times more doses per egg than IIV and thus a fraction of the capital investment of IIV; straightforward technology; single dose may be possible; a live replicating vaccine might induce a broader immune response; no need to quantify HA in a vaccine lot, thus initial batches of pandemic vaccine could be several weeks ahead of IIV; mucosal delivery may induce more relevant immune responses and better protection; and needle-free delivery may facilitate mass immunization and be safer.

Disadvantages: not envisaged currently for interpandemic priming because of theoretical risk of reassortment with wild-type H5N1 virus; containment facilities; and potential contraindications. Other unresolved considerations are to ascertain: its stability at 2–8° C; the delivery method; the filling lines that need to be adapted for the final container; intellectual property on LAIV strains; use of reverse genetics to construct the vaccine strain from the master donor; and the potential need for new correlates of protection in addition to the standard Committee for Medicinal Products for Human Use (CHMP) immunological criteria for licensure.

D. Live attenuated influenza vaccines: cell-culture

Since no manufacturers were in late-stage development with tissue culture-based LAIV at the time of writing this report, it is not possible to be categorical about the advantages and disadvantages of this technology. Producing LAIV using cell culture-based methods could potentially combine the advantages of LAIV in terms of immunogenicity, ease of administration and simplicity of the purification process, with some of the advantages of cell-culture production. Production of LAIV in fermenters should not require the complex purification or concentration steps involved in IIV production. However, some of the advantages of using LAIV in eggs (high yield, ease of scale-up, simplicity and speed of the process) are lost when LAIV are produced in cell culture. Other drawbacks include the high capital investment, uncertainties on which cell lines will be approved for influenza vaccine manufacture, and intellectual property.

However, as for IIV, some advantages may make this route attractive for manufacturers entering the field, for instance if the facilities could also be used to manufacture other tissue or cell culture-derived vaccines, and if the same cell line was used. The yields of LAIV are likely to be far greater than for IIV produced from cell culture; extrapolating from egg-based production, this could be 15–30 fold greater. A smaller facility would therefore produce vaccine for a larger population, and be cheaper to establish.

Conclusions

The analysis showed that egg-based production of LAIV required the least capital investment to establish and maintain, and therefore appears attractive to manufacturers in resource-poor settings. The time required to establish seasonal vaccine production also put LAIV egg-based production at the forefront (within one year), followed by IIV (1–2 years). In addition, the cost per dose is lower due to the very high production yield, fewer hen flocks are needed, QC release is faster, and delivery is needle-free.

Although egg-based production of inactivated virus remains the most widely used technology, the significant capital investment required may be difficult to justify in areas with a limited market for seasonal vaccine. Cell culture-based production of live attenuated or inactivated vaccine requires greater financial investment and access to proprietary technologies, but may have advantages in terms of logistics of vaccine production in the event of a pandemic, and long-term advantages for the manufacturer.

2.3 An appraisal of cell lines for the production of influenza virus vaccines

As mentioned in 2.2 above, growing influenza virus in cell culture has several advantages over egg-based production, particularly by avoiding the need for large quantities of eggs. Other advantages are:

- a more highly purified influenza virus antigen using the same production process for whole viruses, multiple disrupted (split), plus a shorter lead time using LAIV;
- a modern and controlled seed lot system, uniform characterization of cells and reduced risk of unwanted agents;
- robust, consistent and reproducible vaccine production that can be initiated any time and prolonged;
- possible use of avian strains which otherwise would need genetic modification in eggs.

Given such potential for influenza pandemic preparedness, WHO commissioned the establishment of an inventory to enable a clearer understanding of the range of cell lines and vaccine strains available. The focus to date has been on mammalian cell culture-derived vaccine, although avian cell lines are potential sources if further research is conducted on their applicability to influenza and more stable yields can be proven before commercial production.

The report summarized that, to meet the need for robust and commercially viable manufacturing processes and large-scale production requirements unique to influenza, cell lines will ideally:

- 1) allow replication of influenza strains to sufficient titre (only three mammalian cell lines meet this criterion);
- 2) have a precedent in a widely used commercially available vaccine (only one cell line, as the others have been documented as tumorigenic in animal models);
- 3) be able to propagate in a chemically defined medium under serum-free conditions, to avoid labour-intensive process and contamination risks.

The three cell lines in the most advanced stage of development were described.¹⁷

MDCK is the most advanced mammalian cell line. Several companies have adapted these cells to grow under serum-free conditions with at least one in suspension. Cell banks have been tested and characterized to international requirements. Some candidate vaccines have been shown to be clinically non-inferior to egg-derived comparator vaccines. One candidate is currently being considered for marketing in Europe, and the use of MDCK for seasonal and pandemic influenza vaccine is also being pursued in the USA.

Vero cells are already approved for the production of other vaccines (e.g. rabies) for human use. One company has developed a whole-virus IIV using Vero cells that have been further adapted to grow under serum-free conditions, unusually using wild-type influenza viruses as seeds. The company's Vero cell-derived candidate H5N1 vaccine was submitted for licensure with EMEA in 2008.

PER.C6 cells, originally from embryonic human retinal cells, have been extensively characterized and used to produce investigational vaccines, including for influenza. Little public information is available, but PER.C6 cells seem broadly permissive to a wide variety of influenza strains, and are propagated in suspension using animal protein-free and serum-free media.

Intellectual property, regulatory and other considerations

The above cells and corresponding processes are proprietary and unlikely to be shared by the companies involved. This is a serious impediment for any manufacturer interested in establishing a cell-culture process, as it is lengthy and expensive¹⁸ (see also Section 2.5). Another major drawback is the stringent quality controls required by regulatory authorities to assure that the final product is free of adventitious agents.

¹⁷ See the US Food and Drug Administration Internet site for developments on cell lines for influenza vaccines (www.fda.gov/cber/summaries/wilbio120507ak.pdf).

¹⁸ Guidance on the primary regulatory and other requirements to establish and characterize cell lines for producing influenza vaccines can be found on the European Medicines Agency Internet site (www.emea.europa.eu/pdfs/human/bwp/249000en.pdf).

Conclusion

Despite considerable technical, financial and regulatory challenges, several cell-derived products are expected to be commercially available by 2013. This should stimulate cooperation between public and private sectors to facilitate acquisition of this technology by new manufacturers of influenza vaccines.

2.4 Options for live attenuated influenza vaccines

One of the most promising strategies identified in the GAP to increase influenza vaccine production capacity was the expansion of live attenuated influenza vaccine (LAIV) production. In the wake of this consensus, WHO convened representatives from national immunization programmes, regulatory authorities, vaccine manufacturers and public-health scientists in June 2007 to analyse the untapped potential of LAIV¹⁹ (see also Section 3.2 for a comparative analysis of LAIV).

The meeting reviewed the state-of-the-art for established seasonal and candidate pandemic LAIV, and the WHO guidelines on LAIV. Despite extensive positive experience in the Russian Federation and, more recently, in the USA, LAIV represent only a fraction (less than 1%) of global influenza vaccine production, yet their potential advantages are considerable. While the upstream process for LAIV during manufacture is the same as for IIV, they require less complex downstream processing, making them more appropriate for technology transfer to developing countries.

A review of the historical, recent and comparative clinical data indicated that LAIV are safe and effective in the prevention of seasonal influenza. Experience with the Russian LAIV demonstrated excellent safety, although more research is required on immunization in persons with asthma and the immunologically compromised. Certain discrepancies regarding immune response and protection against influenza B illness compared to trivalent IIV required further elucidation, as do the increased risks of hospitalization and wheezing exacerbations in very young children observed in one trial in the USA. Various data presented on LAIV transmission showed that the levels of virus shedding were unlikely to cause either secondary infection or reassortment with wild-type virus, even in trials with children under five years of age in settings where ample opportunity exists for transmission.

LAIV also appear to offer significant promise for indirect protection, potentially resulting in wider community protection through vaccination of schoolchildren. Several studies across the Russian Federation and the USA showed reductions in seasonal influenza-related disease and absenteeism among families and teachers of LAIV-vaccinated children, as well as in the adult population in general. This approach could also serve as a model for pandemic influenza responsiveness.

¹⁹ *Options for live attenuated influenza vaccines (LAIV) in the control of epidemic and pandemic influenza, 12-13 June 2007*. Geneva, World Health Organization, 2007 (www.who.int/vaccine_research/diseases/influenza/meeting_120707/en/index.html).

There is increasing evidence that LAIV is able to protect in the face of antigenic drift. Immediate, pre-antibody development protection has also been observed. The mechanism of possible early protection is not fully explained and remains the focus of research. Contrary to IIV, anti-haemagglutinin antibody response after LAIV administration is not considered a marker of vaccine effectiveness in adults, and correlates of protection for LAIV should therefore be established as a priority for both seasonal and pandemic use.

Implementation aspects

The nasal delivery of LAIV clearly reduces the administration burden on health-care workers and eliminates the need for syringe and needles. However, other implementation issues, e.g. the cold chain, stability and possible multi-dose delivery, need to be optimized for pandemic use.

Production issues include working seed establishment from master strains through reassortment and/or reverse genetics. Specific pathogen free (SPF) eggs are used by one manufacturer to produce LAIV, although this is not a regulatory requirement. Promising results were presented from pilot scale cell-culture production, providing potentially excellent yields and independence from external egg supplies.

Pandemic considerations

Partly due to the containment requirements for live H5N1 viruses, only limited clinical studies with H5 pandemic prototype vaccines exist. These have indicated highly variable infectivity and associated immunogenicity, although recent results obtained with a Russian H5N2 reassortant²⁰ suggest that LAIV is likely to induce an appropriate immune response and protection against H5N1 viruses. Present considerations, due to the low but theoretically possible reassortment with a seasonal virus, argue against mass vaccination with a live rH5N1 vaccine under interpandemic conditions. The potential advantages of a LAIV strategy could come into effect after a pandemic begins.

A few of the recipients of WHO technology transfer grants have indicated their interest to convert seasonal IIV to LAIV production during a pandemic. This conversion could, by 2010, contribute to reaching the overarching goal of the GAP to immunize the world's population within six to nine months. Thus, WHO has been negotiating with the owners of the technology for its transfer to the project.

²⁰ 5th WHO meeting on evaluation of H5N1 influenza prototype vaccines in clinical trials, February 2009 (a detailed summary will be reported in the journal *Vaccine*).

Recommendations

In summary, participants at the meeting recommended that more data be collected in the following areas:

Clinical evaluation

- Special populations, including immunosuppressed and asthmatic individuals.
- Influenza B responses between LAIV and trivalent IIV.
- LAIV trials with H5N1 and other pandemic prototype vaccines.
- Correlates of protection.

Development

- Cell-culture production.
- Regulatory approval for prototype pandemic LAIV vaccines as part of industrial pandemic preparedness plans.

Implementation research

- Potential indirect protection through vaccination of schoolchildren.
- Cold-chain stability and multi-dose formulations.
- Feasibility of seasonal LAIV influenza vaccination programmes in developing countries.
- Scaling up LAIV production and stockpiling.

The feasibility of a WHO collaborating centre for reference seed virus preparation and supply to manufacturers should also be reviewed. Finally, it was recommended that WHO support the ongoing six-year programme of preparation of prototype pandemic LAIV strains for all 16 HA types through reverse genetics technology, since this may pave the way for a stockpile of LAIV vaccine during the interpandemic period.

2.5 Intellectual property related to the production of influenza vaccine

Influenza vaccine production capacity in developing countries will ideally use processes that render high yields, produce vaccine rapidly, avoid supply constraints and use adjuvants for IIV to reduce the level of antigen required. LAIV and the use of conserved antigens to enhance the breadth of immune protection are promising avenues to enhance influenza vaccine supply in developing countries. However, all these approaches are subject to some degree of intellectual property (IP) or know-how protection.

WHO was therefore mandated to review IP as it relates to the manufacture and use of pandemic influenza vaccines. To be of optimal benefit to new manufacturers, WHO evaluated the IP associated with approaches most likely to yield increased global capacity within the next 10 years.

The resulting report²¹ identified patents that should be considered, while highlighting that these are only one aspect of IP that affects the feasibility of local production and regulatory approval of the vaccine. Indeed, technical know-how and access to regulatory dossiers are more significant barriers than patents. The technical know-how – even of conventional egg-derived influenza vaccines – is not readily found outside existing influenza vaccine production plants. Thus, even for procedures for which there are no patents, partnerships with technology holders may be necessary. Similarly, although there is no IP coverage in developing countries on several strains of LAIV, the generation of a regulatory dossier necessitating extensive preclinical and clinical safety data can take years. Finally, the report notes that without a market for seasonal influenza vaccine, the maintenance of a production plant and skilled manpower ready to produce vaccines in the event of a pandemic may represent a potentially significant capital loss.

A brief explanation of the relevance and pitfalls of Patent Cooperation Treaty (PCT) applications is provided along with useful sources of further information. Whether an actual patent should be granted is decided under the jurisdiction of national law, and attention is drawn to the steps and requirements for applying for patents according to the PCT contracting state.

Egg-derived inactivated vaccines

This process is well described in expired patents and thus no patent prevents the production of vaccines in this way. Several improvements to the process have been patented, particularly to improve yields, and these need to be considered.

Whole virus: IP is primarily aimed at the inactivation procedure.

Split virus: a few improvements have been patented.

Subunit vaccines: no recent patents.

Cell-culture derived inactivated vaccines

Three cell lines are currently in late-stage development as substrates for the growth of influenza virus, and several manufacturers have filed for the approval of their vaccines. Several cell lines have been used for many years and can be obtained from public sources. However, regulatory approval requires that master and working cell banks are established and characterized – a very lengthy and costly process – and manufacturers that have undertaken such processes are unlikely to share their characterized cell line. A possible exception is the Vero cell line which can be purchased with full characterization, although IP exists on specific variants of the line.

In addition, there is IP on using cell lines to produce influenza vaccines and on processes involving the cell lines, including the Vero strains, e.g. adaptation to serum-free medium. One manufacturer describes and claims the use of continuous monkey kidney cell line, particularly Vero cells, growing in protein-free medium for propagation of influenza virus. Since Vero cells are the most readily available to new manufacturers, the claims in this patent family need to be considered in detail.

²¹ *Mapping of intellectual property related to the production of pandemic influenza vaccines, 23 October 2007.* Geneva, World Health Organization, 2007 (www.who.int/entity/vaccine_research/diseases/influenza/Mapping_Intellectual_Property_Pandemic_Influenza_Vaccines.pdf).

Primary chicken embryo cell lines, such as chicken embryo fibroblasts (CEF) have also been considered for influenza virus propagation and vaccine production. Since they are used for other vaccines (measles, mumps), their application to influenza could be worth pursuing. One claim related to CEF is flagged so that new manufacturers can investigate whether any equivalent has been filed and granted in their country.

Several patents claim cell-culture derived influenza vaccines with methods to reduce the DNA content of the final vaccine. The yield of influenza virus and viral growth in cell culture can also be enhanced by several methods subject to IP, which are listed in the review.

Live attenuated influenza vaccines

There is no IP on the basic concept of making and using an attenuated influenza virus, and many attenuated strains are available from sources such as American Type Culture Collection of LGC (Laboratory of the Government Chemist) Standards (ATCC). LAIV have been licensed in the Russian Federation and in the USA. Here again, without the original development and regulatory dossier, vaccine development would be lengthy and costly. Several other groups have IP on specific attenuated strains and the means of attenuating influenza vaccines by introducing mutations or insertions in the NS1 gene.

In order to facilitate acquisition of this very promising technology by developing country vaccine manufacturers, WHO negotiated in 2008 a licence with the owner of the Russian LAIV technology outside the former Soviet Union. By virtue of this agreement, developing country manufacturers working with WHO will have access to the reassortants and associated knowledge for both seasonal and pandemic influenza vaccine production.

When the circulating strain is not highly pathogenic and can grow on eggs or cells, classical reassortment can be achieved in a few weeks and is not dominated by IP. For pandemic strains, IP covers the use of reverse genetics to produce seed-strains. Other IP on LAIV includes methods of stabilization to permit the vaccine to be stored in a refrigerator. Other patents, e.g. on methods to stabilize viruses, proteins and vaccines, were also described.

Regulatory approval of the vaccine includes the delivery device, and manufacturers need to identify one that is suitable for delivery and possible storage of the vaccine within the device, some of which are covered by IP.

The use of adjuvants to reduce the antigen level required in inactivated vaccines

Most adjuvants are subject to IP. Two that have had positive clinical results are aluminium salts and oil-in-water emulsions. The use of alum-based adjuvants for pandemic vaccine appears attractive since there are few IP barriers, but to date studies of alum-adjuvanted H5N1 vaccines have yielded modest evidence for dose-sparing or broadened immune responses. Several studies using oil-in-water emulsions have shown a greater dose-reduction potential than aluminium salts, with pandemic strain antigen as low as 2–4 µg. The original patent on submicron oil-in-water emulsions has been revoked in the European Patent Office, although it may still be valid in other parts of the world. Patent holders have indicated that, in the event of a pandemic, they would permit their adjuvants to be used by others. Nonetheless, pre-negotiated agreements and regulatory approval of the final product would still be needed, reducing the independence of local pandemic response.

Having discussed the IP covering the production of pandemic vaccines, the document describes the patent portfolios and other impediments related to the process for reverse genetics and engineering of vaccine strains. This patent portfolio is highly relevant to access to pandemic influenza vaccine, since the reference strains will be produced using this procedure by WHO collaborating centres in countries where the patents have been issued or applied for. In the event of a pandemic, the patent holder has indicated that free access to its IP would be granted to entities developing pandemic influenza vaccine for public health purposes.

2.6 Feasibility of using animal vaccine production facilities to gear up availability of pandemic influenza vaccine

The second GAP approach to increase influenza vaccine production capacity recommended that partial conversion of veterinary vaccine production facilities to produce human influenza vaccines should be analysed. In 2006, the WHO Country Office for the People's Republic of China embarked on a feasibility assessment of converting animal to human vaccine production facilities in interpandemic situations. Currently in China, responsibility for the licensing, manufacturing, regulation and distribution of poultry influenza vaccine lies with the Ministry of Agriculture. The Ministry of Health and the regulatory body for human vaccines considered that the manufacture and regulatory processes for animal and human vaccines were so different that such a proposal would not be feasible in China.

The feasibility of this approach in other countries would need to be carefully assessed in view of the differences between production technologies used for human and veterinary influenza vaccines, and taking into consideration regulatory pathways for human and veterinary medicines.

2.7 Facilitating technology acquisition by developing country manufacturers for influenza vaccine production

Currently, 90% of influenza vaccine production is located in nine countries (largely in Europe and North America) that represent only 10% of the world's population. Local and/or regional influenza vaccine production would redress this situation to some extent, and would also support outbreak response by ensuring greater equity in the deployment of what may be a scarce resource in the early months of a pandemic. Effective technology transfer is arguably the most effective route for developing countries to secure sustainable access to quality influenza vaccination technology.

In October 2006, WHO issued a call for proposals to developing country vaccine manufacturers willing to initiate domestic production of influenza vaccine. The technologies eligible for funding were killed subunit, split or whole virus, live attenuated influenza vaccines, cell-culture or egg-based production. Expectations were for large-scale seasonal influenza vaccine production that would be rapidly operational, cost-effective and sustainable. Grantees were also expected to make available up to 10% of their production to United Nations purchasers in the event of a pandemic.

Six developing country manufacturers received grants of US\$ 2–2.7 million each to establish pilot facilities for the production of seasonal and pandemic influenza vaccine (Table 2). All projects were initiated between June and September 2007. In addition, representatives from each country attended the WHO-organized training courses at NIBSC in the UK in April and November 2008, the first course targeting principally QC staff of the manufacturers, and the second regulatory personnel.

Table 2. WHO technology transfer grants

Country/Institute	Technology	Main achievements at end 2008
Brazil: Instituto Butantan	Egg-based inactivated split and/or whole-virion H5N1 with adjuvant.	New pandemic pilot plant established where 10 experimental lots have been produced: seven H3N2 and three rH5N1.
India: Serum Institute of India	Cell-based inactivated split virus and egg-based LAIV, depending on access to live attenuated strain.	H1N1 and H3N2 strains successfully grown under laboratory conditions. QC system in place.
Indonesia: BioFarma	Fill/finish for egg-based split seasonal vaccine.	Facility established, three clinical grade lots produced and a clinical trial completed.
Mexico: Birmex	Blending, filling, packaging of egg-based inactivated split seasonal vaccine.	Product specific equipment for QC laboratory purchased. Construction and engineering plans for blending facility under validation.
Thailand: Government Pharmaceutical Organization	Egg-based split inactivated vaccine and LAIV, depending on access to live attenuated strain.	Successful laboratory scale production of trivalent seasonal vaccine with QC confirmation. Technology ready to test under pilot plant conditions.
Viet Nam: IVAC	Egg-derived whole-virion, alum adjuvanted vaccine.	Facility under construction. Three rH5N1 experimental lots sent to NIBSC for confirmatory testing for antigen content.

2.7.1 Overview and progress of the technology transfer grants

Brazil

The Instituto Butantan belongs to the São Paulo Office of Health, and manufactures vaccines for the Brazilian market. The Institute had already received technology transfer from a major multinational producer for egg-based split trivalent seasonal influenza vaccine. A plant was built to produce 20 million doses and a smaller plant became operational in 2008 to allow safe processing of eggs and embryos for H5N1 prototype vaccines. Over the past year, Instituto Butantan has produced 10 experimental lots, and trained staff in the production of seasonal and H5N1 vaccines.

The Institute reported that a clinical trial with seasonal low-dose IIV formulated with alum showed adequate responses to H1N1, H3N2 but not to B. The company has produced three rH5N1 lots in the new specialized plant. By the second half of 2009, Butantan plans to be producing seasonal vaccine and to have a stockpile of adjuvant and vaccine prepared for pandemic use.

India

The Serum Institute of India is a private company and a WHO prequalified supplier of numerous vaccines. It has large vaccine production capability but no government support for influenza vaccine production, nor a technology transfer partner. The project has a dedicated team of scientists, a small manufacturing unit and a GMP-compliant analytical laboratory. Experimental work was undertaken on eggs and Vero and MDCK cells for optimum growth conditions. A process has been developed for virus concentration and purification, and parameters developed for virus inactivation using β -propiolactone (BPL). QC tests for assessment of HA content and infectivity titres, and protocols for protein and DNA estimation have been established. Tests to assess immune responses following immunization in preclinical models are under way.

Toxicological studies and final formulation will take 12–15 months. Future plans include immunogenicity studies with different dosages of whole and split vaccines using adjuvants, and possible LAIV production with prospective partners. The estimated number of vaccine doses that could be produced per annum is 23 million IIV or 168 million LAIV.

Indonesia

BioFarma Persero is a government-owned, WHO prequalified vaccine manufacturer, although it has no experience with influenza viruses. Its current aim is to produce 25 million doses of split, seasonal vaccine and capacity to fill/finish 25 million imported pandemic doses. The WHO grant has supported the transfer of expertise from an established influenza vaccine manufacturer, as well as the procurement of equipment. At the end of 2008, the company had trained staff on formulation, filling, QC and regulatory issues. A clinical trial of Indonesia fill/finished seasonal vaccine lot, made from imported bulk, was successfully completed. The company plans to license and start distributing a seasonal vaccine in Indonesia from 2009.

Mexico

Birmex is a government-owned company producing oral polio vaccine and, since 2005, has a technology transfer agreement for measles-mumps-rubella vaccine. The grant is for the design and validation of a plant to fill/finish bulk influenza vaccine, produced by a multinational vaccine manufacturer, and QC equipment. To complement the grant, Birmex will invest up to US\$ 31 million to complete the facility including land purchase, construction, equipment, training and plant and process validation. To date, the architectural plans for the production facility have been approved and support secured from the government and the technology transfer provider.

Thailand

The Government Pharmaceutical Organization has experience in diphtheria-tetanus-pertussis and Japanese encephalitis vaccines. The Thai Government supports the project through its national pandemic plan, including increased use of seasonal vaccine, and has committed US\$ 35 million to building a production plant. The objective is to manufacture 2–3 million doses of seasonal vaccine per year and to convert to LAIV to cover the entire population in a pandemic. Thailand currently imports 500 000 doses of IIV per year. The GMP pilot facility has been validated and equipment for laboratory production installed. A process for IIV for three strains, and analytical methods have been developed. Access to seed strains for LAIV is being negotiated by WHO.

Viet Nam

IVAC is State-owned and the largest national vaccine manufacturer, and is collaborating with the Institute of Biotechnology to produce pilot lots of whole-virion based H5N1 in eggs. IVAC initially plans to produce 500 000 doses of seasonal vaccine with possible expansion up to 3 million doses. Construction of the facility and supporting chicken farm is under way, and the design of production and waste-treatment facilities conceptualized. Reference virus strains for seasonal and H5N1 influenza were obtained from NIBSC and three batches were produced. Work is progressing to initiate clinical trials.

2.7.2 Meeting of international partners

Following the initiation of the above grants, WHO brought together the six developing country manufacturers in October 2007,²² along with vaccine producers from other countries, development banks, donor countries and UNICEF. The meeting reviewed the start-up progress and encouraged networking towards the GAP goals.

The funding agencies and bilateral donors were optimistic that the project would increase global production capacity for influenza vaccine. Technology transfer projects were considered an excellent way to strengthen technical capacity in developing countries to produce vaccines and to respond to emergencies. Several suggestions were made to assure the sustainability of technology transfer capacity, including: regional know-how platforms; a commercial portfolio of vaccines based on regional markets and cooperation; data collection for policy-making; and finance mechanisms. It was also noted that solid business plans and political commitment were prerequisites to sustainability.

²² *Meeting with international partners on influenza vaccine technology transfer to developing country vaccine manufacturers, 29–30 October 2007, Bangkok.* Geneva, World Health Organization, 2008 (WHO/IVB/08.09, whqlibdoc.who.int/hq/2008/WHO_IVB_08.09_eng.pdf).

A second meeting of international partners was held in November 2008 in Pune, India, to review further progress and seek the interest of potential new manufacturers to receive seed funding from WHO to acquire technology to manufacture influenza vaccines. A call for proposal was launched in November 2008 to identify potential new projects for selection in February 2009.

2.7.3 Technical advisory group review

With a view to providing optimum support to the developing country manufacturers, an independent Technical Advisory Group (TAG) was established and first met in February 2008 to review the progress of the grantees. The six TAG members – with expertise in either regulatory or manufacturing processes – each took responsibility to review and present one of the projects.

It was agreed that most projects had made significant progress. The TAG recommended that all manufacturers provide WHO with details of their discussions with their national regulatory authority on the proposed licensing pathway for the influenza vaccine. It was also proposed that a separate laboratory be available to produce working seed lots, and that a reliable egg supply be established. TAG members also made site visits to the grantees to discuss the issues that had been raised.

2.8 Technology transfer hub to support influenza vaccine production in developing countries

During the first phase of the technology transfer project described in 2.7, a major barrier was finding manufacturing partners prepared to transfer their technology. While two of the six grantees were able to negotiate technology transfer agreements for the formulation/fill-finish steps of the manufacturing process, the transfer of bulk manufacturing technology was unsuccessful. This caused delays in initiating credible programmes for some manufacturers. Indeed, while a number of consultants with expertise in the field have agreed to assist in the development phase, setting up all the processes and documents ex nihilo at each site is a daunting task.

A technology platform for IIV production was therefore considered a promising solution in the absence of technology transfer providers. This novel approach brings together available research, production knowledge, technical expertise, documentation, clinical dossiers and standard operating procedures under one “technology hub” that will distribute the synthesized know-how package and training modules to developing country manufacturers. The choice of the technology (egg-based, whole-virion, inactivated vaccine) was guided by the fact that it is tried and tested, patent-free, and less demanding and costly than cell culture. The ultimate aim is to provide developing country manufacturers with one-stop access to a robust technology package and associated services, in a cost-effective and time-efficient manner.

Applicants were invited to submit letters of intent and, in December 2007, the Netherlands Vaccine Institute (NVI) was awarded a start-up grant to establish the technology hub. NVI is a government-supported institution producing a subset of vaccines against infectious diseases for the Dutch population, and has long-established research expertise and manufacturing competence. NVI is also known for providing technology assistance to developing country manufacturers, such as for *Haemophilus influenzae* type b vaccine production.

Funding for the first phase of the project has enabled the installation of equipment and the initial process development for IIV. Subject to continued funding, the project will carry out the preclinical and clinical steps to transfer pilot production technology to selected manufacturers, with training courses using a special manual for technology transfer containing all information on the facility, equipment, production process, assays, validation and lot release. It is hoped that the hub will be fully operational in 2009, and that the approach could eventually be applied to other vaccines or technologies.

2.9 Business plan for the global pandemic influenza action plan

A business plan to refine the GAP activities and cost estimates was developed in collaboration with an external consultancy company.²³ The business plan evaluates the short- to medium-term (2007–2017) options to be able to produce enough vaccine to immunize the world's population within six to nine months of the transfer of the prototype strain to industry. This time frame is deemed critical to mitigate the effects of the first wave of a pandemic. Taking into account current challenges and based on key assumptions, the business plan proposed a combination of three solutions, each of which was then assessed against six criteria: technical feasibility; capacity; delivery time; ease of implementation; risk; and cost.

Solution 1. Promote seasonal vaccine programmes. This was fundamental to create greater capacity. It is also cost-effective in reducing health-care spending and loss of workdays. Concerns included the high cost of influenza vaccine, which may divert funds from other public health priorities. Since capacity in 2010 is projected to be substantially higher than forecast demand, another issue was the need for incentives for industry to maintain such production levels. Finally, it was noted that even if each country achieved the highest rate of seasonal influenza vaccination currently achieved in the same economical status stratum (high, middle or low income), demand would still not create the capacity needed to meet the GAP goal.

Solution 2. Maintain production capacity beyond seasonal need after 2010. The main issue here is flexibility in maintaining capacity, e.g. rotating production lines and ensuring that supplies, equipment and human resources are available and functional at short notice. As noted in Solution 1, encouraging industry to maintain capacity and regular batch testing would be needed to meet surge demand.

Solution 3. Convert IIV to LAIV capacity at the onset of a pandemic. Facility conversion is a rapid technique that could bridge the supply–demand gap by 2012, based on prudent estimates that a dose of trivalent IIV yields 15–30 courses of pandemic LAIV. Considerations included the outstanding clinical and regulatory work to broaden the indication for LAIV, the significant up-front preparation for conversion, and IP hurdles. It was also suggested that establishing new plants in regions without access to pandemic influenza vaccine would be as cost-effective as converting existing capacity to LAIV production.

²³ *Business plan for the global pandemic influenza action plan to increase vaccine supply.* Geneva, World Health Organization, 2008 (www.who.int/entity/vaccine_research/documents/Report%20McKinsey%20Business%20Plan%20Flu3.pdf).

Other options. New technologies might dramatically shorten the time required to generate vaccine, and the major avenues currently being researched for better cross-protection and production methods were highlighted, e.g. mammalian cell-culture derived vaccines and recombinant (DNA, viral-vectored and virus-like particle) vaccines. However, these solutions appeared some 5–10 years away from mass production. A chart was provided that lists the many developing countries that are about to start, or have expressed interest in producing seasonal influenza vaccine. Lastly, and although it might appear promising at first sight, the technical, logistic and financial hurdles facing a switch from animal to human influenza vaccine production during a pandemic made that option unfeasible (see Section 2.6).

The business plan also considered three essential enablers and their implications for pandemic influenza vaccine preparedness.

Enabler 1. A robust supply and delivery chain. Delivery of billions of pandemic vaccine will require guaranteed cold chains, ancillary supplies and qualified health-care personnel, sufficient numbers of which are lacking in many developing countries. The business plan recommended investigating new regional fill/finish capacity to meet the expected shortfall, considering stockpiles of ancillary supplies, and using the cold-chain network used to implement the Polio Eradication Initiative.

Enabler 2. Immunize essential services from disease and/or death early in the pandemic with vaccine held in stockpiles. This strategy complements the use of antivirals. (A potential drawback of stockpiled vaccine is that it may not protect against the pandemic virus, should this be very different from currently circulating H5N1 strains.)

Enabler 3. Policy, regulatory and coordination issues. The wide range of issues included the import and export of vaccines during a pandemic; optimizing and possibly harmonizing national regulatory pathways for approval of pandemic vaccine; technology transfer; and indemnity considerations for secondary manufacturers.

The total cost of the three solutions, funding for research and the enablers, would rise to US\$ 3.8–4.1 billion annually by 2012 and continue at that level through to 2017. Most costs were for increasing demand for seasonal vaccines. The incremental costs to global health donors is estimated at US\$ 1.1–1.4 billion per year.

Finally, it was acknowledged that although global coordination will become increasingly complex, this must be addressed, and all stakeholders convened to take the business plan forward.

2.10 Advisory group of the GAP to increase supply of pandemic influenza vaccines

The GAP is not a WHO plan. It was adopted, and should be implemented, by the global community. An international, independent advisory body was therefore established to review the GAP priorities in line with advances in science and technology, to monitor achievements and challenges in implementing the plan, and to make recommendations for future priority action. The ten members of the GAP Advisory Group met at WHO, Geneva in October 2007²⁴ and in Pune, India, in November 2008. A summary of their deliberations is provided below.

October 2007

Promising advances in research and development (R&D) were presented by industry observers and others (see Section 3 on clinical research). Major progress had been made in developing H5N1 vaccine formulations that will allow substantial antigen sparing in case of a pandemic, three of which had demonstrated immunogenicity with as little as 1.9–7.5 µg HA, formulated with proprietary adjuvants. As a result of these efforts, the current potential maximum capacity had risen to more than 2.5 billion monovalent adjuvanted immunization courses per year (two 5 µg doses) in 2008, with the potential to rise to over 10 billion in the coming years. This was a significant increase in vaccine production capacity compared with when the GAP was prepared in 2006.

The group noted the completion of the global influenza vaccine survey in June 2007 and its conclusions. Members were also apprised of the six technology transfer grants awarded to developing country manufacturers to increase production capacity in their regions. In terms of the number of immunizations available to the global community, it was appreciated that such new producers would not compete with the multinationals. However, the additional in-country capacity may well be critical to ensure that developing countries have access to some vaccine in the early months of a pandemic. Members also discussed the advantages of the technology training hub to compensate for the scarce technology transfer sources to developing countries.

A project to determine influenza vaccine strategies for broad global access was presented under the auspices of PATH. The pros and cons of priming with H5N1 vaccines, of stockpiling H5N1 vaccines, and of excess capacity were debated. These priority issues are being considered by a special SAGE Working Group (see Section 1.5.3 above).

The GAP business plan described in Section 2.9 was a major item on the agenda. While requesting that some assumptions be revisited before its finalization, members welcomed the overall analysis presented. The fact that it had been developed by independent consultants in discussion with country representatives and other stakeholders would facilitate buy-in by the international community. The feasibility of the business plan, on the other hand, would depend on underlying IP issues and political considerations that will need to be taken into account. The following specific comments were made:

²⁴ *First meeting of the advisory group on the global action plan (GAP) to increase supply of pandemic influenza vaccines, 19 October 2007.* Geneva, World Health Organization, 2008 (WHO/IVB/08.10, whqlibdoc.who.int/hq/2008/WHO_IVB_08.10_eng.pdf).

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- Increased influenza vaccine production required a four-pronged approach: (i) creative financial strategies; (ii) strong marketing; (iii) learning from previous campaigns; and (iv) leveraging sister United Nations organizations and partners. GAVI, in particular, should be approached as a financial partner, and a mechanism such as the PAHO revolving fund explored.
 - Implementation of the GAP should strengthen national immunization programmes and surveillance. Moreover, it may improve the world's ability to conduct mass vaccination campaigns and strengthen vaccine regulatory systems.
 - The business plan is novel and thus entails some obvious risks. Notably, if there is no influenza pandemic within the next five years, there may be loss of interest, political awareness and investment. A major potential risk is also the lack of a public health structure in communities to piggyback on the growing influenza vaccine production capacity.
 - The feasibility of converting a production facility from trivalent IIV to monovalent LAIV in a defined time frame needs to be assessed, as well as the cost of new facilities.
 - An important engine to achieve the business plan is financial. The right approach may be to host the GAP under the umbrella of the International Health Regulations as a global health security issue, or under health systems strengthening. The business plan should aim to align itself with other organizations, harmonize strategies with donors and maintain stakeholder commitment.

Members recommended that WHO's priorities in 2008 should be to develop a marketing strategy for the business plan along with an operational plan, and to define financial requirements and sources. Additional priorities were to:

- maintain global commitment through information, education and communication activities;
- address potential liability issues associated with the business plan;
- investigate the seasonal influenza disease burden in developing countries as part of ongoing national surveillance activities;
- develop reproducible assays to evaluate the immunogenicity of influenza vaccines and establish adequate correlates of protection; and prioritize the efficacy of potential cross-reactive vaccine candidates to induce broad-spectrum protection.

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Members examined the GAP for continued relevance in the light of the evolving landscape, and agreed that the three original approaches to achieve the GAP goal of enhancing pandemic influenza vaccine supply remained valid. On the other hand, progress within each approach had been irregular. Impressive advances have been made in reducing the gap between current capacity and pandemic demand. Yet this potential will be overturned unless certain hurdles are overcome, such as developing vaccines that induce broad-spectrum immunity. It was therefore recommended that WHO update the GAP in 2009 to reflect the latest priorities. Reinforcing their recommendations made in October 2007, the Advisory Group prioritized the following issues that should be highlighted in the revised document and in future WHO activities.

GAP approach 1: increase use of seasonal influenza vaccine

- Gather more data in developing countries on the disease burden and economic impact of seasonal influenza. This will allow a cost-effectiveness analysis of vaccination and may increase demand.
- Conduct a new survey of country policies on current and projected use of seasonal influenza vaccine.
- Intensify high-level political awareness.
- Emphasize the critical link between seasonal influenza vaccine use and pandemic vaccine availability.

GAP approach 2: increase production capacity, independent of seasonal influenza vaccine use

- Encourage continued technology transfer to developing country vaccine manufacturers.
- Publish the latest study commissioned on influenza vaccine production capacity in order to allow a fuller analysis of its assumptions and results.

GAP approach 3: research and development

- Conduct more research into new and improved seasonal vaccines.
- Intensify efforts to develop vaccines that can induce broad-spectrum immunity.
- Carry out discussions with regulatory authorities to decrease hurdles for new technologies.

In addition, modalities for access to the international H5N1 vaccine stockpile should be clarified.

The GAP Advisory Group is scheduled to meet again at the end of 2009.

3. Clinical research

The third approach of the GAP acknowledged and encouraged the research and development being undertaken by the research community – and in particular the vaccine industry – to design more potent and effective vaccines that are: (a) capable of inducing protective responses after one dose, and/or (b) induce broad-spectrum and long-lasting immunity against both seasonal and pandemic influenza strains. To achieve this, a number of areas of clinical research that warrant special attention were noted:

- Enhanced protective efficacy and immunogenicity of existing vaccine types: aside from long-term assessment of the molecular basis of immunogenicity to design more potent vaccines, a priority is to evaluate novel adjuvants that allow higher immunogenicity and thus antigen sparing.
- Novel vaccines that induce broad-spectrum and long-lasting immune responses: such vaccines would significantly simplify the logistics of vaccine production, potentially improve efficacy in high-risk groups, and ultimately lead to greater availability of vaccine at a lower cost.
- Improved evaluation of vaccine performance: define correlates of protection in humans to enable registration of vaccines based on comparative immunological data.
- Alternative delivery routes: the intradermal route, for example, could make 2–5 times more vaccine available.

This Section summarizes the activities carried out to date under the auspices of WHO in the area of clinical research into new and improved vaccines in support of the GAP goals.²⁵

3.1 Evaluation of pandemic influenza prototype vaccines in clinical trials

Given the enormous challenges of producing and regulating a vaccine against a pandemic strain, WHO initiated a forum in November 2005 to stimulate activities and develop a research agenda to accelerate the development of candidate vaccines. In the space of two and a half years, four meetings have been held to evaluate pandemic influenza prototype vaccines in clinical trials.

²⁵ Further details of all meetings on the evaluation of pandemic influenza prototype vaccines in clinical trials can be found at www.who.int/vaccine_research/diseases/ari/en/index.html.

At the first two meetings (November 2005 and May 2006), only limited information on clinical trials of pilot vaccines were available. Results showed that H5N1, H9N2 and H5N3 candidate vaccines were generally safe and well tolerated, although immunogenicity results were highly variable, and dependent upon vaccine formulation, antigen content and immunization schedule.

At the time of the third meeting in February 2007, 16 manufacturers from 10 countries were developing prototype pandemic influenza vaccines against H5N1, five of which also had prototype vaccines against other avian viruses. Over 100 experts discussed the 20 projects presented, and the 40 clinical trials ongoing or completed at that time. Results showed that whole virus preparations appeared to be more immunogenic than equivalent doses of split vaccine. Alum adjuvanted split vaccines, in striking contrast to some of the more promising alum adjuvanted whole-virion vaccines, showed only modest increases in immunogenicity over unadjuvanted vaccines and, moreover, not sufficient to allow significant dose sparing. Some split vaccines formulated with newer adjuvants had shown encouraging immunogenicity which would probably allow dose sparing. Recommendations focused on (a) seed strain selection and distribution; (b) surveillance of emerging viruses; (c) clinical evaluation priorities; (d) vaccine performance; and (e) priorities for WHO research.

The fourth meeting on the evaluation of prototype pandemic influenza vaccines took place in February 2008. The growing number of manufacturers with active programmes concentrating on H5N1 influenza vaccines and other novel subtypes had allowed the accumulation of much valuable information. Around 100 experts at the meeting evaluated data on the immunogenicity of candidate H5N1 vaccines in recent clinical trials that are studying safety, dose response and possible antigen sparing, as well as cross-reactivity of the antibody responses elicited by available H5N1 prototype vaccines.

As presented at previous meetings, all preparations evaluated in clinical trials were shown to be generally safe and well tolerated in healthy adult volunteers and, when tested, in children and the elderly. Non-adjuvanted split or subunit candidate H5N1 avian influenza vaccines had demonstrated poor immunogenicity in healthy adult volunteers, as two doses of up to 90 µg influenza H5 haemagglutinin induced seroconversion in only about 50% of recipients. Supplementation of the vaccine with aluminium salts resulted, at best, in moderate improvement of immunogenicity. In contrast, supplementation of the split and subunit H5N1 vaccines with oil-in-water adjuvants resulted in remarkably improved immunogenicity, allowing significant antigen sparing and inducing broad-spectrum, cross-clade reactive anti-H5N1 antibodies that persisted for at least six months.

Three H5N1 whole-virion inactivated vaccines had been tested in Phase II–III trials, two of which are alum adjuvanted and the third, produced directly from a wild-type H5N1 isolate, had no adjuvant component. All three were shown to be highly immunogenic.

LAIV produced in the USA were derived by reassortment between avian influenza viruses H5N1, H9N2 or H7N3 and a temperature-sensitive, cold-adapted (ca) master donor strain derived from H2N2 virus. Trials showed the H5N1 ca reassortant to be poorly infectious and immunogenic in healthy volunteers, whereas another avian-human ca reassortant vaccine, H5N2, under study in the Russian Federation, apparently showed good replication and immunogenicity in humans. Whether the fact that the master strain carrying the ca mutations used to generate the Russian avian-human reassortants was the Leningrad 17 strain, which differs from the backbone strain (Ann Arbor) used in the trials in the USA, explains the discrepancy, deserves additional study.

Since comparison of different vaccines or adjuvants is hindered by a lack of properly standardized antibody (Ab) assays, elaboration of standard operating procedures (SOPs) for haemagglutinin-inhibiting antibodies (HAI) and neutralizing Ab assays, and production of international reference reagents, such as reference influenza antibodies, are urgently needed. Efforts to develop and disseminate a serum clade 1 H5N1 antibody standard were subsequently undertaken by the NIBSC.

The fifth consultation on clinical trials of H5N1 and other prototype pandemic vaccines was held in February 2009.

3.2 Influenza vaccines that induce broad-spectrum and long-lasting immune responses

In 2004, WHO initiated a project to promote the development of a new generation of influenza vaccines that induce broad-spectrum and long-lasting immune responses and provide cross-protection against divergent influenza viruses. Such vaccines would overcome many of the problems facing annual seasonal influenza vaccination, better meet the needs of developing countries, and contribute significantly to the control of an influenza pandemic. In follow-up to the first and second meetings on this topic, held in February 2004 and December 2005 respectively, the third meeting of experts convened in December 2007 to review the current status of research, as described below.²⁶

Remarkable progress had been made in the development of new adjuvants, particularly oil-in-water emulsions. Supplementation of the split and subunit influenza vaccines with MF59, AS03 or AF03 resulted in greatly improved immunogenicity, allowing significant antigen sparing and inducing broad-spectrum antibodies. New adjuvants were being developed, often based on toll-like receptor (TLR) ligands, that can be added to a subunit vaccine or covalently conjugated to the antigen. These adjuvants enhance the antibody response to subunit recombinant vaccines and may open the door to single-dose pandemic vaccines, although most of these approaches have yet to be tested outside the mouse model.

²⁶ Girard M et al. Report of the third meeting on influenza vaccines that induce broad spectrum and long-lasting immune responses. World Health Organization, Geneva, 3–4 December 2007. *Vaccine*, 2008, 26:2443–2450.

The mechanism of broad-spectrum cross-protection observed after natural influenza virus infection can be partly explained by the production of secretory immunoglobulin A (SIgA) which, due to its polymeric nature, strongly cross-reacts with different influenza virus strains. One way to broaden and increase influenza vaccine protection would therefore be through the induction of mucosal SIgAs. The intranasal and sublingual applications which elicit both mucosal and systemic immune responses were discussed at the meeting, along with intradermal (ID) vaccination.

Data on seasonal LAIV demonstrated a high level of protection, including against drift variants, evidence of herd immunity through the vaccination of children and the potential for early, possibly interferon-based, protection shortly after vaccine administration. There is some evidence of greater protection than that induced by IIV, although head-to-head comparisons are limited. Also, the duration of protection and characterization of the immune memory induced are yet to be determined. Data were also reviewed on a LAIV based on a non-replicative deletion mutant. A discussion on options for LAIV development can be found in Section 2.4 above.

The meeting reviewed the advantages and disadvantages of influenza vaccines based on conserved influenza virus proteins. These vaccines could be stockpiled and might provide protective immunity prior to the availability of HA-based, strain-matched vaccines; they may also be able to replace strain-matched seasonal vaccines and suppress the need for annual immunization. However, since correlates of protection for these vaccines are not the same as for HA vaccines, new standards and correlates of protection should be developed. It was emphasized that the only protection efficacy data available with vaccines based on conserved influenza viral proteins had been obtained in animal models, and their translation to protection in humans would be difficult. It is probable therefore that vaccines based on conserved proteins will need to be directly tested in efficacy trials in human volunteers.

A session on new technologies for the development of influenza vaccines reviewed data on virus-like particle vaccines, live recombinant influenza virus vaccines based on human adenovirus, modified vaccines with Ankara and Newcastle disease virus as vectors, and plant-derived vaccines. The possible protective efficacy of these new types of vaccines in humans is virtually unknown, and more has to be learnt on their immunogenicity and principal characteristics before they can be fully evaluated.

It was noted that the potential of improved or novel influenza vaccines has led to a number of unresolved regulatory issues. These include specifications for safety testing of candidate vaccines, standardized markers of protection for clinical evaluation, laboratory methods for testing adjuvanted vaccines, thermal stability, special considerations relating to vaccines that combine novel antigen(s) with conventional inactivated vaccine, and quality issues. Regulatory authorities need persuasive information that new vaccines provide cross-reactive and long-lasting immune responses.

Recommendations on further research, in line with those formulated in the consultations summarized above, included:

- studies to better define immune correlates of protection, including for LAIV;
- qualified assays and reagents to enable head-to-head comparisons of immunogenicity, safety and efficacy of different influenza vaccine concepts in animals and humans;

-
- studies on antigen sparing, broadening and inducing long-lasting immune responses;
 - alternative delivery routes;
 - the role of adjuvants and immunomodulators;
 - stabilization strategies;
 - studies on vaccines based on conserved viral proteins;
 - production of expression technologies (e.g. egg and cell culture-based, novel generation vaccines).

The next meeting on influenza vaccines that induce broad-spectrum and long-lasting immune responses is scheduled for the second half of 2009.

3.3 Dissemination of data on clinical trials of pandemic influenza prototype vaccines

As at June 2008, more than 70 clinical trials of candidate H5, H7 or H9 influenza vaccines were ongoing or completed. While most of these have focused on healthy adults, new data are now emerging on the safety and immunogenicity of vaccine candidates in the elderly and in children.

In response to requests from Member States and collaborators in pandemic influenza preparedness, WHO has compiled a database of non-restricted information on these trials.²⁷ Originally developed using data compiled by IFPMA, the database is regularly updated and complemented with data from technical meetings convened by WHO, publications and direct contacts with manufacturers and investigators in charge of clinical trials. The Excel presentation of the data allows users to filter according to 12 different variables. However, because of inherent variability in the HAI and neutralization antibody assay systems used to measure immunogenicity, and the lack of standardized methods for these assays, direct comparisons of results from different clinical trials are ill-advised. The time frame of the trials, along with hyperlinked references and further comments are also provided.

The database shows that several manufacturers have established formulations likely to meet regulatory requirements. In Europe, two H5N1 inactivated vaccines were granted EMEA approval on the basis of their mock-up dossier in 2007. In the USA, one H5N1 split inactivated influenza vaccine was licensed in April 2007 for emergency use, and in Japan, two H5N1 vaccines were approved in October 2007. In China, an H5N1 inactivated vaccine was approved in April 2008, and another in Hungary. Two further H5N1 vaccines were approved for use by EMEA and TGA (Therapeutic Goods Administration, Australia) in April and May 2008 respectively. Some studies suggest that vaccination with currently available H5N1 prototype vaccines can also induce immune response against antigenically drifted H5N1 virus isolated at different times in a variety of geographical locations, similar to that seen with seasonal influenza viruses.

WHO encourages all those involved in influenza vaccine trials to share information on planned and ongoing activities for inclusion in the database.

²⁷ www.who.int/vaccine_research/immunogenicity/immunogenicity_table.xls.

4. Regulatory response to human pandemic influenza vaccine preparedness

Many of the regulatory issues related to the development and use of influenza vaccines, particularly pandemic vaccines, are integral to – and thus are described in – the policy, production and clinical research sections of this report. This Section supplements the discussions on the regulatory requirements, potential pathways and novel options, to ensure that an eventual pandemic influenza vaccine can be available and reach the targeted populations within the shortest space of time.

4.1 WHO Expert Committee on Biological Standardization

The WHO Expert Committee on Biological Standardization is the authoritative body for global written standards on the quality, safety and efficacy requirements for all biologicals, including vaccines.²⁸ Several consultations convened by WHO since 2006 have focused on regulatory preparedness for pandemic influenza vaccines that are described in this report.

WHO supports national regulatory authorities to:

- develop capacity and national regulations/guidelines to enable timely and competent authorization of clinical trials and registration/licensing of influenza vaccines;
- establish and implement lot release and QC testing for influenza vaccines consistent with international standards;
- develop operational pharmacovigilance guidelines for seasonal and pandemic influenza vaccines.

²⁸ See www.who.int/biologicals, in particular *WHO guidelines for preclinical evaluation, clinical evaluation and quality control of vaccines, biosafety risk assessment and Guidelines for the production and control of human influenza pandemic vaccines*.

4.2 Informal consultation on regulatory preparedness for human pandemic influenza vaccines

This workshop was held in Geneva in June 2007 to promote international convergence on regulatory matters of quality, safety and efficacy of pandemic influenza vaccines.²⁹ National regulatory authorities, national control laboratories, academia, public health institutions and industry representatives from 21 countries convened to update the draft WHO guidelines on regulatory preparedness for human pandemic influenza vaccine. Presentations from regulatory authorities and industry on the state-of-the-art in human pandemic influenza vaccine quality, safety, efficacy and post-marketing surveillance were discussed. Regulatory convergence was achieved on many outstanding regulatory issues through joint development of the guidelines. Regulatory uncertainties at that time included the prequalification of pandemic influenza vaccines and agreement on immunogenicity criteria to assess candidate vaccines.

Following this consultation, the revised guidelines were reviewed and endorsed by the Expert Committee on Biological Standardization in October 2007, and are currently in preparation for publication in the WHO Technical Report Series.³⁰

4.3 Networking for regulatory preparedness

The outcome of the informal consultation on regulatory preparedness went beyond the preparation of the guidelines to the formation of a network of key players engaged in influenza vaccine regulation. The current regional/country regulatory capacity and preparedness to perform influenza vaccine batch release will be determined by a survey of national control laboratories, the outcome of which is expected in the first half of 2009. The survey may also identify ways to streamline vaccine batch-release procedures that build mutual confidence between NRAs.

In-country support for NRA strengthening was undertaken in Indonesia (October 2007), Thailand (June 2008), India (July 2008), and Viet Nam (August 2008). NRA-assisted site visits to the vaccine manufacturers in Indonesia and Thailand – recipients of WHO grants to increase influenza vaccine production capacity – were also conducted. Specific gaps that require further technical support were identified in regulatory functions of marketing authorization and licensing, post-marketing and adverse event following immunization (AEFI) surveillance, lot release and laboratory access, regulatory inspections of biosafety and GMP compliance, and authorization and approval of clinical trials.

Parallel to the information collected during the visits, a report is in preparation on the status of the regulatory functions and preparedness of all six grantee countries (Brazil, India, Indonesia, Mexico, Thailand and Viet Nam).

²⁹ Informal consultation on regulatory preparedness for human pandemic influenza vaccines, 14–15 June 2007, Geneva. Geneva, World Health Organization, 2007 (www.who.int/vaccine_research/diseases/influenza/meeting_140607/en/index.html).

³⁰ www.who.int/biologicals/expert_committee/BS%202074%20influ%20plus%20line%20numbering.pdf.

Since these country visits, the eighth meeting of the Developing Country Vaccine Regulatory Network, in May 2008, included a session on regulatory considerations for influenza vaccines. In addition, a one-week training was provided on quality control testing for lot release of influenza vaccines (November 2008), and a three-day workshop offered on clinical trial design for influenza vaccines (October 2008).

4.4 Immune correlates of protection against influenza A viruses in support of pandemic vaccine development

Increasingly, research into vaccines against novel human influenza viruses has highlighted the urgency to identify immune correlates of protection to assist regulatory evaluation of pandemic influenza vaccines. WHO, in collaboration with the US Food and Drug Administration and the US National Institutes of Health, therefore convened a public workshop on this subject in December 2007.³¹

All influenza vaccine manufacturers, including those involved in the development of pandemic vaccines, were represented. About 100 scientists from academia, industry and regulatory authorities were joined via webcast by a further 100 participants. The workshop provided a state-of-the-art review of the immune response to influenza to better inform the regulatory evaluation of candidate vaccines, and also identified a series of gaps in knowledge for priority research.

Participants confirmed that anti-HA antibodies were the key correlate of immunity for influenza. These antibodies prevent infection, and there is good evidence that they provide long-lasting protective immunity from homotypic challenge. Considerable redundancy in the human immune response was also noted. Anti-NA helps to clear the infection and is thus a desirable additional correlate. Anti-M2 had shown a protective role in animal models, but proof in humans is lacking. It was agreed that cellular immunity may have a role, as convincing data are now emerging. However, it was too early to evaluate these additional facets of the anti-influenza immune response for regulatory purposes.

The workshop concluded that the regulatory evaluation of candidate pandemic influenza vaccines, and vaccines against novel influenza viruses such as H5N1, present distinct challenges. Consensus was that the higher the antibody response, the greater the likelihood of protection and the broader the immune response are likely to be. Thus, induction of a high level of anti-H5 HA antibodies by a vaccine candidate is desirable. To assess the breadth of response to H5 clades, it was suggested that investigators focus on 3–4 circulating clades where disease has been documented in humans, and update the data as new clades emerge. Sufficient sera from clinical trials should therefore be set aside to allow for future studies, especially to identify the degree of cross-immunity with new clades.

Given the limited understanding of the immune response against H5, experts recommended that candidate vaccines be studied in animal models, e.g. ferrets, to evaluate cross-protection. The best correlate of protection in immunization/challenge experiments was a reduction in virus titre, although it remained unclear what amount of reduction constituted cross-protection.

³¹ The presentations, discussions and recommendations can be found at www.fda.gov/cber/pandemic/panflu121007.htm.

The meeting summarized that a more programmatic approach to pandemic vaccine trials using standardized assays and reference reagents would facilitate comparison of clinical trial outcomes and expedite vaccine development.

Immediately following the public workshop, two WHO closed sessions were held.

The first session considered the implications of the workshop, conclusions for the WHO guidelines on regulatory preparedness for human pandemic influenza vaccine, and for evaluation of vaccines in the international H5N1 stockpile. It was agreed that current WHO guidance, which provides three criteria for assessment of anti-HA antibodies, remained valid. However, since the most important criterion is the proportion of clinical trial recipients achieving a titre of HAI of > 40, the guidelines should reflect this modification. The meeting also recommended that cross-protection offered by vaccines in the H5N1 stockpile be studied in animal models, and the cross-immunity induced compared in neutralization tests against H5 clades currently infecting humans. This would progress the standardization of such methods and generate valuable data.

The second session sought to establish a research agenda to study correlates of immunity. Participants recommended further study on the development of human adult challenge models with influenza viruses, and on improved methodology for assays, particularly for mucosal immunity. Other priority clinical studies included challenge studies in children using LAIV shedding as the challenge tool, and natural history studies. Consensus was also reached on several studies to bridge human and animal models. Finally, the need to quantify the NA content and conformational integrity in vaccines for QC purposes was raised.

4.5 Pharmacovigilance and vaccine safety

Safety issues related to pandemic influenza vaccines are reviewed by the Global Advisory Committee on Vaccine Safety. As part of its mandate to strengthen NRAs, particularly in developing countries, WHO drafted guidelines on post-marketing surveillance of influenza vaccines at a working group meeting in June 2007. Since Thailand uses some 500 000 doses of seasonal influenza vaccine per year, it was selected as a location to explore ways to improve analysis and investigation of AEFIs. It is expected that, after final editing, the guidelines will be published in the first half of 2009.

Technical assistance was provided to Indonesia and Thailand to identify any shortcomings in their spontaneous reporting systems for AEFI and to improve data analysis and causality assessment. AEFI surveillance currently focuses on infants and children, as they are the most frequently exposed to vaccines. As a result of the assistance, AEFI reporting from target groups after seasonal influenza immunization improved, as did the quality of information on the use of seasonal influenza vaccines.

A workshop on causality assessment of AEFI was held for Thai and Vietnamese professionals in November 2007, and for Indonesian experts in March 2008. Operational guidelines for AEFI surveillance for influenza vaccines were reviewed by the influenza vaccine subgroup of the Global Advisory Committee on Vaccine Safety in 2008, and will be peer reviewed in 2009 for practicability in developing country settings by the national regulatory and public health authorities of Indonesia and Thailand.

5. Conclusion

The Global Pandemic Influenza Action Plan to Increase Vaccine Supply was launched in May 2006 as a three-tiered framework to mitigate the potentially dire consequences of a pandemic influenza outbreak. The objective remains the same: to decrease – or even eliminate – the shortfall between the expected demand for a pandemic vaccine and its projected production capacity, within the shortest possible time.

Progress towards this goal has been encouraging. In 2006, the production capacity for seasonal influenza vaccine was 350 million doses. Today, this capacity has already doubled, and should double yet again by 2013 with the advent of tissue culture-based vaccines, to exceed 1.7 billion doses. This is not counting promising ongoing research to improve existing vaccines, to reduce the amount of antigen required per dose or, further ahead, to develop new technologies that could dramatically shorten the time required to generate vaccine. However, this increasing seasonal production capacity already outstrips seasonal vaccine demand, so that measures need to be taken both to increase seasonal use and maintain the potential for rapid pandemic production.

Cooperation among all stakeholders has also been remarkable. Several multinational vaccine manufacturers have pledged over 110 million doses to the international H5N1 influenza vaccine stockpile. Others have agreed to waive intellectual property rights to their technology for public-health purposes in the event of a pandemic. Donor governments have enabled the financing of technology transfer to allow influenza vaccine production in otherwise vulnerable developing countries.

But what if political commitment started to wane? What if support is not sustained to ensure regulatory preparedness for pandemic vaccine or to support countries in their seasonal influenza vaccine programmes? Experience over the last two years has emphasized more than ever the correlation between global seasonal influenza vaccine production capacity and pandemic preparedness.

In a relatively short space of time, this would entail the closure of influenza vaccine production plants that can no longer commercially justify their increased capacity. In turn, this would annul the tremendous effort and investment of the international community in pandemic influenza preparedness to date and, most importantly, this would leave the majority of the world's population vulnerable to a known and largely containable health threat.

WHO will continue to fulfil its coordinating role, working with its Member States and all partners to achieve the objectives laid down in the GAP. Priorities for the next two to five years must therefore be:

- *to increase the use of seasonal influenza vaccine:* support political awareness; surveillance; the collection of disease burden, social and economic impact data; and national policy on seasonal influenza vaccination programmes.
- *to increase influenza vaccine production capacity:* determine mechanisms to support industry to maintain production capacity levels; assist developing country vaccine manufacturers to develop the capacity to produce influenza vaccines; enhance regulatory preparedness for the licensing and release of vaccines, including from the international H5N1 stockpile; and strengthen the technology transfer hub.
- *to encourage research and development:* inter alia, for improved vaccines, including LAIV and new technologies. The development of better, broader-spectrum, longer-duration influenza epidemic (seasonal) vaccines should also be encouraged. Availability of vaccines that could be administered every few years (not annually as is currently the case) would allow more countries to introduce influenza vaccination into their immunization programmes.

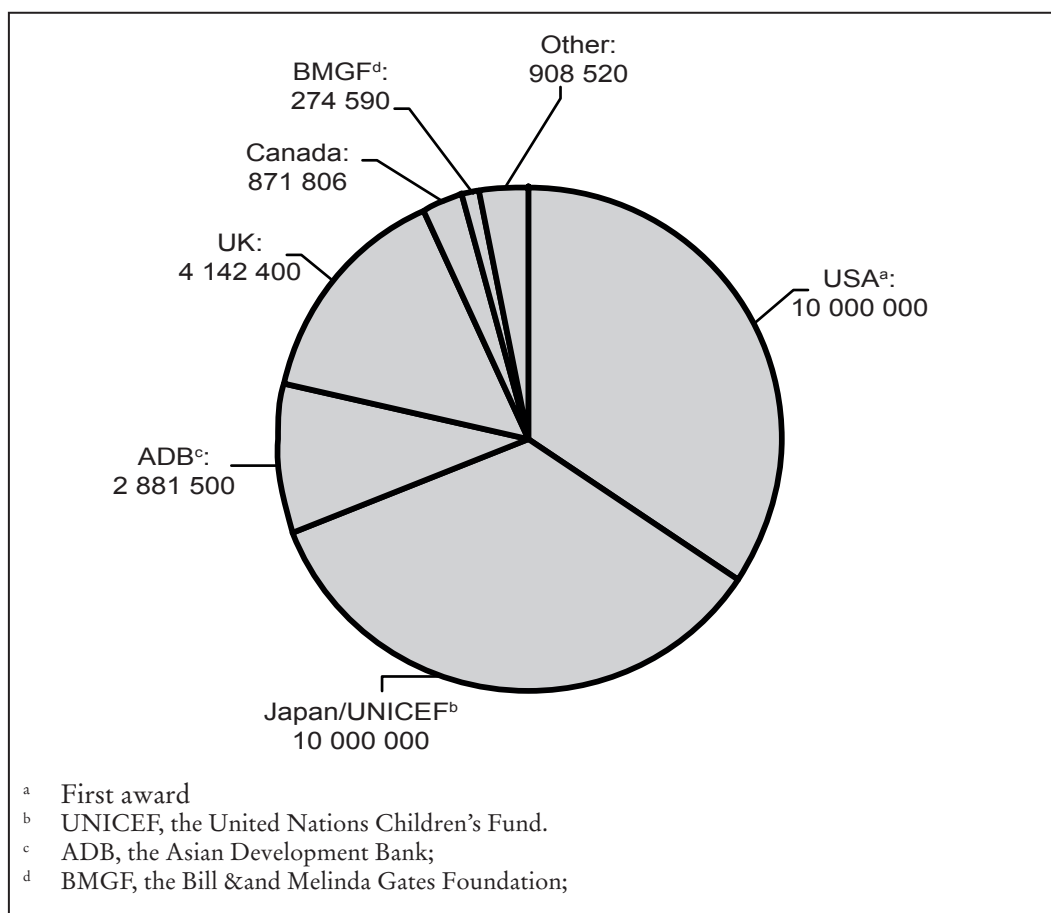
The Global Action Plan is as valid today as ever. Its success depends upon the unrelenting commitment of international organizations, governments, scientists, the donor community, the vaccine industry, regulatory authorities and health-care workers everywhere. Previous influenza pandemics have hit with no warning. In the twenty-first century, for the first time, we have an opportunity to be prepared.

Annex:

Breakdown of resources

During the period 2006 to 2008, a total of US\$ 29 060 816 was received to support the activities of the Global pandemic influenza action plan to increase vaccine supply. The figure below shows its breakdown.

**Contributions in US dollars to the
Global Pandemic Influenza Action Plan
2006 - 2008**



The resources needed for the next biennium to sustain the priority activities outlined in this report are estimated at US\$ 15 million per year.

“Influenza pandemics are historically recurring events. We are wise to prepare.”
Dr Margaret Chan, Director-General of the World Health Organization. Report to the WHO Executive Board, 124th session, Geneva, Switzerland, 19 January 2009.

The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization, Vaccines and Biologicals (IVB).

IVB's mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director's Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.

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